

## RESEARCH PAPER

# Kinetic Study of Lornoxicam Hydrolysis

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### ABSTRACT:

Gastrointestinal tract (GIT) side effects due to the local action of lornoxicam considered the most common problem that associated with using of this analgesic drug. Masking of the enolic alcohol OH group of lornoxicam to overcoming this problem was the aim, however, applying Williamson ether synthesis led to amide hydrolysis. Therefore, the objective of this study was shifted to study the hydrolytic kinetics and the influence of different bases as a function of time and temperature in the reaction media.

The effects of all bases used in the study on the hydrolysis process of lornoxicam have been studied; NaOH was found to be the strongest followed by Na<sub>2</sub>CO<sub>3</sub> and K<sub>2</sub>CO<sub>3</sub>. All three temperatures (25°C, 50°C and 80°C) have approximately similar effect except reflux condition that accelerates the hydrolysis process compare with the others. The hydrolysis process is proportional with time.

Williamson ether synthetic procedure that followed to synthesize lornoxicam prodrugs was failed despite attempting different conditions. Using bases were induced the hydrolysis process of lornoxicam. The hydrolysis rate accelerated under reflux more than other conditions. In addition, reaction time gives more hydrolysis process.

KEY WORDS: lornoxicam; NSAIDs; amide hydrolysis; kinetic study.

DOI: <http://dx.doi.org/10.21271/ZJPAS.32.1.8>

ZJPAS (2020) , 32(1);65-74 .

### 1.INTRODUCTION :

One of the most consumed drugs over the years either by prescription or over-the-counter was NSAIDs. (Bacchi *et al.*, 2012) Discovery of NSAIDs since 1899 led to an important advancement in the painkillers field, they belong to a wide class of therapeutic agents ranging from the classic drug aspirin to the recent development of selective COX-2 inhibitors in the 1990s.(Rao and Knaus, 2008)

Oxicams are an important class of NSAIDs drugs which do not contain a carboxyl group. The term “oxicam” used to describe NSAIDs belonging to enolic acid class, which differs structurally from other classes of NSAIDs; they are containing a fused thiazine dioxide ring and an extended different carboxamide substitution. (Xu *et al.*, 2014)

Piroxicam was the first member of this class introduced in 1982 in the United States by the Pfizer. After piroxicam, other oxicams, including meloxicam, isoxicam, tenoxicam, and lornoxicam compound **1**, were introduced and they gained a huge acceptance in the treatment of acute and chronic inflammatory conditions. (Gouda *et al.*, 2017)

Lornoxicam **1** is a relatively new NSAIDs belongs to oxicam class with a potent analgesic, anti-inflammatory and antipyretic properties. The drug

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#### Article History:

Received: 25/08/2019

Accepted: 08/10/2019

Published: 25/02 /2020

was first marketed in 1995 and it is in clinical use in many European countries. (Homdrum *et al.*, 2006) The drug differs from other oxycam compounds in its rapid onset, short duration of action (the half-life is about 4 hrs.). Lornoxicam is the most potent balanced cyclooxygenase inhibitor, the ratio of COX 1: COX 2=1:1. (Kar *et al.*, 2016).

Although lornoxicam has lower side effects due to its short duration of action, (Rawal *et al.*, 2010) it still causing a wide range of adverse effects like other members of NSAIDs. GIT side effects due to the local action mechanism considered the most common problem that associated with using of these analgesic drugs (Russell, 2001). Many studies were conducted to overcome this problem by synthesis of prodrugs that are pharmacologically inactive derivatives of active drugs. Prodrugs undergo chemical and/or enzymatic biotransformation after administration resulting in the release of active agents. The parent drug subsequently elicits the desired pharmacological effect. (Halen *et al.*, 2009)

There are many studies indicate that the enolic hydroxy group of oxycams play an important role in their physico-chemical and pharmacological properties. Therefore, derivatization of this enolic group via alkylation or acylation is expected to change all these properties. (Jayaselli *et al.*, 2008) This is exemplified by the development of the ampiroxicam, an ether carbonate derivative of piroxicam, droxicam, piroxicam pivalic ester and cinnoxicam, piroxicam cinnamate. (Nakka *et al.*, 2011) These derivatives are stable under gastric conditions and cause lower GIT irritation due to masking alcoholic OH group. They are sufficiently labile toward hydrolysis to allow release of the parent drug after absorption. (Jornada *et al.*, 2015)

In this work, masking of enolic OH group of lornoxicam by using base and alkyl or acyl halide was the aim however, using base to produce alkoxide ion according to Williamson ether synthesis (Massah *et al.*, 2007, Hallmann *et al.*, 2015) led to amide hydrolysis. Numerous research reports on degradation of lornoxicam under hydrolytic conditions (especially basic conditions) are available in literature (Modhave *et al.*, 2011, Sindhu *et al.*, 2015) however, There were no previous studies explained hydrolysis process of lornoxicam inside the reaction media. Therefore, the objective of our study was shifted to study the

hydrolytic kinetics and the influence of different bases and conditions (temperature and time) in the reaction media.

## 2. MATERIALS AND METHODS:

This experimental study had been done at Hawler Medical University/ College of Pharmacy/ Pharmaceutical and Organic Chemistry Lab, between 2<sup>nd</sup> of January 2018 to 8<sup>th</sup> of April 2019.

### 2.1 Statistical Analysis

The data were entered and analyzed by using Origin pro 2017(64-bit) SR<sub>2</sub> b9.4.2.380 and Excel 2010.

#### General procedure for the synthesis of prodrugs of lornoxicam

To a stirred solution of (2.5 mmol) of the following bases (NaOH, Na<sub>2</sub>CO<sub>3</sub> or K<sub>2</sub>CO<sub>3</sub>) in 20 mL of solvent, (2.5 mmol) of lornoxicam was added. The solution stirred at room temperature for 2 h. an equivalent volume of alkyl or acyl halide (RX) was added to the homogenous solution, and stirred for 1-7 days at room temperature or under heat effect (at 25°C, 50°C and reflux), then the progress of the reactions was followed by TLC, After completion of the reaction, the solution was added to the ice bath with continuous stirring until a precipitate was obtained. The precipitate was filtered, washed more than one time with ice water and left to dry at room temperature, rotary evaporator was used to evaporate the solvent for some compounds. Ethanol was used to recrystallize all synthesized products. Final step was confirmed for all synthesized products by different techniques such as: TLC, measuring of melting point and using FTIR apparatus.

#### 2.2 Kinetic study for lornoxicam hydrolysis: Determination of wavelength of maximum absorption

A stock solution (100 µg/ml) was prepared by using 10 mg of drug dissolved in 100 ml 0.05N NaOH. An UV-visible spectroscopic scanning (200–450 nm) was used to determine the λ<sub>max</sub> for the detection of lornoxicam using 0.05N NaOH as a blank, figure 5 (A). (Bhavsar *et al.*, 2010)

#### Calibration Curve:

Six solutions at different concentrations (5-30 µg/ml) were prepared from the standard stock

solution. Absorbance for all samples were recorded, calibration curve was plotted and evaluated by its correlation coefficient ( $R^2$ ). Calibration curve shows straight line with a correlation coefficient ( $R^2$ ) = 0.999 and (p value <0.001).

### Study of the effects of different bases and temperatures on the reaction:

To study the effect of the base on the reaction media, the following procedure was used: (2.5 mmol) of one of the following bases (NaOH,  $\text{Na}_2\text{CO}_3$  or  $\text{K}_2\text{CO}_3$ ) was added to 250 ml of Distilled water, 0.1 gm of lornoxicam was added to the solution and the solution stirred at 25°C, 50°C, 80°C and on reflux, samples taken every 6 hrs. for 3 days and analyzed by UV-visible spectrophotometer to measure the absorbance. Concentrations were also calculated by using absorbance.

### 3.RESULTS:

IR spectrums had been recorded for all synthesized compounds. After attempting different conditions to prepare ester of lornoxicam, the reaction was failed to occur and the IR spectrums of most of synthesized compounds have no peak of ester. However, the peak of ester appeared in some IR spectrum figures (2) and (4) but, this peak mixed with the

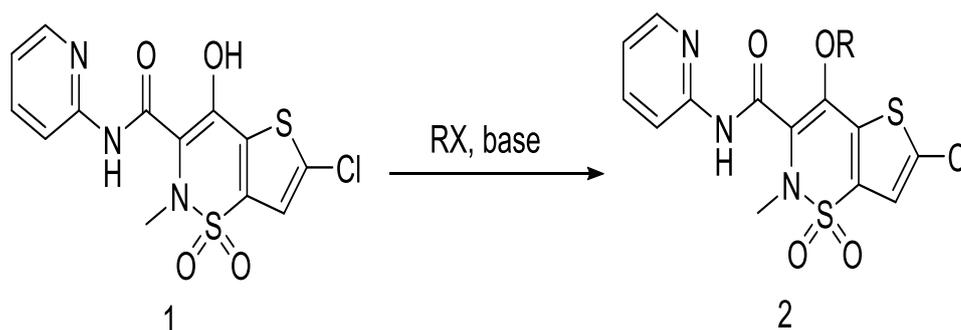
hydrolysis of amide linkage. (The amide hydrolyzed to carboxylate then the carboxylate esterified to an ester, figure (4)).

The maximum absorbance ( $\lambda$  max) of lornoxicam (compound **1**) and the hydrolyzed product (compound **4**) also determined by UV-spectroscopic apparatus. The  $\lambda$  max of lornoxicam was 375.06 nm while 232.24 nm was the  $\lambda$  max for the hydrolyzed compound, figure (5).

The kinetic study for the hydrolysis process studied by using different bases (NaOH,  $\text{Na}_2\text{CO}_3$  and  $\text{K}_2\text{CO}_3$ ) at different temperatures 25°C, 50°C, 80°C and on reflux. Figure (6) explains effect of both bases and temperatures on the hydrolysis process.

### 4.DISCUSSION:

Ether and ester derivatives of lornoxicam **2** have been prepared by various procedures (Jayaselli et al., 2008, Siddiqui *et al.*, 2010, Redasani *et al.*, 2017, Aras Najmaddin Hamad, 2018) using different bases alkyl and acyl halide (shown in Scheme 1), and all the attempted conditions were listed in Table (1).



R=  $\text{CH}_3$  ( $\text{CH}_2$ )<sub>2</sub>,  $\text{CH}_3$  ( $\text{CH}_2$ )<sub>3</sub>,  $\text{CH}_3$  ( $\text{CH}_2$ )<sub>4</sub>,  $\text{CH}_3$  ( $\text{CH}_2$ )<sub>5</sub>, 3-( $\text{NO}_2$ )  $\text{C}_6\text{H}_4\text{CH}_2$ ,  $\text{CH}_3\text{CH}_2\text{CO}$ ,  $\text{C}_6\text{H}_5\text{CO}$ , 4-(Br)  $\text{C}_6\text{H}_4\text{CO}$ , 4-( $\text{NO}_2$ )  $\text{C}_6\text{H}_4\text{CO}$ , 4-( $\text{CH}_3$ )  $\text{C}_6\text{H}_4\text{CO}$ . X = Br. or Cl. and base is (NaOH,  $\text{Na}_2\text{CO}_3$  or  $\text{K}_2\text{CO}_3$ )

**Scheme (1).** Synthetic strategy for ether and ester lornoxicam derivatives **2**. see Table (1).

**Table (1):** Attempted conditions for the synthesis of ether and ester lornoxicam prodrugs.

No.	Base	Alkyl or acyl halide	Solvents	Condition	Time	Occurrence of reaction
1	NaOH	Bromo propane	DMSO	r.t.	24h.	-ve
2	NaOH	Bromo butane	DMSO	r.t.	24h.	-ve
3	NaOH	Bromo propane	DMSO	r.t.	24h.	-ve
4	Na <sub>2</sub> CO <sub>3</sub>	Bromo butane	DMSO	r.t.	24h.	-ve
5	Na <sub>2</sub> CO <sub>3</sub>	Bromo hexane	DMSO	50 °C	24h.	-ve
6	K <sub>2</sub> CO <sub>3</sub>	Bromo pentane	Acetonitrile	r.t.	5days	-ve
7	Na <sub>2</sub> CO <sub>3</sub>	Bromo propane	Ethanol	Reflux	5h.	-ve
8	NaOH	Bromo pentane	Ethanol	Reflux	24h.	-ve
9	K <sub>2</sub> CO <sub>3</sub>	3-Nitrobenzyl chloride	Methanol	Reflux	10h.	-ve
10	K <sub>2</sub> CO <sub>3</sub>	3-Nitrobenzyl chloride	Ethanol	Reflux	24h.	-ve
11	K <sub>2</sub> CO <sub>3</sub>	Propoyl chloride	Ethanol	r.t.	7 days	-ve
12	K <sub>2</sub> CO <sub>3</sub>	Benzoyl chloride	Ethanol	r.t.	7 days	+ve
13	TEA	Benzoyl chloride	Chlorform	r.t.	4 days	+ve
14	K <sub>2</sub> CO <sub>3</sub>	4-bromo benzoyl chloride	Ethanol	Reflux	4 days.	-ve
15	TEA	4- bromo benzoyl chloride	Chlorform	25° C	2 days	-ve
16	TEA	4- bromo benzoyl chloride	Chlorform	25° C	7 days	-ve
17	K <sub>2</sub> CO <sub>3</sub>	4- bromo benzoyl chloride	Ethanol	r.t.	7 days	+ve
18	K <sub>2</sub> CO <sub>3</sub>	4- bromo benzoyl chloride	Ethanol	25° C	2 days	-ve
19	K <sub>2</sub> CO <sub>3</sub>	4- bromo benzoyl chloride	Ethanol	25° C	10h.	-ve
20	K <sub>2</sub> CO <sub>3</sub>	4- bromo benzoyl chloride	DMSO	25° C	24h.	-ve

21	K <sub>2</sub> CO <sub>3</sub>	4- bromo benzoyl chloride	Ethanol	25° C	4h.	+ve
22	K <sub>2</sub> CO <sub>3</sub>	4.Nitro benzoyl chloride	Ethanol	25° C	2days	+ve
23	K <sub>2</sub> CO <sub>3</sub>	4. Methyl benzoyl chloride	Ethanol	25° C	24h.	-ve
24	NaOH	4. Methyl benzoyl chloride	Ethanol	25° C	24h.	-ve

According to Williamson ether, synthesis of prodrugs of lornoxicam were made as shown in scheme (1), by using firstly NaOH to produce alkoxide and then different alkyl halides (bromopropane, bromobutane, bromopentane and bromohexane) were used to attack this alkoxide via SN<sup>2</sup> mechanism and produce ether derivatives. However, the reaction did not progress as expected. Different conditions were tested including the addition of different bases such as Na<sub>2</sub>CO<sub>3</sub> and K<sub>2</sub>CO<sub>3</sub> instead of NaOH and using different solvents such as DMSO, acetonitrile and ethanol. All these attempts did not get positive results when detected by TLC and FT-IR.

After failed reactions by using aliphatic alkyl halide and different bases, aliphatic alkyl halide has been replaced by the aromatic (3-Nitrobenzyl Chloride), since it is supposed to be more reactive, high concentration of base and different solvents were used., There was even no product by using aromatic alkyl halide.

After that, aliphatic acyl halide (propoyl chloride) has been tried to produce ester prodrug in ethanol in the presence of K<sub>2</sub>CO<sub>3</sub> as a base. The solution stirred for one week followed by TLC, no reaction was occurred.

Aromatic acyl halides (benzoyl chloride, 4-bromo-benzoyl chloride, 4-nitrobenzoyl chloride and 4-methylbenzoyl chloride) and K<sub>2</sub>CO<sub>3</sub>, NaOH or TEA were used to produce alkoxide and the solvents were ethanol, DMSO or chloroform, the reactions were done under different conditions, as listed in the table (1).

There is a clear effect of the concentration of the acyl halide on the reaction observed in the FT-IR spectrum, which shows one single, sharp and clear peak at 1715 cm<sup>-1</sup> figure (2) when small concentration of the acyl halide (1 equivalent) has been used, while using high concentration (3 equivalent) give two peaks of ester at 1716 and 1785 cm<sup>-1</sup> figure (4). The esterification reaction

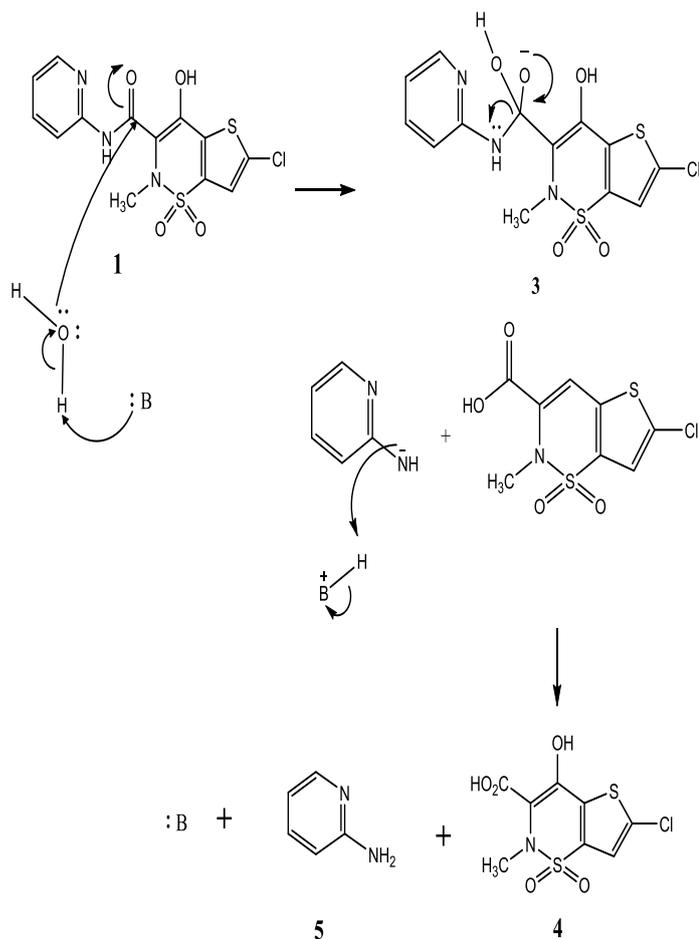
occurred, however, accompanied by hydrolysis of the amide linkage. As a result, we found the hydrolysis was interested issue, therefore, hydrolysis process and the influence of some variables on the reaction media was studied.

This hydrolysis confirmed by loss of NH peak of amide of the lornoxicam and instead 2 peaks belong to primary amine (2-aminopyridine compound 5) were appeared around 3090-3500 cm<sup>-1</sup> as in figure (2).

Moreover, when high concentration of acyl halide (3 equivalent) has been used, two peak of ester appeared indicated that two reaction process occurred one on the enolic OH and the other on the carboxylic acid side chain and this also confirms the occurrence of amide hydrolysis, figure (4).

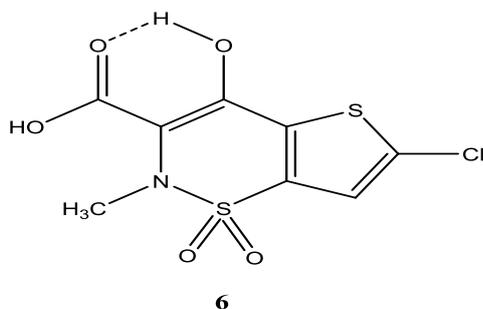
There is a clear difference between the UV-visible spectrum of the starting material and the hydrolyzed product as in figure 5 (A) and (B). The λ max of lornoxicam was 375.06 nm while 232.24 nm was the λ max for the hydrolyzed material. The difference in λ max confirms that a new different product was produced during the reaction but it was not possible to identify the product by using UV-visible spectrophotometer so, IR spectroscopy was used to determine the structure of the hydrolyzed product, figure (3).

The IR spectrum of the hydrolyzed product under a basic condition (NaOH) shows that an extremely broad absorption occur at a region between 3700-2400 cm<sup>-1</sup> indicating the presence of OH group that belongs to the carboxylic acid side chain for compound 4, figure (3). In addition, carbonyl stretching absorption which usually occurs at 1730-1700 cm<sup>-1</sup> undergo shifting to a lower frequency due to hydrogen-bonding and appeared at 1637 cm<sup>-1</sup> as shown in scheme (3). (Pavia *et al.*, 2008)



**Scheme (2):** The hydrolysis mechanism of lornoxicam under basic conditions.

Scheme (2) shows the mechanism of lornoxicam hydrolysis under basic condition. When  $\text{Na}_2\text{CO}_3$  and  $\text{K}_2\text{CO}_3$  used the hydrolysis process followed a mechanism as shown in scheme (2), while when  $\text{NaOH}$  utilized as a base, the  $\text{OH}$  group of  $\text{NaOH}$  will attack the carbonyl carbon in the structure of lornoxicam directly to give the first intermediate and compound 4 will be in the form of sodium carboxylate salt.



**Scheme (3):** hydrogen bonding that occurs in the hydrolyzed product.

The hydrolysis of lornoxicam occurred before the esterification reaction was completed; it is difficult for this reaction to occur due to different reasons. The presence of enolic  $\text{OH}$  group is important to complete the reaction but sometime this group disappeared may be due hydrogen bonding that occurred inside the structure of lornoxicam or due to Tautomerism. Tautomerism very common in oxicam group and all members in this class can present in more than one tautomer form depending on the surrounding conditions. (Jayaselli *et al.*, 2008, Franco-Pérez *et al.*, 2011, Ivanova *et al.*, 2015) The amide linkage is also prone to hydrolysis by the presence of base as a catalyst. Numerous research reports on degradation of lornoxicam under hydrolytic conditions (especially basic conditions). (Modhave *et al.*, 2011, Shah *et al.*, 2014)

The effect of different bases on the hydrolysis of lornoxicam was studied,  $\text{NaOH}$  was used at different temperature. The concentration of lornoxicam decreased with time, at the beginning of the reaction the concentration was approximately  $13 \mu\text{g/ml}$  and after 72 h. declined to about  $7.5 \mu\text{g/ml}$ , this occurred at all temperatures except with reflux, the concentration decreased sharply from  $11.1 \mu\text{g/ml}$  to  $3.5 \mu\text{g/ml}$ . Figure 6 (A) shows that the time affects the process of hydrolysis, by increasing the time the rate of the hydrolysis was increasing. The temperatures ( $25$ ,  $50$  and  $80^\circ\text{C}$ ) affected the hydrolysis process in a similar manner, but the rate of the hydrolysis reaction was increased on the reflux condition which means that reflux has the greatest effect on the rate of the reaction.

The second utilized base was  $\text{Na}_2\text{CO}_3$ , in which at all temperatures the starting material concentration at zero time was  $\approx 12 \mu\text{g/ml}$  decreased to  $\approx 8 \mu\text{g/ml}$  at the end of the reactions, while, on the reflux, the concentration changing from  $11.5$  to  $6 \mu\text{g/ml}$ . The concentration decreased in all reactions when the time was increased as seen in figure 6 (B).

In addition lornoxicam underwent hydrolysis by using  $\text{K}_2\text{CO}_3$  as a base, the concentration reduced approximately by  $4.5 \mu\text{g/ml}$  at the first three reactions while the changing was  $\approx 6 \mu\text{g/ml}$  at the fourth reaction (reflux condition). From figure 6 (C), it is obvious that at reflux condition the hydrolysis rate was faster than the others and the time had also an obvious effect, by rising the time the hydrolysis of lornoxicam increased.

All bases have been compared during the study for hydrolysis process of lornoxicam, NaOH was found to be the strongest base followed by  $\text{Na}_2\text{CO}_3$  and  $\text{K}_2\text{CO}_3$ . Temperatures and time have an obvious effect on the hydrolysis process. (Muhamad *et al.*, 2016) According to the effect of temperatures, the three conditions (at 25, 50 and  $80^\circ\text{C}$ ) have similar effect during all reactions with the exception of reflux condition that accelerate the hydrolysis rate more than the other conditions.

### 5.CONCLUSION:

The synthesis of lornoxicam prodrugs applying Williamson ether synthetic procedure was failed and the hydrolysis of the drug occurred despite using different bases ( $\text{Na}_2\text{CO}_3$ ,  $\text{K}_2\text{CO}_3$  and NaOH) attempting many solvents (DMSO, acetonitrile, chloroform and ethanol), at various temperatures (starting from room temperature up to refluxing) and trying different alkyl halides and acyl halide.

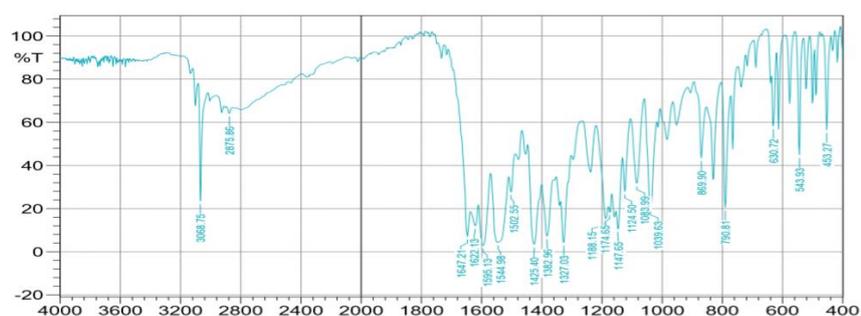
Among all bases, NaOH was the strongest base to induce hydrolysis process, followed by  $\text{Na}_2\text{CO}_3$  and  $\text{K}_2\text{CO}_3$ . Three temperatures  $25^\circ\text{C}$ ,  $50^\circ\text{C}$  and  $80^\circ\text{C}$  have similar effect during all reactions with the exception of reflux condition that has higher effect on the hydrolysis rate. The time affects the degradation of lornoxicam by the same manner in all reactions, by rising the hours of the reactions the hydrolysis process increasing also.

### Acknowledgements:

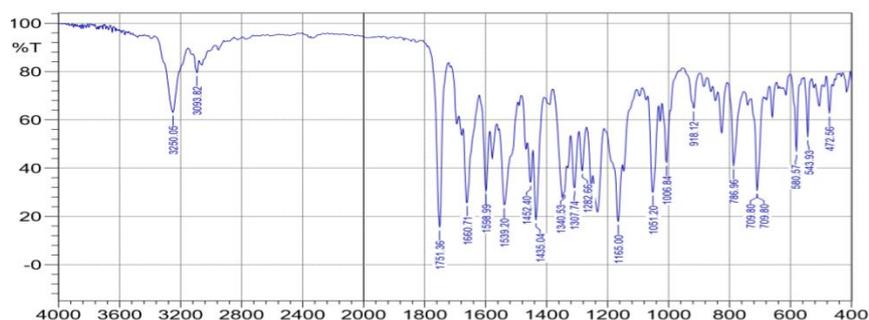
I would like to express my sincere gratitude and thanks to Dr.Kezhal S. Mahmood, Mr. Sarbast M. Ahmed and Miss Asmaa Ghanm for their help and guidance.

### Conflict of interest:

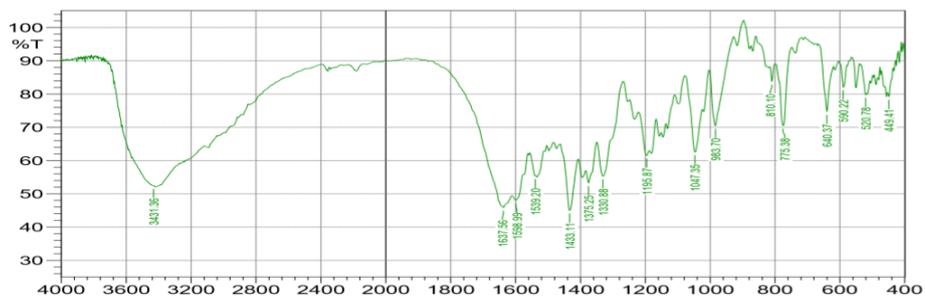
Authors have no conflict of interest.



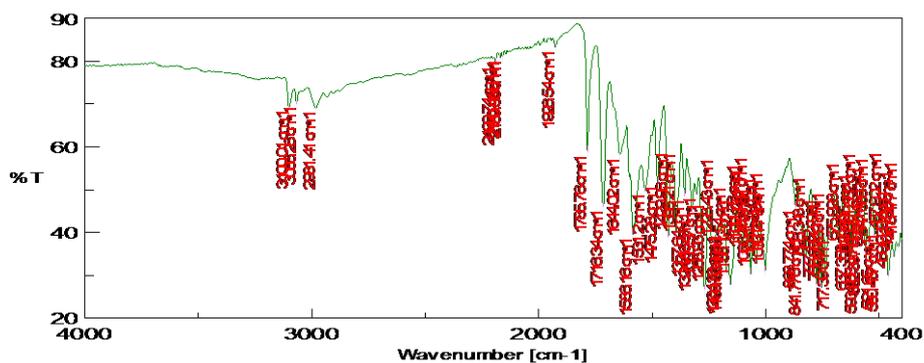
**Figure 1:** IR spectrum of lornoxicam (compound 1).



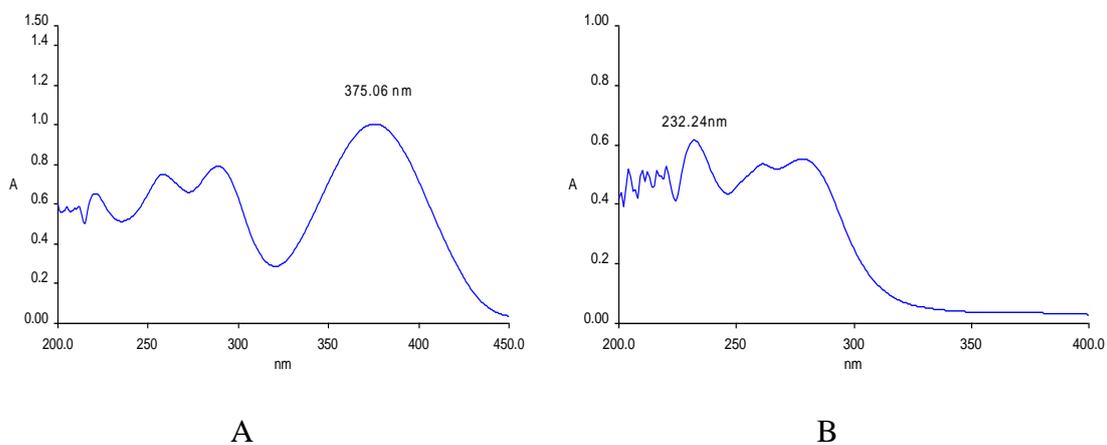
**Figure 2:** IR spectrum of ester product (compound 2 when R=benzoyl chloride).



**Figure 3:** IR spectrum of the hydrolyzed product under basic condition (NaOH), compound 4.

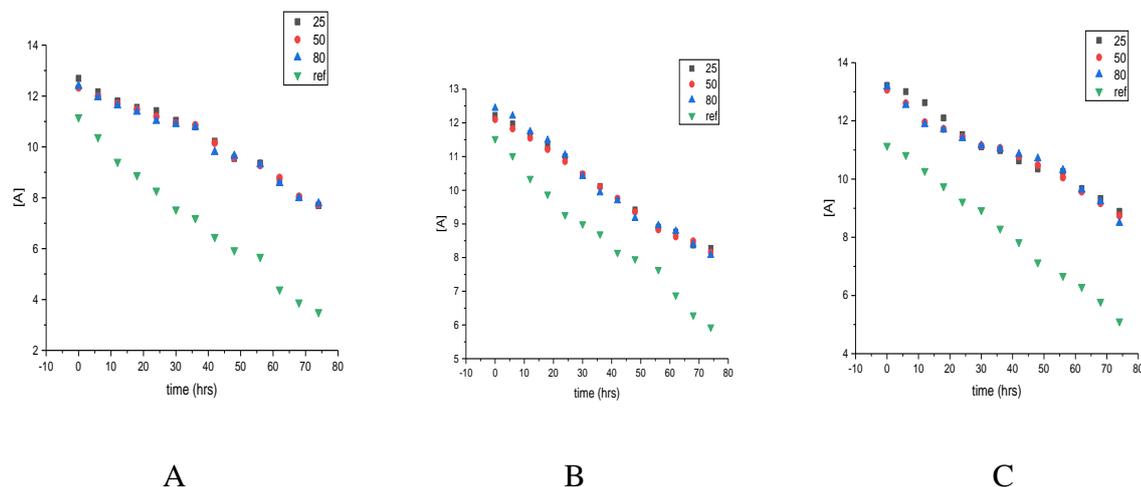


**Figure 4:** IR spectrum of ester product (compound 4 when acyl halide=4-bromo benzoyl chloride (3eq.))



**Figure 5:** UV- spectrum of A: lornoxicam with maximum absorbance at 375.06 nm.

B: the hydrolyzed product under basic condition (NaOH) with maximum absorbance at 232.24 nm.



**Figure 6:** The hydrolysis process at different temperatures by using different bases, A: NaOH, B: Na<sub>2</sub>CO<sub>3</sub>, and C: K<sub>2</sub>CO<sub>3</sub>. [A] is the concentration of lornoxicam.

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