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Kinetic Study of Ketoprofen Degradation According To Standards Methods of International Commity of Harmonisation by HPLC.

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ABSTRACT

The kinetic study of the decomposition of ketoprofen according to standards of ICH in the three mediums: acid (HCl 2N), basic (NaOH 2N) and oxygenated H_2O_2 30% by HPLC was carried out. Kinetics parameters of each reaction of degradation and its speed, its partial order as well as the order of the reaction, the kinetics apparent constant, the time of half-reaction for each medium of degradation were calculated in this study.
Keywords: ketoprofen, ICH, HPLC, degradation, kinetic

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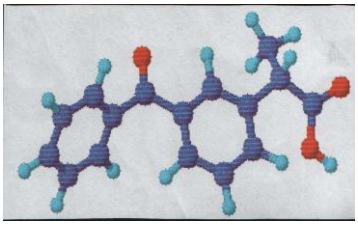
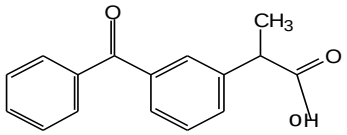
INTRODUCTION

The kinetic of degradation according to standards' establish by the international conference of harmonization (ICH) [1, 2], allows to study the reactivity of the active ingredient with respect to various mediums of stress. The study of this reactivity belongs to the study of stability of the molecule. It is within this framework there that this work at summer made on ketoprofen called also (RS)-2-(3-benzoylphényl) propionic acid (figure 1) and who belongs to the family of Anti-inflammatory drugs not stéroïdien propionic derivatives [3]. This molecule has an action primarily of an anti-inflammatory drug [4-6] but also antalgic and antipyretic one. Moreover it is also antiagrégant plate. Its principal mechanism of action is the inhibition of the cyclooxygénase and prostaglandins [7,8] which make it possible to have the feeling of pain during the ignition.

The object of this paper is to follow the decomposition of ketoprofen under various conditions of stress and to know the kinetic parameters of each reaction of degradation thanks to the liquid chromatography high performance duly used in literature [9-14].





Ketoprofen

Figure 1: Chemical Structure of ketoprofen

EXPERIMENTAL

Equipments and products

Module HPLC is composed from a pump and a UV-visible detector SHIMADZU, an injector RH EODYNE 7125, a loop of injection of 20µl, a column C_{18} (SUPELCOSIL TM LC-18-DB) and of a pH meter SCHOTT CG 825.Ketoprofen is gotten from The National Laboratory of Drugs Control of Tunisia like Octyl sulphates sodium. The acid, hydrogen peroxide, sulphate sodium and the sodium chloride are from Prolabo(France).

Chromatographic conditions

The mobile phase used is made up of: acétonitril – phosphate buffer- water (43:2:55)v/v with 0,3 millimole/litre of OSS (Octyl sulphate of sodium) at pH=4,5 for the basic and oxygenated solutions and with pH=6 for the acidic one. The detection is fixed at the wavelength 233nm.

Degradation of ketoprofen

Three 100mg of the product is dissolves in three 20ml of ethanol then are adjusted with the solutions HCl 2N, NaOH 2N, H_2O_2 30%v/v until 100ml respectively. Then the three solutions are heated under backward flow during 12 hour. On takes 0,5ml from acidic and basic solutions which have neutralizes with 0, 5ml respectively NaOH 2N, HCl 2N to stop the reaction, then one dilutes until 5ml with the mobile phase. The 0,5ml of oxygenate solution is diluted directly by the mobile phases, and these last solutions are injected.

RESULTS AND DISCUSSION

Table I Indicates the Quantity of ketoprofen for the three mediums to t = 0s

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Table I: Quantity of the active ingredient for each medium with t=0s

Nature of the medium of degradation	Quantity µmole L^{-1}	Quantity mg for 100ml
HCL (2N)	39,78372	101,17
NaOH (2N)	39,36296	100,10
H_2O_2(30% v/v)	39,43374	100,28

Kinetics of degradation

The evolution of the concentration of ketoprofen after the acid, basic hydrolysis and oxygenation by H_2O_2 according to time, shows a linear line for the three mediums (Fig 2,3, 4).

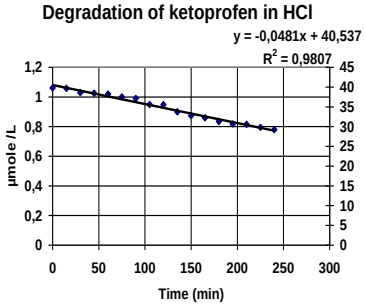

Figure 2: Evolution in acidic medium

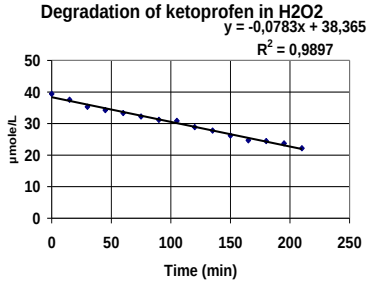

Figure 3: Evolution in oxygenate medium

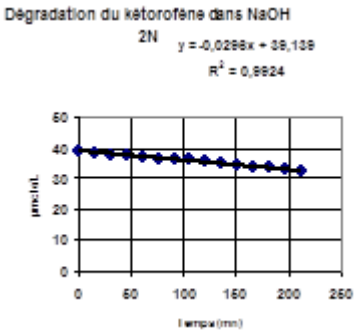

Figure 4: Evolution in basic medium

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Kinetics parameters

Being given that the initial ketoprofen concentration is much weaker than that of the acid, the base and the hydrogen peroxide, one can estimate that the concentration of these last are practically constant during the reaction and that of ketoprofen passes from an initial value.
$[Ket]_0$ to a zero value to the time which tends towards the infinite one: $t = t_\infty$ those equations speed are written:

$V_{Ket}= -d [Ket] /dt = k_{Ket} [Ket]^{\alpha} [HCl]^{\beta} = k'_{Ket} [Ket]^{\alpha}$ with $k'_{Ket} = k_{Ket} [HCl]^{\beta}$ in acidic medium

$V_{Ket}= -d[Ket]/dt = k_{Ket} [Ket]^{\alpha} [NaOH]^{\beta} = k'_{Ket} [Ket]^{\alpha}$ with $k'_{Ket} = k_{Ket}[NaOH]^{\beta}$ in basic medium

$V_{Ket}=-d[Ket]/dt=k_{Ket}[Ket]^{\alpha} [H_2O2]^{\beta}= k'_{Ket} [Ket]^{\alpha}$ with $k'_{Ket}= k_{Ket} [H_2O2]^{\beta}$ in oxygenate medium

Determination of the value of the partial order

We are in the case of the transfer of variable about $\alpha + \beta$ to α. The order required is then a partial order. To determine his value one limits oneself initially to the whole orders 0, 1, 2 and the 3. Values of $k'_{Ket\ (i)}$ for i various taking away carried out each 15 min.

For order 0 one calculates: $k'_{Ket\ (i)} = [Ket]_0 - [Ket]/ t$

For order 1: $k'_{Ket\ (i)} = \ln[Ket]_0 - \ln[Ket]/ t$

For order 2: $k'_{Ket\ (i)} = 1/ [Ket] - 1/[Ket]_0 / t$

For order3: $k'_{Ket\ (i)} = 1/ [Ket]^2 - 1/[Ket]_0^2 /2 t$

The best value of the order is that which gives the smallest relative variation table II, the suggested order will be that or the values of $k'_{Ket\ (i)}$ according to time will give a line. In order to confirm the partial order one plots the curve representing the variations of [Ket] according to time (graphic method). If it is a segment of line the order is well that suggested.

Table II: calculation of the relative variation for each value of the order.

Order	0	1	2	3
ER : relatif variation	25,4378124 %	31,4123768%	37 ,4827209%	43 ,7444385%

With: $ER = \left| \frac{k'_{Déb} - k'_{Fin}}{k'_{Déb} + k'_{Fin}} \right| x100$

Determination the apparent constant of kinetics

The calculation of the apparent constant kinetics k' is carried out starting from the linear transform of the curve [Ket]=f(t).These amounts determining the slope of this line which is equal to $-k_{Ket}$. Thus one finds according to the equation of the curve which is: $[Ket] = -k'_{Ket} + [Ket]_0$

The law speed in the case of order 0 is written: $V_{Ket} = - d[Ket]/dt = k'_{Ket}$

Determination of the time of the half reaction

Knowing that at $t_{1/2}$, [Ket] is equal to $[Ket]_0 /2$, and with according to the equation [Ket]=f(t) we have $t_{1/2} = [Ket]_0 /2k'_{Ket}$. In the three mediums the suggested order is 0, the graphic method confirmed it to us Figures 2, 3, and 4. The determination of the constant kinetics is deduced from the equations [Ket]=f(t) and $t_{1/2}$ Table III

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Table III: kinetics parameters of decomposition of ketoprofen in the three mediums

Dégradation medium	HCl 2N	NaOH 2N	H_2O_2 30% v/v
Partial order	0	0	0
Equation [Ket]=f(t) $[Ket]= -k'_{Ket}\,t + [Ket]_0$	[Ket]=-0,0481t+40,537	[Ket]=-0,0296t+39,139	[Ket]=-0,0783t+38,365
R^2	0,9807	0,9924	0,9897
Apparent kinetics constant (s^{-1}): k'_{Ket}	$288,6 .10^{-2}$	$177,6 .10^{-2}$	$472,98 .10^{-2}$
Speed of the reaction ($mole.m^{-3}\,s^{-1}$): $V_{Ket} = d[Ket]/dt = k'_{Ket}$	$288,6 .10^{-2}$	$177,6 .10^{-2}$	$472,98 .10^{-2}$
time of the half-reaction (s): $t_{1/2} = [Ket]_0/2k'_{Ket}$	$252,83.10^{2}$	$396,68 .10^{2}$	$146,00 .10^{2}$

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