



## Analytical study releasing the new of Prodrug (Paracetamol - Naproxen) using Uv-vis spectrophotometric method.

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### Abstract

This study aims to compose an effective ester Prodrug as well as reducing or removing the side effects of it and to Study of Naproxen release from the Prodrug. This is represented by the following steps: Preparing of Naproxen acid chloride from Naproxen by reacting it with Thionyl Chloride then Preparing of ester group from the reaction of hydroxyl group of paracetamol and the acid chloride of Naproxen. The structural formulas of the prepared compounds were characterized using spectral methods (FTIR, H-NMR and C<sup>13</sup>-NMR) then the studying of the release for the drug was conducted in acidic and basic medium pH (4, 10). The study showed that the speed of release in the basic medium was faster than that in the acidic medium. So most of the release process will take place in the intestine and not in the stomach.

### Introduction

#### Prodrugs

They are ineffective therapeutic compounds (pharmacologically inactive) that turn to an effective metabolic form. They are thus different from the soft drugs which are effective in themselves, but they turn to an ineffective metabolic form[1]. It is a pharmaceutical term that indicates the ineffective compounds which automatically turn into effective medicinal and pharmaceutical drugs in the presence of the enzyme after being absorbed by the tissue of the infected organ within the body of the organ. According to the International Union of the Applied Chemistry, the prodrug is defined as the compound that suffers from life transformation before its pharmaceutical effect appears.

The Prodrug is considered a suitable effective factor in the treatment process that is modifying the chemical structure of the active biological compound to form a new compound. It indicates the mechanism of the drug with no pharmaceutical effectiveness only after its life transformation and getting a better and effective metabolic treatment[2].

The first appearance of the prodrug was in the field of antibiotics that started in the discovery of Penicillin by Felmeng (1928), then the Sulfonamide by the scientist Bronetisol who began to make artificial antibiotics, followed by the scientist Domek who

was granted the Nobel Prize in Medicine in (1938) because he gave the first structure of the Prodrug in the field of antibiotics[3].

In 1958 the term Prodrug was launched by the scientist (Albert) it indicated the ineffective pharmacognecy that suffers from a transformation in its connection with effective biological compounds without harming with cells and non-effected tissues[4].

Increasing understanding about the nature of illnesses urged the researchers to reach a new and developed formula for medicines to target certain places in the body without touching the non-effected cells[5]. The scientific research is continuous in developing effective therapeutic and selective systems for diseases that Man encounters and identifying the mechanism of action of these drugs. The great development in the Gene -Directed Enzyme Prodrug Therapy led to the development of the science of the Prodrug as the most complex complications of the therapy was of vital inhibition .This treatment is also a selective inhibitor, that it attacks a certain enzyme in itself [7].

This is different in the case of the cancerous tumors and therefore the efficiency of the drug will appear by the extent of change in a certain tumor[7]. The Prodrug is characterized as being a compound with

high molecular weight and high efficiency. The drugs compete to connect the effective site of the enzyme so the formula of the enzymes and their effective sites play an important role in the action of the Prodrugs[8].

The Prodrugs have many advantages:

Improving the condition of the patient (reducing pain or injury) absorption, biological diffusion and cellular metabolism [9].

The purpose of using Prodrugs is the selective attack towards COX-2 enzyme which is responsible for inflammation and pain cases instead of inhibiting both of COX-1 and COX-2 and therefore, inhibiting the biological formation of Prostaglandin.

Naproxen belongs to non-steroidal anti-inflammatory drugs holding the carboxylic set that contains Propionic acid which provides replacement locations at (position 2) of the Aromatic cycle that is characterized by containing a single Enantiomer

Chiral (Verma.*et.al*, 2009). Naproxen is used to treat Gout, Rheumatism, analgesic and an anti-antibiotic.

Paracetamol or Acetaminophen which is used in the USA. It is a widely used analgesic and hypothermic drug Generally, it is used to treat fever, headache and slight pain. Paracetamol is also useful in treating other severe pains in combination with non-steroidal anti-inflammatory drugs or with opium analgesic Paracetamol is a basic component in many cold and flu prescriptions

In this study preparing of Naproxen acid chloride from Naproxen by reacting it with Thionyl Chloride then Preparing of ester group from the reaction of hydroxyl group of paracetamol and the acid chloride of Naproxen then study the speed of release in the different acidic and basic medium.

## Experimental

### Apparatus Used:

**Table (1) the apparatus used and the manufacturing companies .**

| T | Name of Apparatus   | Manufacturing Company   |
|---|---|---|
| 1 | Shimadzuft-IR8400S; Fourier Transform-Infrared Spectrophotometer Infrared Spectrometer (FTIR) | Shimadzuft-IR8400S;Fourier Transform-Infrared Spectrophotometer |
| 2 | UV-Vis Double Beam Spectrophotometer  | Azzota Corporation/ United states<br>SE6100PCS                  |
| 3 | Melting Point Meter Apparatus   | Digital Electro Thermal Melting Point Apparatus                 |
| 4 | Electric Oven of Diminished Pressure  | NapcoCo. Ltd. Japan   |
| 5 | ph-meter  | Beckman (American)  |
| 6 | HNMR  |   |
| 7 | Thin layer Chromatography(TLC)  | Merck   |

### Preparing Naproxen Chloride

Thionyl Chloride (2.00ml) is added to 2.21g (9.6mmol of Naproxin) carboxylic acid and mixed well for 2 hours in a water bath. The excess of Thionyl Chloride was distilled by using vacuum pressure the produced acid chloride yield was (91.1%).

### Loading Pharmacological Substance

Paracetamol (0.272g, 1.8 mmol) was dissolved in (2ml) of DMF with gentle heating and then (2.5ml) of triethylamine (Et<sub>3</sub>N) was added. The solution of acid chloride was added drop by drop to the Paracetamol solution by separating funnel stirred magnetically and a change in color to dark brown was observed . The mixture was left to be stirred for 24 hours to complete the reaction. The resulting precipitate was dissolved in absolute ethanol and then precipitated in distilled water for several time.

### Thin Layer Chromatography (TLC)

By using the (TLC) technique chemical reactions were followed, and the purity of the compound (Prodrug) was determined by using an aluminum sheet covered with Silica gel (0.25 mm) which represent the stationary phase while the mobile phase was ethyl acetate/chloroform(1:3) .The spot of the prepared compound was developed by iodine vapour. The spectra of UV, H-NMR and C<sup>13</sup>-NMR were measured.

### Studying the Drug Release

### $\lambda_{max}$ for Naproxen Drug

The spectrum of U.V of the pharmaceutical substance of (100ppm) in absolute ethanol was recorded by using 1cm quartz cell. showing  $\lambda_{max}$  at (263nm).

### Standard Curves of pure Naproxen and paracetamol Drug

The standard curves of the Naproxen (10-30) ppm and for paracetamol (2.5-20) ppm were constructed by drawing the relation between the concentration and absorbance.

### $\lambda_{max}$ for Paracetamol Drug

The spectrum of U.V of the pharmaceutical substance Paracetamol (10) ppm of paracetamol in absolute ethanol by using 1cm quartz cell. Wavelength of  $\lambda_{max}$  was (249nm).

### Buffer Solutions(British pharmacopeia)

#### Buffered copper sulfate solution pH 4.0.

Dissolve 0.25 g of copper sulfate R and 4.5 g of ammonium acetate in diluted acetic acid (0.1 M) and diluted to 100.0 mL with the same solvent.

#### Ammonium chloride buffer solution pH 10.0.

Dissolve 5.4 g of ammonium chloride in 20 mL of water, add 35.0 mL of ammonia and diluted to 100.0 mL with distilled water R.

### In vitro Studying the Amounts of the released Drug in the acidic and basic media.

To pharmaceutical substance(5x10<sup>-3</sup>)g in a beaker of 50ml, 30ml of the buffer solution with (pH=4) or the buffer solution (pH=10) were added. The study was

carried out at 25°C with continuous stirring. The concentration of released paracetamol and naproxen at different times was determined by UV-visible spectrophotometry at 257nm as well as by HPLC technique.

### Results and Discussion

This includes two main parts: The organic part that consists preparing the prodrug and the analytical part that includes studying the drug release in acidic and basic medium to identify the best pH of fast rate of release

#### Organic Synthesis Part

This part aims to get rid of the acidic property of the Naproxen. The acidic property cause big problems and damage in the stomach. It is necessary to get rid of the acidic feature by transforming it into another form of the drug by eliminating Hydrogen and preparing a Prodrug. A Paracetamol molecule was chosen as a drug carrier as a pharmacological compound which is not strange to the body and it has a clear metabolic course.

The choosing of Paracetamol to prepare Prodrug and formation of a system of decay under control because Paracetamol is characterized with the existence of active Hydroxyl group to enter in many interactions and doesn't contain toxic groups for the living being and it has the ability to decompose biologically inside the body

#### Naproxen

It belongs to (NSAIDs) group and it works to reduce the hormone causing pain and inflammation. Naproxen belongs to the derivative drugs from Propanoic that needs an acidic medium to be

absorbed. This may cause Gastric ulcer. These drugs reduce the level of the Prosta Glanden as well as they have a direct negative effect on the mucosa of the stomach[10]. Some studies found that the Omeprazol drug reduces the absorption of the Naproxen because Omeprazol reduces gastric acidity. The purpose of using Prodrugs Is the selective orientation towards COX-2 Enzyme only that is responsible for inflammation and pain instead of inhibiting both Enzymes COX-1 and COX-2 and therefore inhibiting the biological formation of PG[11]. In this study, the chemical structure of Naproxen was modified without affecting its medicinal properties and transforming it to an esteric derivative absorbed in a basal medium (small intestine) instead of the acidic medium (stomach) and so giving it a longer time to be absorbed by the different body tissues After taking the infrared spectrum of the Naproxen, the following band are appeared (table 2):

Table (2) show the band are appeared

| Band region<br>cm <sup>-1</sup> | Assignment                             |
|---------------------------------|--|
| 3207                            | O-H group                              |
| 3002                            | stretching of the (C-H) aromatic group |
| 2970                            | stretching of aliphatic group          |
| 1681                            | stretching of (C=O) group              |
| 1500 1458                       | stretching of the (C=C)                |
| 1458                            | bonding of (C – C) group               |
| 1392                            | bonding of (C – H) aromatic group.     |
| 1226                            | stretching of the (C – H)              |
| 1027                            | stretching of the (C – O)              |
| 862                             | bonding of the (O – H) group.          |

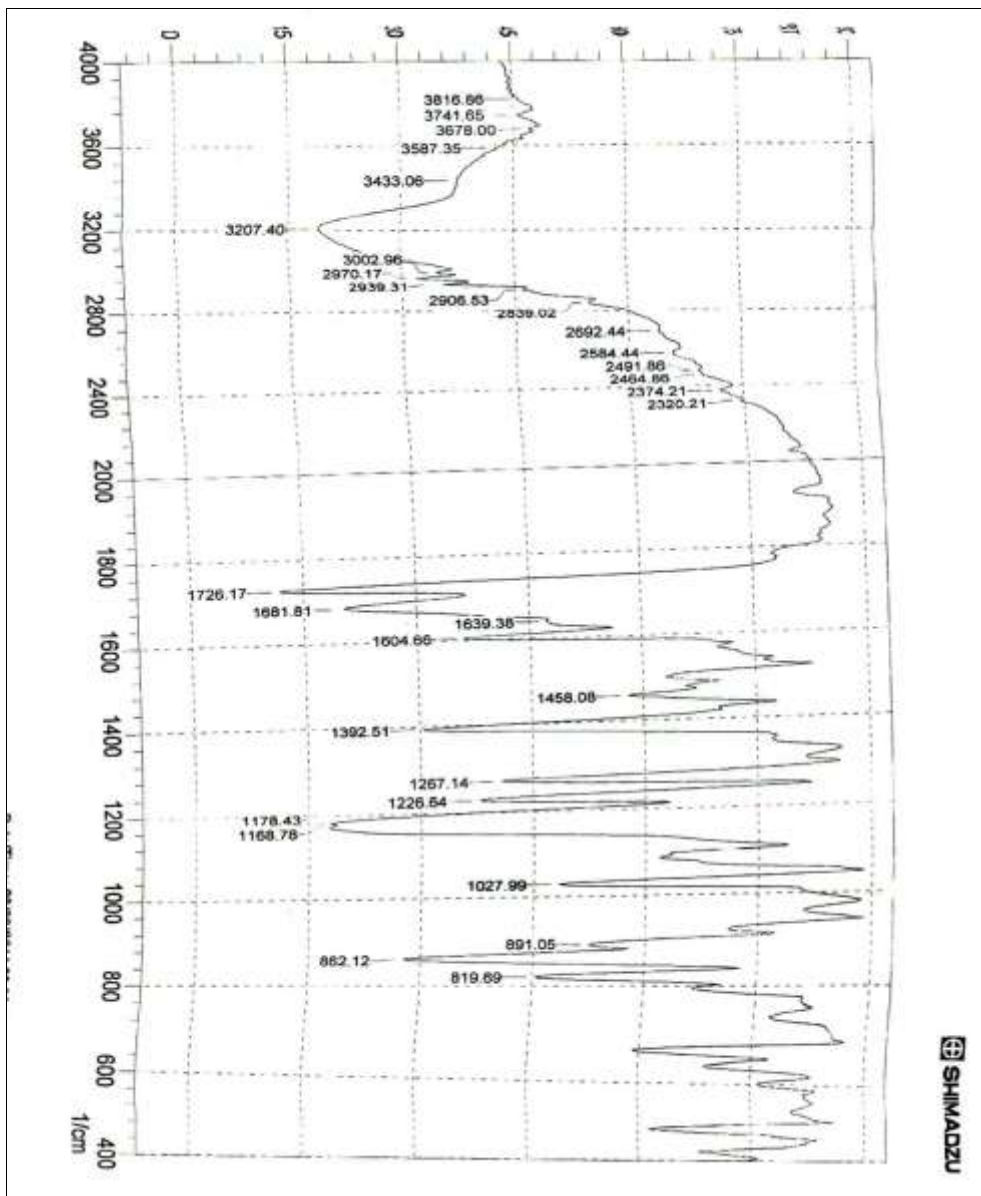
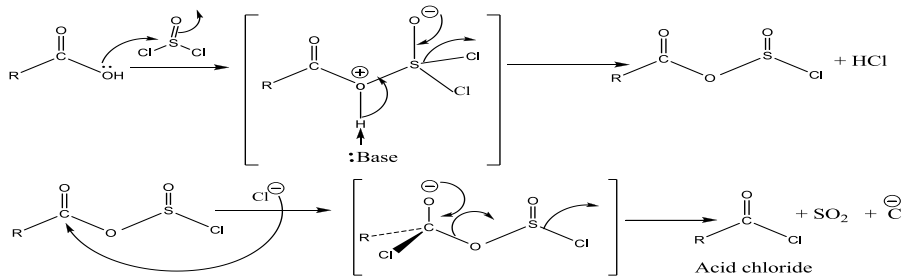


Figure (1): FT-IR spectrum of naproxen

**Characterization of Naproxen Acid Chloride**

The pharmaceutical acid chloride was synthesized by the interacting the pharmaceutical acid with Thionyl chloride (SOCl<sub>2</sub>) with moderate reflux for an hour. The hydroxyl group is replaced by the Carboxylic

acid (of the drug) with chloride to give acid chloride and two occasional outputs SO<sub>2</sub> and HCl with volatile properties that easily disappears. The mechanism tracks the following interaction (SN1 mechanism).



The melting point of Naproxen Chloride is 118C<sup>0</sup>. Naproxen Chloride is an active compound that interacts quickly with the compounds that contain an active Hydrogen atom and so the pharmaceutical acid chloride of the Naproxen was used directly.

**Synthesis of Prodrug Ester of Naproxen**

The Prodrug ester of Naproxen was synthesized by the interaction of Naproxen Chloride with Paracetamol after dissolving it in DMF and heating it slightly in the presence of Tri-ethyl-amine. The

mixture was left for stirring for 24 hours at room temperature to give the derivative compound (Prodrug) as Semisolid (29.1%).

The compound was diagnosed by the spectral techniques (H NMR, C NMR,) to check the synthetic formula and to assure the occurrence of the esterification and synthesis of Prodrug.

**<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):** The spectrum showed a peak at  $\delta$  8.49 ppm (d, 1H) related to the proton of the amino group (NHCO), and multiple peaks at  $\delta$  7.80 – 7.70 ppm (m, 5H) related to two different groups of protons, one is for the naphthalene rings protons and the another one is for the phenyl ring protons. In addition, the spectrum showed

multiple peaks at  $\delta$  7.38 – 7.13 ppm (m, 5H) related to the naphthalene rings protons and for the phenyl ring protons. Furthermore, multiple peaks at  $\delta$  4.07 – 4.01 ppm (m, 1H) were shown and related to the tertiary methine group (CH<sub>3</sub>CH), as well as a single peak at  $\delta$  3.89 ppm (s, 3H) related to the methoxy group (CH<sub>3</sub>O), and multiple peaks at  $\delta$  1.46 – 1.42 ppm (m, 3H) are related to the methyl group (CH<sub>3</sub>CH). Moreover, the spectrum showed peaks at  $\delta$  2.5 and 3.3 ppm which were related to the residual solvent peaks of DMSO and water, respectively, and peaks at  $\delta$  1.07 and 3.8 ppm are related to ethyl acetate used for the purification process.

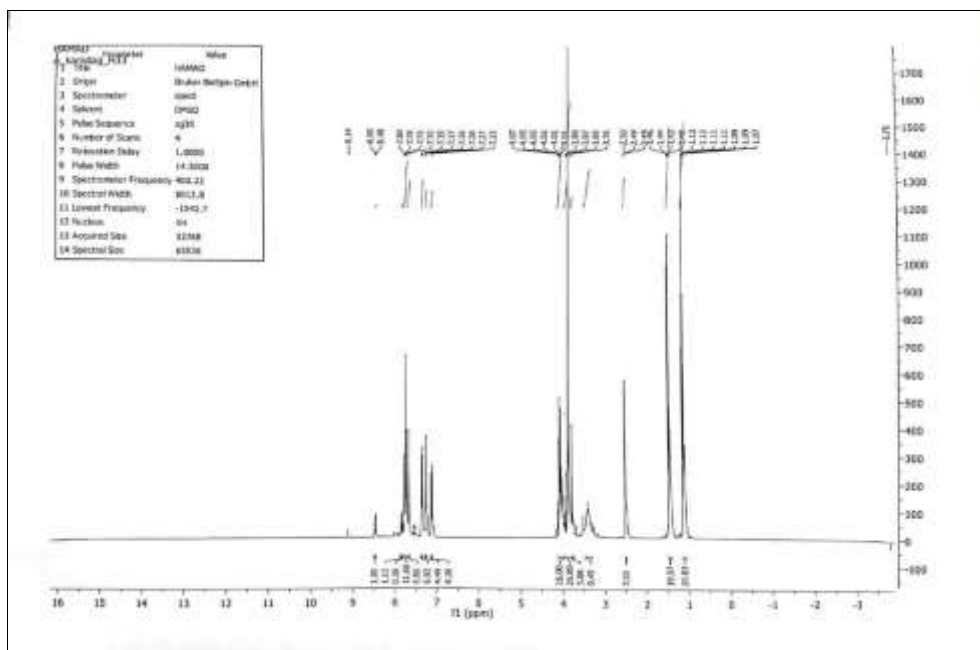


Figure (2) The H- NMR for the Prodrug

**<sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>):** Table (3) shows the peak of NMR spectrum and figure 3

Table (3) Peaks of NMR spectrum for the Prodrug

| Peak of NMR spectrum at $\delta$ | related to                  |
|----------------------------------|-----------------------------|
| $\delta$ 174.3 ppm               | both of the carbonyl groups |
| $\delta$ 157.7 ppm               | naphthalene rings           |
| at $\delta$ 136.2 ppm            | phenyl ring                 |
| at $\delta$ 133.7 ppm            | the phenyl ring             |
| $\delta$ 129.6 ppm               | the naphthalene rings       |
| $\delta$ 60.7                    | the methoxy group           |
| at $\delta$ 44.9                 | tertiary methyl group       |
| 18.9 ppm                         | methyl group                |
| $\delta$ 18.7 ppm                | ethyl acetate               |

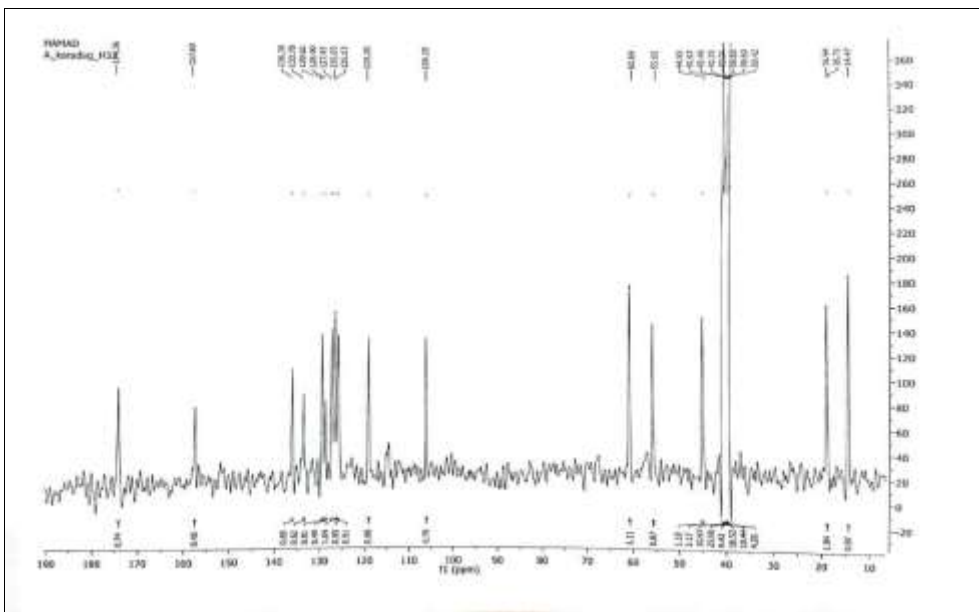


Figure (3) the tow C<sup>13</sup>-NMR

It is worth mentioned here that the number of peaks in the spectrum are less than the actual number of carbons in the compound. This is because of the overlapping of the peaks which each other, as they are showing very close to each other, especially those for the naphthalene and phenyl rings.

**Analytical Part**

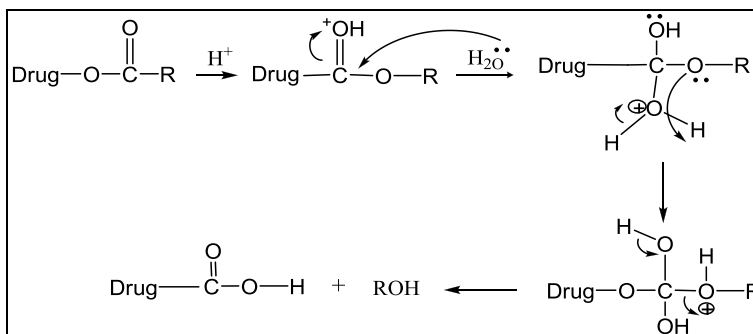
This part includes the study of Naproxen decomposition in the synthesized Prodrug within basic and acidic media to identify within which media the drug can give the highest absorption within the

least time rate and to Find out the range of the drug stability .

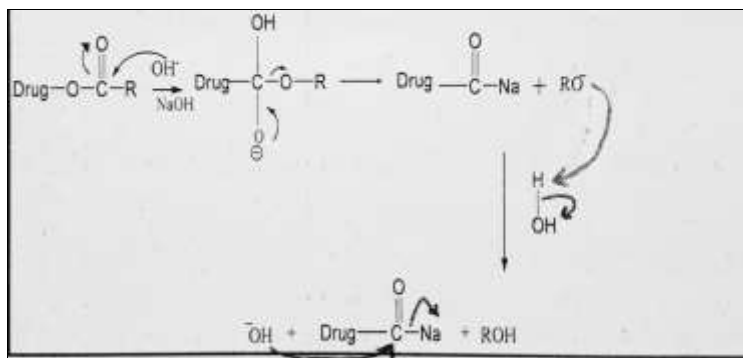
**The Study of Naproxen release from the Prodrug**

The effective group in the synthesized drug is the ester linkage that can be decomposed *in vivo* by the decomposing Enzymes or by hydrolysis in different acidic and basic medium as was done in this study and according to the proposed mechanism in the acidic and basic media:

**Mechanism of Decomposition in the Acidic Medium.**



**Mechanism of Decomposition in the Basic Medium.**



The purpose of studying the release of Naproxen in acidic and basic medium from the ester Prodrug is

because Naproxen is decomposed causing great health hazards and ulcers. In this study ,naproxen was

transformed into ester Prodrug and study the extent of the stability of prodrug for 2 hours without decomposition.

Naproxen contains an acid carboxylic group that can be transformed to an ester Prodrug. It can be suitable and comfortable because the ester is decomposed to give an effective drug in the basic mediums with no side effect.

But W.Wang *et al* found that an increase in hydrolysis of the drug by synthesizing the Prodrug was one of the advantages of the Prodrug by increasing the range of absorption to the longest time and increasing its stability in the acidic mediums. The release of the these is a relationship between the substituted groups on phenolic ring and the speed of decomposition. These compensators increase the speed of release in basic mediums more than that in the acidic medium.

In this study, Naproxen decomposes from the Prodrug at different times in acidic and basic medium is studied by using Ultraviolet spectroscopy at the length wave ( $\lambda_{max}$  257nm). It represents the highest

value of absorption of the drug then estimating the Naproxen decomposition from the Prodrug in the different acidic and basic functions. The results showed that the concentration of the released Naproxen increased by the increase in the acidic function and the synthesis of the compound itself does not dissolve in water and has high stability in the stomach. The current study corresponds to the study of Chun and Shau who noticed an increase in dissolution of the ester prodrug in basic medium. This empathized that the synthesized drug in this study is an ester Prodrug.

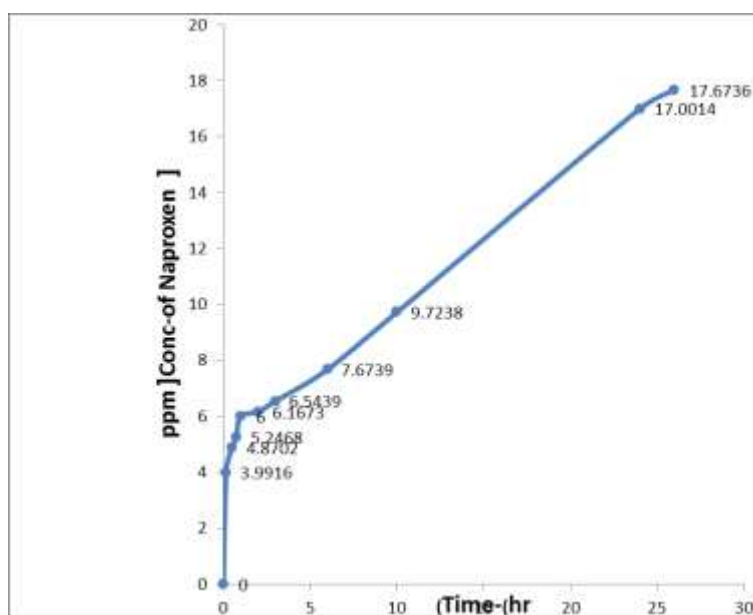
Figures (4) and (5) explain the concentration of the released Naproxen with changing in time at different basic and acidic medium.

Table (4) showed the concentration of the released Naproxen with time at pH=4.

Table (5) showed the concentration of the released Naproxen with time and percentage of Naproxen release when the acid function is established at pH=4.

**Table (4) Concentration of Released Naproxen at pH=4**

| Time (hr.) | Conc. of Naproxen released (ppm) | Released (%) | Conc. of Paracetamol released (ppm) | released (%) |
|------------|----------------------------------|--------------|-------------------------------------|--------------|
| 0          | 0                                | 0            | 0                                   | 0            |
| 0.166      | 3.9916                           | 22.5852      | 0.7428                              | 22.5610      |
| 0.5        | 4.8702                           | 27.5568      | 0.9746                              | 29.6015      |
| 0.75       | 5.2468                           | 29.6875      | 1.0739                              | 32.6175      |
| 1          | 6.0000                           | 33.9488      | 1.2726                              | 38.6526      |
| 2          | 6.1673                           | 34.8958      | 1.3167                              | 39.9921      |
| 3          | 6.5439                           | 37.0265      | 1.4161                              | 43.0111      |
| 6          | 7.6736                           | 43.4185      | 1.7141                              | 52.0623      |
| 10         | 9.7238                           | 55.0189      | 2.8951                              | 87.9328      |
| 24         | 17.0041                          | 96.2121      | 3.1710                              | 96.3127      |
| 26         | 17.6736                          | 100          | 3.2924                              | 100.00       |

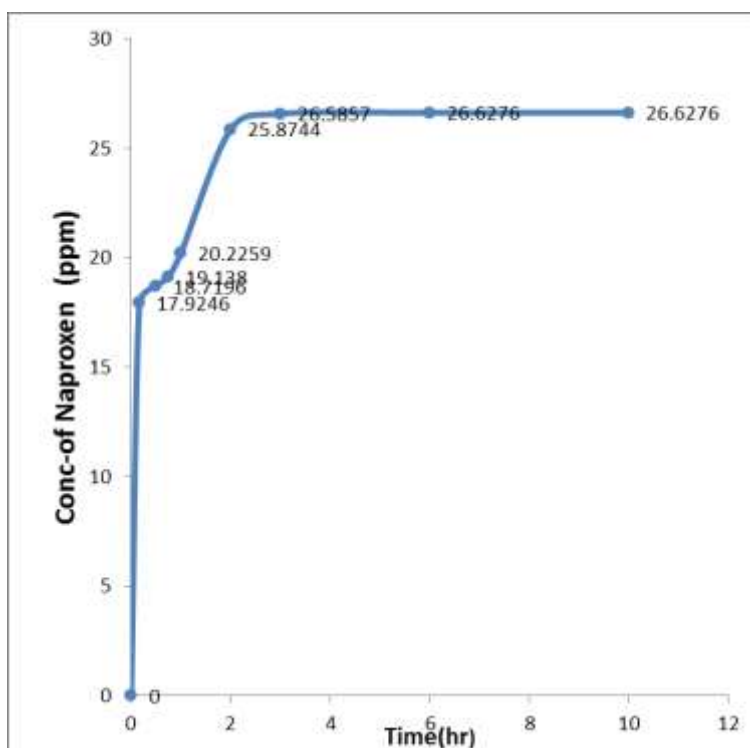


**Figure (4): Concentration of Released Naproxen at pH=4**

Table (5) Explains Concentration of the Released Naproxen with time and percentage when the acid function is established at pH=10

**Table(5): Concentration of Released Naproxen at pH=10**

| Time (hr.) | Conc. of Naproxen released (ppm) | Released (%) | Conc. of Paracetamol released(ppm) | Released (%) |
|------------|----------------------------------|--------------|------------------------------------|--------------|
| 0          | 0                                | 0            | 0                                  | 0            |
| 0.166      | 17.9246                          | 67.3161      | 4.4183                             | 65.8062      |
| 0.5        | 18.7196                          | 70.3017      | 4.6280                             | 68.9295      |
| 0.75       | 19.1380                          | 71.8730      | 4.7384                             | 70.5738      |
| 1          | 20.2259                          | 75.9585      | 5.0253                             | 74.8469      |
| 2          | 25.8744                          | 97.1716      | 6.5154                             | 97.0405      |
| 3          | 26.5857                          | 99.8429      | 6.7030                             | 99.8346      |
| 6          | 26.6276                          | 100          | 6.7141                             | 100.00       |
| 10         | 26.6276                          | 100          | 6.7141                             | 100.00       |



**Figure (5) Concentration of Released naproxen at pH=10**

The tables (4,5) showed that the speed of decomposition of the Prodrugs differ depending on the acidic function. It has been noticed from the stability of the Prodrug that drug release speed increases in the basal medium more than that in the acidic medium. This corresponds with that published [12]. The reason for this is that esters are easily connected with strong Nucleophile like the hydroxyl group to produce an intermediate composition from the connection of hydroxyl group on the carbonyl group [13].

As well as, it was noticed that the Prodrug has high stability in the acidic medium. It was found that after 3 hours from the beginning of the release in both basic and acidic medium, the concentration of the Prodrug was at (6.5439ppm) and a percentage was (%34.79452), but the concentration of the released Prodrug at pH=10, was (26.5854ppm) and the percentage was (%72.17949). While after 6 hours ,the

concentration of the released Naproxen at pH=4 was (7.6739ppm) with a percentage of (%44,10959)..And at pH=10, the concentration of the released Naproxen was (26.6276ppm) and the percentage was (%100). The results of this study demonstrated that pH=10 is considered the best for releasing the Prodrug and that the best absorption of the Prodrug will be in the intestine and not in the stomach. This is in agreement with the published research in this regard [14].

The rate of release of the Prodrug at pH=10 produces the fastest release and better than the rest of the acidic and basal function (pH4). At pH=4 the percentage of release was less in the basic medium because the ester is of less decomposition in the acidic medium. This is in agreement with result in the literature [15].

The results showed that the fastest period for drug decomposition was at the acidic function pH=10, this corresponds with Shanbhag (2012)[16]. The study of



drug decomposition from the (Prodrug) proved that the Prodrug did not dissolve in water and its solubility is very little in the gastric juice (acidic medium) [16]. This may give the compound a chance

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## دراسة تحليلية لتحلل الدواء المصاحب الجديد (باراسيتامول-نابروكسين) باستخدام طريقة طيف الأشعة فوق البنفسجية

حمد علي عبدالله ، فدعم متعب عبدون ، هناء كائن صالح

قسم الكيمياء ، كلية العلوم ، جامعة تكريت ، تكريت ، العراق

### الملخص

يهدف البحث الحالي إلى تكوين دواء مصاحب استري فعال مع التقليل من التأثيرات الجانبية أو إزالتها، وكذلك دراسة تحلل نابروكسين من الدواء المصاحب. وتمثل بالخطوات التالية..

تحضير كلوريد حامض نابروكسين من تفاعل نابروكسين مع كلوريد الثايونيل ثم تفاعل الأسترة لمجموعة الهيدروكسي في المركب الحامل الباراسيتامول مع كلوريد حامض نابروكسين لينتج استر نابروكسين.

تم تأكيد الصيغة التركيبية للمركب المحضر باستخدام الطرق الطيفية ( $^1\text{H-NMR}$ , FTIR and  $\text{C}^{13}\text{-NMR}$ ) ثم أجريت دراسة تحلل الدواء المصاحب في وسط حامضي ووسط قاعدي عند pH (4 , 10) للتأكد من حدوث عملية تحلل الدواء إذ بينت الدراسة أن سرعة التحلل في الوسط القاعدي أسرع من التحلل بالوسط الأحامضي وبهذا فإن معظم التحلل سيتم في الأمعاء الدقيقة وليس في المعدة.