

SEPARATION, ANALYSIS, AND CONDUCTIVITY MEASUREMENTS OF ACTIVE PHARMACEUTICAL INGREDIENT (API) OF KETOPROFEN

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Abstract:

The compound Ketoprofen, which is a propionic acid derivate and nonsteroidal anti-inflammatory drug (NSAID). The aims of the following study are to determine an appropriate method for separation of the API Ketoprofen (ketofan) from its original drug, to measuring the conductivities of different concentration of the API, studying the effect of UV wave on the API, drawing its Ph. curve. The active substance was separated by extraction, where it was discovered that the active substance dissolves in ether, not dissolved in water, and from this experiment an appropriate amount of the pure active substance was obtained. The conductivity and the percentage of dissolved salts of the compound were measured using a conductive probe. The obtained values were monitored in a curve showing the relationship between the different Ketoprofen concentrations and the conductivity. Thus, electrical conductivity can be used as a measure of concentration. The change in conductivity values was concluded after the compound was exposed to ultraviolet rays, where the significant effect of sunlight on the active substance was confirmed. To identify the PH curve of the active substance was used acid base Titration.

Keywords: Ketoprofen, Active Pharmaceutical Ingredient, Conductivity measurements, Separation, Analysis.

I. INTRODUCTION

1.1.1. Pharmacological of Ketoprofen:

Ketoprofen is a propionic acid derivate and no steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic effects. Ketoprofen inhibits the activity of the enzymes cyclooxygenase I and II, resulting in a decreased formation of precursors of prostaglandins and thromboxane's, the resulting decrease in prostaglandin

synthesis, by prostaglandin synthase, is responsible for the therapeutic effects of ketoprofen ^[1]. Table 1 showed the physiochemical properties of Ketoprofen.

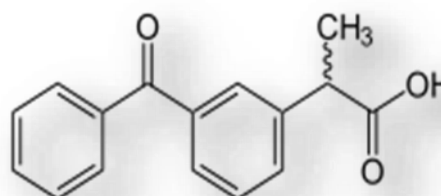


Figure (1): Ketoprofen structure.

Table 1: Physiochemical properties of Ketoprofen.

IUPAC Name: known as 2-(3-benzoylphenyl) propionic acid.	Brand names: Ketoflam-Fastum Gel-Ketonal Metorex – Oruvail - Ketolek ^[2]
Molecular Formula: C ₁₆ H ₁₄ O ₃	Molecular Weight: 254.28 g/mol
Melting Point: 94 °C	Molar mas: 254.285 g•mol ⁻¹
Density: 1.2±2.1 g/cm ³	Boiling Point: 1.1±342.4 °C at 760 mmHg
Flash Point: 228.8±20.5	Smell: odorless
Appearance: white or off-white	Solubility: 51 mg/L (at 22 °C)

1.1.2. Medical uses of Ketoprofen:

Ketoprofen is typically used for severe toothaches that cause gum inflammation or inflammatory symptoms associated with arthritis. Ketoprofen use for symptomatic treatment of acute and chronic rheumatoid arthritis, osteoarthritis, primary dysmenorrhea and mild to moderate pain associated with musculoskeletal trauma, postoperative (including dental surgery) and postpartum pain. Musculoskeletal pain is being treated with topical ketoprofen patches..^{[3][4][5]} Table 2 showed the adverse effects of

Table 2: Adverse effects of Ketoprofen.

(1-3%)	(3-9%)	(>10%)
<ul style="list-style-type: none"> Insomnia Depression Peripheral edema Bronchospasm Congestive heart failure 	<ul style="list-style-type: none"> Upper GI ulcers Nausea Diarrhea Abdominal pain Constipation 	<ul style="list-style-type: none"> Increased liver function Dizziness Headache Impaired renal function disorder
Cardiovascular Risk	NSAIDs may increase risk of serious cardiovascular thrombotic events, myocardial infarction (MI), & stroke, which can be fatal and risk may increase with duration of use	
Gastrointestinal Risk	GI adverse events may occur at any time during use & without warning symptoms ^{[6][7][8]}	
Pregnancy & Lactation:	Pregnancy exposure to non-aspirin NSAIDs during pregnancy was documented in approximately 7.5% of cases of spontaneous abortions and describe the risk of kidney problems in unborn babies that result in low amniotic fluid. ^{[9][10]} They recommend avoiding NSAIDs in pregnant women at 20 weeks or later in pregnancy. ^{[9][10]} , in Lactation unknown whether excreted in breast milk, not recommended.	

Ketoprofen.

1.1.3. Drug-drug interaction of ketoprofen:

The following medication interactions were investigated using 200 mg/day dosages of ketoprofen. When using Orudis (ketoprofen) at doses exceeding 50 mg as a single dose or 200 mg of ketoprofen daily in conjunction with strongly bound medications, it is important to consider the potential for enhanced interaction.

Table 3: Drug-drug interaction.

Aspirin	Concomitant administration of ketoprofen and aspirin is not generally recommended because of the potential of increased side effects.
Diuretics	Hydrochlorothiazide, given concomitantly with ketoprofen, produces a reduction in urinary excretion Patients taking diuretics are at a higher risk of developing renal failure secondary to a reduce in renal blood flow caused by prostaglandin inhibition
Digoxin	Ketoprofen and digoxin were concomitantly administered ketoprofen did not change the serum levels of digoxin.
Methotrexate	Ketoprofen may cause changes in the elimination of methotrexate leading to increase serum levels of the drug and increased toxicity.
Warfarin	Because of the synergistic effects of warfarin and NSAIDs on gastrointestinal bleeding, people who take both medications at the same time are more likely to experience severe GI bleeding than people who take either medication alone [9].

1.1.3 Mechanism of Action of Ketoprofen:

Ketoprofen undergoes metabolism in the liver via conjugation with glucuronic acid (glucuronidation) by UGT enzymes, hydroxylation of the benzoyl ring by the CYP3A4 and CYP2C9 enzymes, and reduction of its ketone moiety (a carbonyl functional group, i.e. with carbon-oxygen double bond)^{[11] [12][13]} Ketoprofen is used for its antipyretic, analgesic, and anti-inflammatory properties by inhibiting cyclooxygenase-1 and -2 (COX-1 and COX-2) enzymes reversibly, which reduce production of proinflammatory prostaglandin precursors. ^{[12] [14]} Table 4 showed the pharmacokinetics of Ketoprofen.

Table 4: Pharmacokinetics of Ketoprofen.

Bioavailability: 90%	Absorption: is rapidly and well-absorbed orally, with peak plasma occurring.
metabolized in the liver.	Enzymes inhibited: Cyclooxygenase
Half-life: 2-4 hr. (immediate release); 3-7.5 hr. (ER)	Routes of administration: By mouth, topical, intravenous within 0.5 to 2hours.
Elimination: Approximately 80% of a dose of ketoprofen is eliminated in the urine and feces during a 24-hour period.	

1.1.4 Pharmacodynamics of Ketoprofen:

Ketoprofen is a non-steroidal anti-inflammatory agent (NSAIA) with analgesic and antipyretic properties. The pharmacologic effects of ketoprofen, which block prostaglandin production, are similar to those of other classic NSAIDs. Rheumatoid arthritis, osteoarthritis, dysmenorrhea, and mild discomfort are all conditions that ketoprofen is used to treat. ^[15] Table 5 showed the dosage forms and strengths of Ketoprofen.

Table 5: Dosage Forms and Strengths of Ketoprofen.

Tablet/Capsule	50mg 75mg 150mg
Capsule, extended-release:	200mg
Oral suspension	12.5mg
Gel for topical	2.5%
Injectable solution	100 mg

1.2. Separation Method for Active Pharmaceutical Ingredients:

Using the difference in density between the active pharmaceutical ingredient (API) and the excipients in a pharmaceutical formulation, the API and the excipients can be physically separated. Standard methods can then be used to properly characterize the API. During the process of density separation, the API is not dissolved, and the crystal form of the API is not changed.

1.2.1. Electrophoresis:

It is used in laboratories to separate macromolecules based on size. The technique applies negative charge so proteins move towards a positive charge Electrophoresis is used extensively in DNA, RNA and protein analysis.

1.2.2. Extraction:

- **Liquid-liquid extraction:** Organic compounds are often extracted from aqueous solutions using a reparatory funnel and a hydrocarbon solvent such as hexane; this technique is referred to as liquid-liquid extraction.
- **Solid phase extraction:** Solid-liquid extractions are often used to extract natural compounds from natural sources, such as plants ^[16]. With this method, the target compound or compounds are selectively dissolved by the solvent, leaving the undesirable, insoluble solid behind.

1.2.3. Filtration:

Mesh, bag and paper filters are used to remove particulates suspended in fluids (e.g., fly ash) while membrane processes including microfiltration, ultrafiltration, Nano filtration, reverse osmosis, dialysis (biochemistry)

utilizing synthetic membranes, separates micrometer-sized or smaller^[17].

1.2.4. Centrifugation:

Is a mechanical process that include the use of the centrifugal force to separate particles from a solution according to their size, shape, density, medium viscosity and rotor speed the denser components of the mixture migrate away from the axis of the centrifuge, while the minimum dense components of the mixture migrate towards the axis^[18]

1.2.5. Crystallization:

Is the process by which a solid forms, where the atoms or molecules are highly organized into a structure known as a crystal. Some of the ways by which crystals form are precipitating from a solution, freezing, or more infrequently deposition directly from a gas. Attributes of the resulting crystal depend hugely on factors such as temperature, air pressure, and in the case of liquid crystals, time of fluid evaporation.^[19]

1.2.6. Thin-layer chromatography (TLC):

Is a largely employed laboratory technique used to separate different biochemical on the basis of their relative attractions to the stationary and mobile phases^[20].

1.2.7. High-performance thin-layer chromatography (HPTLC):

Is an enhanced form of thin-layer chromatography (TLC). A number of enhancements can be made to the basic method of thin-layer chromatography to automate the different steps, to induce the resolution achieved, and to allow more accurate quantitative measurements.

1.2.8. Spectrophotometry:

Is a branch of electromagnetic spectroscopy concerned with the quantitative measurement of the reflection or transmission properties of a material as a function of wavelength Spectrophotometry uses photometers, known as spectrophotometers that can measure the intensity of a light beam at different wavelengths^[21].

1.2.8.1. Types of Spectroscopy:

• 1.I.R of ketoprofen:

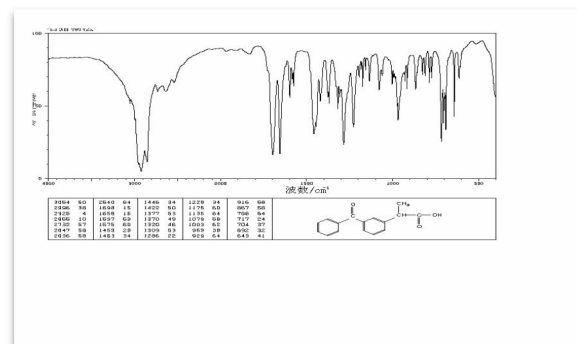


Figure (2): I.R Ketoprofen structure.

• C13-MNR of ketoprofen:

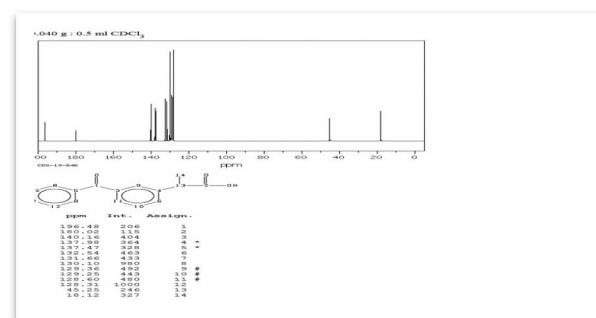


Figure (3): C13 of ketoprofen structure.

1.3. Conductivity Technology:

1.3.1. Conductivity:

Conductivity is an essential measurement for many applications^[22] ^[23]. It is a quick and simple method of determining the purity of water when done correctly. Before beginning to measure conductivity, it is necessary to comprehend a few fundamental concepts. There are three key definitions to begin with:

- The flow of charged particles is known as electrical current (measured in Amps, A).
- The ease with which those charge particles flow through a substance or solution is known as conductance, and it is expressed in Siemens, S.
- Conductivity, expressed in Siemens per centimeter, or S/cm, is the conductance (S) measured through a material or solution over a certain distance.

- The charged particles that move through a metal wire are called electrons, but in a solution, they are called ions. These ions' examples.

- **The size of the current depends on** ^{[24] [25]}:

Ion characteristics include size, movement, and charge.

- The solvent's characteristics include its viscosity and dielectric constant.

- Ion concentration: conductivity can be used as a gauge of concentration because the more ions present, the higher the conductivity.

- Temperature: Generally speaking, conductivity increases with the number of ions in a solution; sample stability, purity, and handling can all have an impact on sample reading accuracy.

1.3.2. Resistivity:

Sometimes it is simpler to use resistivity and resistance as the measure because the conductivity of some solutions, such pure water, is so low..

1.3.3. Concentration and Total Dissolved Solids (TDS):

- Because conductivity and ion concentration are related, conductivity can be used to calculate total dissolved solids (TDS) and assess solution concentration.
- **Concentration:** Some species ionize more completely in water (e.g., NaCl & HCl than others do ^[22]. This means that their solutions are more conductive as a result. Any acid, basic, and salt has a unique concentration vs. conductivity characteristic curve. It is necessary to calibrate using solutions with known concentrations and compositions..
- **TDS:** There are lots of assumptions when calculating a TDS value from a conductivity value ^[26]. Typically, a conversion factor is applied, and this will change based on the type of solution. NaCl solutions are typically used to calibrate these conversion factors. The usage of a NaCl solution assumes that Na⁺ and Cl⁻ are the primary ions present.

1.3.4. Conductivity and temperature:

Conductivity induces with temperature. This increase is significant, between 1.5 and 5.0% per °C. So, if you measure the same solution at different temperatures, you will get a different conductivity unless a temperature correction is used. Temperature compensation is therefore required for conductivity measurements.

1.3.5. Measuring conductivity:

Measuring conductivity can be achieved in a variety of ways. The most common method is using a conductivity probe as seen in Figure 15. These directly test the conductivity using two or more platinum electrodes.

1.4. Acid-Base Titrations:

- An acid-base titration is a quantitative analysis of acids and bases; through this process, an acid or base of known concentration neutralizes an acid or base of unknown concentration.
- The titration progress can be monitored by visual indicators, pH electrodes, or both. The reaction's equivalence point is the point at which the titrant has exactly neutralized the acid or base in the unknown analytic; if you know the volume and concentration of the titrant at the equivalence point, you can calculate the concentration of a base or acid in the unknown solution ^[27].

1.4.1. End point:

Endpoint is what is actually measured, a physical change in the solution as determined by an indicator or an instrument mentioned above^[28]

1.4.2. Equivalence point:

This is the point at which equivalent amounts of the reactants and products have reacted.

1.4.2.1. Equivalence Point Indicators:


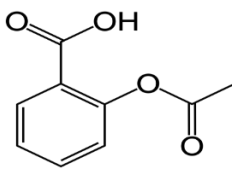
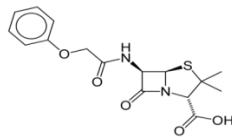
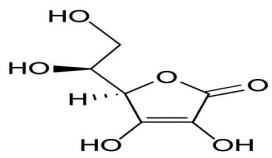
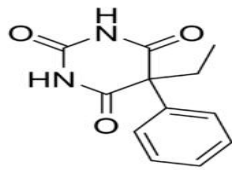
Below are some common equivalence point indicators:

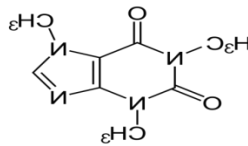
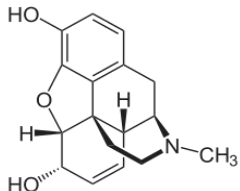
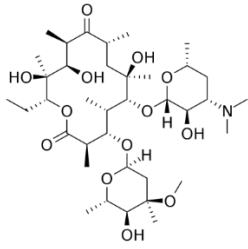
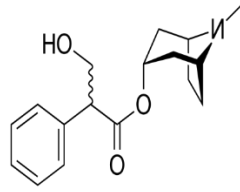
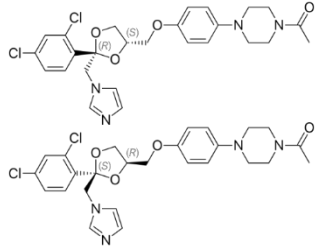
- Strong acid-strong base titration: phenolphthalein indicator that showed in figures 16 & 17.
- Weak acid-weak base titration: bromthymol blue indicator.
- Strong acid-weak base titration: methyl orange indicator the base is off the scale (e.g., pH > 13.5) and the acid has pH > 5.5: alizarine yellow indicator.
- The base is off the scale (e.g., pH > 13.5) and the acid has pH > 5.5: alizarine yellow indicator
- The acid is off the scale (e.g., pH < 0.5) and the base has pH < 8.5: thymol blue indicator^[29].

1.5. Acidic and basic drugs:

Table 6 showed that examples of Acidic and basic drugs.

Table (6): Acidic and basic drugs example.

Drugs	PH	Structure
Theophylline	Weak acid	
Acetylsalicylic Acid (aspirin)	Weak acid	
Penicillin V	Acidic	
Ascorbic Acid (vitamin C)	Acidic	
Phenobarbital	Weak acid	

Caffeine	Basic	
Morphine	Basic	
Erythromycin	Basic	
Atropine	Basic	
ketoconazole	Basic	 [30]

2. OBJECTIVE:

- To determine an appropriate method for separation of the API of ketoprofen (ketofan) from its original drug.
- To measuring the conductive of different concentration of the API.
- Studying the effect of UV wave on the API.
- Drawing PH curve of API.

II. MATERIAL AND METHODS

2.1. Materials, equipment and Devices:

2.1.1. Chemical Material:

- ketoprofen sustained: release (SR) hard gelatin capsules produced by: AMRIYA PH distilled ARM. IND Alexandria –Egypt.
- Distilled water.
- Ether.
- Ethanol.

2.1.2. Equipment:

- Automatic burrete.
- Measuring Cylinders Class.
- Separation Funnel.
- Glass Beaker.
- Stainless-Steel-lab-Spatula.
- Erlenmeyer flask.
- Retort Stand with clamp and Boss Head pack.
- Mortar and Pestle.

2.1.3. Devices:

- PH Meter.
- TDs & Ec Diagram.
- Digital Melting Point Apparatus.
- Sensitive balance.
- Hotplate magnetic stirrer.
- Magnetic-stir.

2.2. Procedure:

2.2.1. 1st purification by extraction (separation of active ingredient of ketoprofen by ether):

- 12 capsules of ketoprofen drug were taken, then the capsule was emptied after emptying the granules was taken.

- A mortar and pestle were used to crush the granules of ketoprofen.
- The granule powder was transformed into labeled 250 ml Erlenmeyer flask, followed by adding 30 ml of distilled water and 30 ml ether after that was putted on the stirrer for couple of minutes until the powder was dissolved.
- The reparatory funnel was placed in the stand, then the mixture of drug to be extracted was added into it (make sure the stopcock closed).
- The reparatory funnel was taken out of the stand and holder tightly at the stopper and the stopcock then inverted slowly and vent (open the stopcock) towards the back of the hood. A sound of whistle was heard when the pressure is released.
- The reparatory funnel was placed back in the stand, waited a couple of minutes, which allow the layers to separate, (the mixture was separated into 3 layers).
- The stopcock was opened and drained the middle and the bottom layer into a clean beaker (excipient and water), then separated the desired upper layer alone in clean beaker (ether and active ingredient) looked like clear liquid.
- The procedure was repeated by add the excipient and water mixture and add 10 ml of ether into Erlenmeyer flask then putted into the stirrer to dissolve, the mixture was transformed again into the reparatory funnel and repeated again the separation process.
- Previous step was repeated again.
- The mixture of active ingredient and ether was putted to dry for 5 days at room temperature.
- Melting point apparatus was used to confirm the identification of a sample of ketoprofen or to establish it is purity.
- First capillary tube was taken and sealed at one end by inserting the tip into a flame near the base of the flame and turning the tube around the fingers.
- The tube was packed by pressing the open end into a small amount of the sample of the crystalline powder of ketoprofen on filter paper.
- The crystals were transformed from the open end to the bottom of the tube by tapped the bottom gently on the bench top.
- A densely packed column of crystals about 3 mm high in the tube is all that is required.
- The packed capillary tube was inserted into melting point apparatus then started (the device is cooled before use).
- The sample was observed through the lens on the front of the apparatus, started to melt at 93 °C (melting point of ketoprofen 93°C).

2.2.2. 2nd acid base titration (to determine the acidity concentration of pure ketoprofen):

- A 300mg of pure ketoprofen crystal was weighted, then added 50ml water and 50ml of ethanol into labeled 250 ml beaker and putted the beaker on stirrer for 45 min until pure ketoprofen drug was dissolved.
- The pH meter was standardized with bottled water (Known pH).
- The pH of mixture was measured by Immerse the electrode in it without adding 0.1M NaOH (pH 4.5).
- 0.1 M of NaOH was prepared by taken 500ml of distilled water into a cleaned and dried 1000 ml volumetric flask.
- 2 gm. of Sodium hydroxide was added to the volumetric flask of distilled water with continues stirring and allowed to cool to room temperature.
- The electrode was cleaned thoroughly with distilled water.
- Then the titration process was started: The pH was recorded each time 1mL of 0.1M NaOH was added.
- Started to notice for the region where the pH begins to change rapidly with each time 1ml of 0.1M NaOH added.
- After passed the equivalence point by several mL of 0.1M NaOH added the titration process was stopped.
- The values were recorded and the curve drew.

2.2.3 3rd measuring EC, ppm and PH of ketoprofen solution after adding NaOH:

- 100ml of water and 100ml of ethanol was added into labeled 250 ml beaker.
- The pH, EC and ppm of mixture was measure by Immerse the electrode in it without adding pure ketoprofen crystal and 0.1M NaOH.
- 100mg of pure ketoprofen powder was weighted and added to the previous mixture then putted the on stirrer for 15 min until pure Naproxen drug was dissolved.
- The followed equation was used to know the amount need it from 0.1M from NaOH:

$$V \times N = N$$

$$V (L) \times 0.1 = Wt. / M.$$

$$V (L) \times 0.1 = 100 \text{ mg} / 254.4$$

$$V (L) \times 0.1 = 0.393 \text{ mol}$$

$$V (L) = 0.393 / 0.1 = 3.93 \text{ ml (NaOH)}$$

- The beaker was removed from the stirrer after 15 min and added the known volume heeded of 0.1M NaOH (4ml).
- The pH, EC and ppm of mixture was measured by Immerse the electrode in it and recorded.
- 4 ml of 0.1M NaOH and 100mg of ketoprofen crystal was added again to the mixture then putted on the stirrer for 15 minute to dissolve, after that the pH, EC and ppm of mixture was measured.
- The previous step was repeated until reach (0,80g) of crystal ketoprofen.
- The values were recorded each time in measurement and putted in curve.

2.2.4 4th Measuring PH, EC and ppm of after exposure it under the UV Lamp:

- 100mg of pure ketoprofen powder was weighted, 100ml water and 100ml of ethanol all was added into labeled 250 ml beaker then putted on stirrer for 45 min until pure ketoprofen crystal dissolve.
- The PH, EC and ppm of mixture was measured before exposure it under the UV Lamp.
- Make sure to not expose eye and skin to shortwave ultraviolet light, as rays may be harmful to unprotected eyes and skin.
- ketoprofen solution was exposed to ultraviolet lamp for one hour and the PH, EC and PPM was measured.
- The previous step was repeated every hour until reach six hours, which was done quickly and precisely each time when measure PH, EC and PPM.

III. RESULTS & DISCUSSIONS

3.1. Separation of ketoprofen by extraction method:

The extraction method was used to separate the active substance of ketoprofen, as ether was used as a solvent, because the active substance did not dissolve in water and from this process an appropriate amount of pure ketoprofen was obtained.

3.2. Electrical conductivity of ketoprofen:

After measuring the conductivity of a compound containing equal proportions of water and ethanol, different concentrations of the active substance of ketoprofen were added to it, then a certain amount of sodium hydroxide was added from that. It was observed that the conductivity of ketoprofen increases with the increase of the active substance and thus it became possible to know the concentration of ketoprofen in other solutions by using electrical conductivity

as well as Determination of the solubility of ketoprofen in various solvents.

The reason for adding sodium hydroxide to the compound is to convert the solute into a salt to be able to measure the conductivity. The greater the number of ions, the higher the conductivity, so the conductivity can be used as a measure of concentration.

The table (7) shows the increase in electrical conductivity and the percentage of dissolved salts with an increase in the different concentrations of ketoprofen, and this is shown more clearly through the figures (18), (19) and (20).

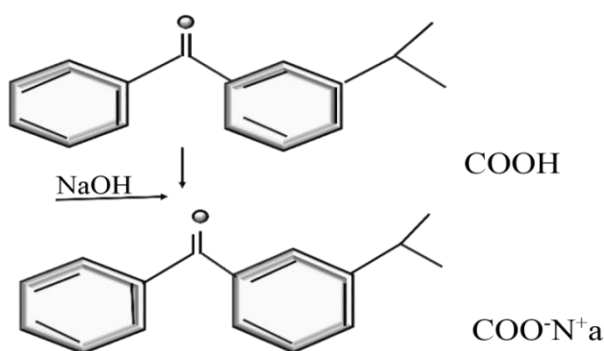


Figure (4): Interaction between NaOH & Ketoprofen.

3.2.1. Calculation of the amount of NaOH needed per 100 mg of ketoprofen:

$$\text{NaOH} = \text{KTP}$$

$$V \times n = n$$

$$V(L) \times 0.1 = \frac{Wt}{M.Wt}$$

3.2.2 ketoprofen concentration:

$$M = \frac{N}{V(L)} = \frac{WT}{M.WT \times V(L)}$$

Table (7): The conductivity values and the percentage of dissolved Salts with different concentrations of ketoprofen.

NO	pH	EC	PPM	WIEGTH	Concentration
0	7	3	2	0	0
1	5.9	54	27	100	7.8×10^{-3}
2	5.9	97	49	200	1.5×10^{-2}
3	6	142	71	300	2.3×10^{-2}
4	6	183	91	400	3.1×10^{-2}
5	6	227	113	500	3.9×10^{-2}
6	6	267	133	600	4.7×10^{-2}
7	6.1	307	153	700	5.5×10^{-2}
8	6.1	349	174	800	6.2×10^{-2}

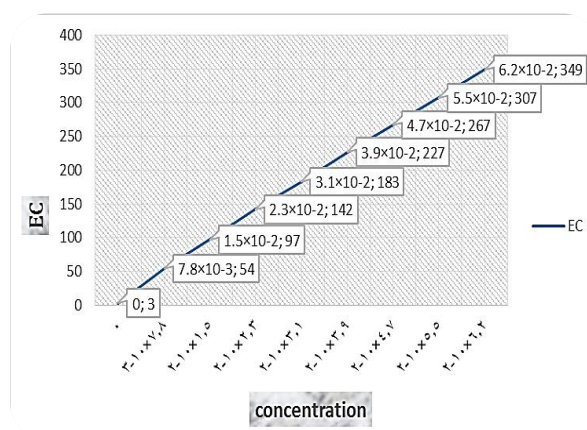


Figure (5): Relationship between the different ketoprofen concentrations and the conductivity.

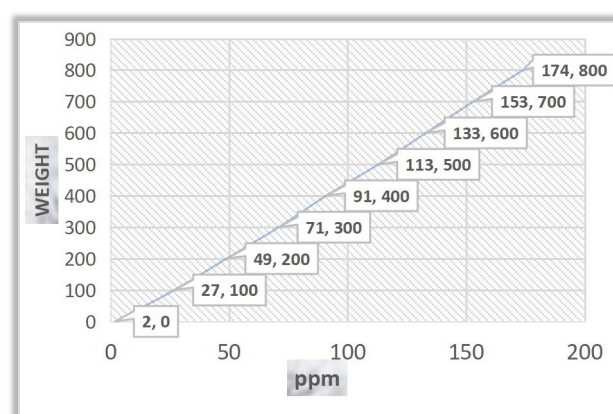


Figure (6): Relationship between soluble weight and ketoprofen concentrations.

3.3 The effect of ultraviolet radiation on ketoprofen:

When a solution containing a certain concentration of ketoprofen was exposed to ultraviolet rays, a change in the conductivity values was observed with the change in the duration of exposure to the radiation, as an increase in the conductivity, the percentage of soluble salts and the pH was observed with an increase in the duration of exposure and the reason for this change is that increasing the concentration leads to more breakdown of the compound, thus we obtain Outputs more, We showed that in table 8 and figure 21.

Table (8): The values of PH, EC, and ppm, after several hours of UVL exposure.

TIME	PH	EC	PPM	WIEGTH
0	6.7	56	28	100
1h	6.9	61	31	200
2h	7.1	67	33	300
3h	7.2	75	35	400
4h	7.3	79	38	500
5h	7.4	70	39	600
6h	7.5	81	40	700

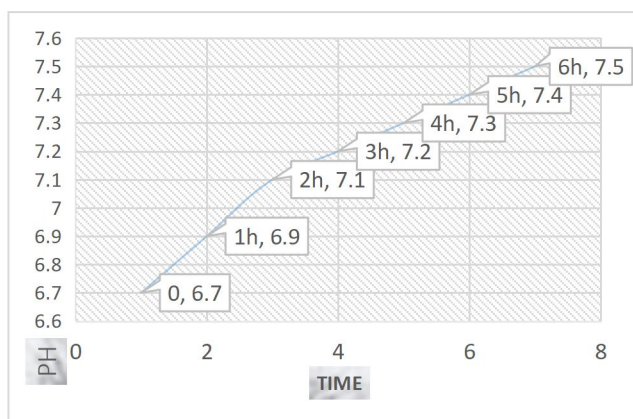


Figure (7): The relationship between conductivity and the number of hours of exposure to UV lamb.

3.4 Acid base titration of ketoprofen:

It was observed in this experiment that the acidity of ketoprofen appears to be stable with a slight increase every time we add 1ml of NaOH until it reaches a certain point, and it increases suddenly and returns to stability. The reason for using this process is to know the PH curve of the active substance. We showed that in table 9 and figure 22.

Table (9): increases in PH values with increasing the amount of NaOH.

NHON	PH	NHON	PH
0	4.5	9ML	5.7
2ML	4.6	10ML	5.8
1ML	3.7	11ML	6.2
3ML	5.1	12ML	6.6
4ML	5.2	13ML	7.1
5ML	5.3	14ML	11.3
6ML	5.4	15ML	12.4
7ML	5.5	16ML	12.7
8ML	5.6	17ML	12.9

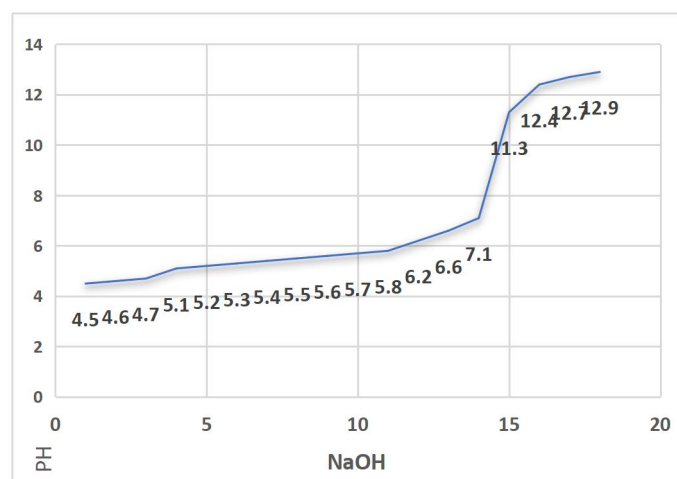


Figure (8): Relationship between sodium hydroxide and ketoprofen acidity.

CONCLUSION

In this work four experiments were performed:

- Separation of the active substance from the drug from this we concluded that the best way to separate is to use ether because we discovered that the active substance of ketoprofen does not dissolve in water, but rather dissolves in ether. The advantage of ether is that it does not mix with water, Therefore, when using the separation funnel, the active substance floats on the surface with ether and we get they are pure after the ether has evaporated, by knowing the appropriate method to separate the drug, we can use the expired active ingredient for industrial purposes instead of destroying it or discarding it in the soil because some compounds are not degradable.
- Measuring the conductivity of the active substance, we attended different concentrations of the active substance,

the conductivity of these concentrations was measured, and we concluded that the conductivity increased with the increase of the active substance and the increase was a linear increase, and it was discovered by drawing the diagram as a relationship between conductivity and concentration.

- The extent to which the active substance is affected by ultraviolet rays, so we took a concentration (100 mg) of the active substance and presented it at different time intervals to the ultraviolet rays and we measured the conductivity and we discovered that the conductivity changes with increasing time, and we noticed that when measuring the conductivity of the compound after two days, the change in the values of The conduction to the compound is evidence that the compound has re-broken and thus the conductivity has changed ,After exposure to ultraviolet rays, the drug breaks down and can turn into a toxic substance.
- By comparing the results of measuring the conductivity and acidity between ibuprofen, naproxen and ketoprofen, the conductivity values of these drugs increased, but the acidity values of ibuprofen and naproxen decreased while increasing in ketoprofen, and this different behavior between drugs calls for questions and needs to be studied.
- The diagram pH of the active substance, which is the relationship between the sodium hydroxide and the pH of the active substance, and when drawing the diagram, we get the PH curve for that.

RECOMMENDATIONS

This result obtained from this conductive trimetric technique warrant further investigation and analysis measurement such as HPLC, IR and mass spectroscopy cause the extensive use of painkiller increase over the years and their wastage, for that these measurements it can help us study more physiochemical and pharmacological properties of drugs, decrease effect of expired drug on the environment, and determine it is quality.

ACKNOWLEDGMENTS

We thank International Qurina University- Benghazi – Libya, where we conducted the experiments of this study inside the laboratories of the Faculty of Pharmacy there.

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