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

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Abstract*:*

The drug used was Naproxen is NSAID from propionic acid class used to treat pain. This study was aimed to determine a suitable separation method for active pharmaceutical ingredient from tablet solid dosage form, maintaining the environment through separation of an API from expired drug, discover the effect of sunlight on API, determine the pH of active ingredient and put it in curve and to measure the EC and PPM of the drug. In the experiment a mortar and pestle were used to crush 5 tablets of Naproxen then used 50ml of ether and 50ml of distilled water (1:1) as solvent, stirrer to enhance solubility and separatory funnel for extraction process then dried at room temperature 25Ċ for four days. melting point apparatus was used to confirm identification of the pure sample of Naproxen and acid base titration to determine the acidity concentration of it .The EC,PPM and pH was measured by(Adwa PH meter , AD31 Waterproof Conductivity-TDS-TEMP Pocket Testers) ,the measurement started after taken 100mg of Naproxen powder crystal dissolved in 50ml ethanol and 50ml of distilled water followed by addition of known volume of NaOH 4ml the measurement was repeated eight times with addition of 4ml of NaOH and 100mg of Naproxen powder each time of measurement, then the last measurement was done after exposure under UV lamp by using 100mg of Naproxen powder dissolved in 50ml ethanol and 50ml of distilled water and with addition of 4ml of NaOH .The results presented showed a formed crystal of pure Naproxen after Four days , for purity identification melting point apparatus was used , sample start to melt at 152Ċ as listed, noticeable increase in EC,PPM and pH values ,proportionally related with the weight because of interaction between acidic group in Naproxen (COOH) with NaOH, relationship between weight and Concentration was determined curve plotted shown increase in concentration each time the weight increase which result increase in electrical conductivity of the drug ,then pH was determined and curve plotted through acid base titration. In the last measurement viewed Change in drug Solution values EC, TDS and pH after UV exposure for six hours due to breaking of drug salt particles. This method proposed here it was considered to be simple, cheap and acceptable which fulfill the aims needed.

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

I. Introduction

Naproxen is a nonsteroidal anti-inflammatory drug a propionic acid class of medications.[1] Is a nonselective COX inhibitor used to treat pain, Onset of effects is within an hour and last for up to twelve hours.[1] IUPAC name:(+)-(S)-2-(6-Methoxynaphthalen-2-yl) propionic acid. fig (1) describes Naproxen chemical structure. As an NSAID, Naproxen appears to exert its anti-inflammatory action by decreasing the production of inflammatory mediators called prostaglandins.[2] Naproxen was patented in 1967, and verified for medical use in the United States in 1976.[3][1][4] It is available over the counter and as a generic medication.[5][6] In 2017, it was the 71st most commonly prescribed medication in the United States, with more than eleven million prescriptions.[7][8]Available as both an immediate release and as an extended release tablet. The extended-release formulations (sometimes called "sustained release," or "enteric coated") take longer to take effect than the immediate release formulations, and therefore are less useful when immediate pain relief is desired. Extended release formulations are more useful for the treatment of chronic, or long-lasting, conditions, in which long term pain relief is desirable.[9]

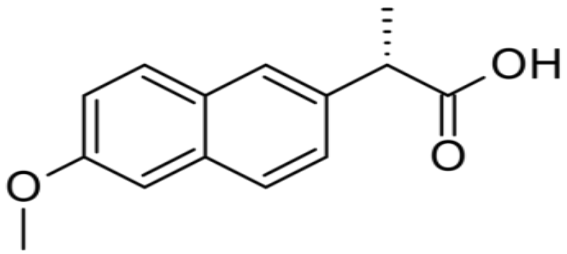


Figure (1): Chemical structure of Naproxen.

1.1.2. Physiochemical and pharmacological properties:

Table (1): Physiochemical properties of Naproxen.

Physiochemical properties	
Molar mass.	230.263 g·mol^{-1}
Melting point.	152–154 °C (306–309 °F).
Boiling point.	402-403 C.
Flash point.	154.5 C.
Density.	154.5 g / ml.
Smell.	Odorless.
Appearance.	White crystalline powder.
Experimental Solubility.	100 mM in DMSO; 50 mM in 1eq. HCl.[10] DMSO 47 mg/ml. [10] Soluble in water (>3 mg/ml at 25 °C), (highly soluble in water at high ph.). methanol, DMSO, DMF (100 mg/ml), chloroform, dichloromethane, ether, ethyl acetate or tetrahydrofuran. highly lipid soluble.

1.1.3. Mechanism of action: Works by reversibly inhibiting both the COX-1 and COX-2 enzymes as a non-selective COXIB.[11][12][13][14][15] This results in the inhibition of prostaglandin synthesis. In the body, prostaglandins function as signaling molecules that cause inflammation.

1.1.4. Pharmacokinetic of Naproxen:

Table (2): Pharmacokinetic of Naproxen.

Pharmacokinetics	
Bioavailability	95% (by mouth)
Protein binding	%99
Metabolism	Liver (to 6-desmethylnaproxen)
Elimination half-life	12–17 hours (adults) [16]
Excretion	Kidney

1.1.5. Pharmacodynamics:

Naproxen is a non-selective NSAID and is useful as an analgesic, anti-inflammatory and antipyretic.[16] the pharmacological activity of it can be attributed to the inhibition of cyclooxygenase, which in turn decreases prostaglandin synthesis in various tissues and fluids including the synovial fluid, gastric mucosa, and the blood.[17]

1.1.6. Structure Activity Relationship:

• Maximum activity was found at substitution in the 6th – position.
• Small lipophilic groups are active analogues with CH3O is most potent.

- Derivatives with larger group substitutions are found to be less active.
- It was discovered that 2-naphthylpropionic acid derivatives were more active than their comparable acetic acid counterparts..
- The activity is maintained by substituting groups that can be metabolized to carboxyl groups for the carboxyl group..
- (+)-S-enantiomer is found to be more potent.[18]

1.1.7. Common brand names:

Its marketed under various brand names, Accord, Aleve, Anaprox, Apranax, Nalgesin, Naposin, \ Naprogesic, Naprosyn, , Proxen, Nopain, and Soproxen.[19] It is also available as the combination Naproxen/esomeprazole magnesium in delayed release tablets under the brand name Vimovo.[19][20]

1.1.8. Medical uses:

- To treat a variety of inflammatory conditions and symptoms that are due to huge inflammation, such as pain and fever.[3]. Inflammatory sources of pain that may respond to Naproxen's anti-inflammatory activity are conditions such as migraine, osteoarthritis, kidney stones, rheumatoid arthritis, psoriatic arthritis, gout, ankylosing spondylitis, menstrual cramps, tendinitis, and bursitis.[5]
- Naproxen sodium is used as a "bridge therapy" in medication overuse headache to slowly take patients off other medications.[21]

1.1.9. Adverse effects:

- The majority include dizziness, drowsiness, headache, rash, bruising, and gastrointestinal upset.[3][5] Heavy use is associated with higher risk of end-stage renal

disease and kidney failure.[3][22] Naproxen may cause muscle cramps in the legs in 3% of people.[23]

- Gastrointestinal : Naproxen can cause gastrointestinal problems, such as heartburn, constipation, diarrhea, ulcers and stomach bleeding.[24]
- Cardiovascular :COX-2 selective and nonselective NSAIDs have been linked to higher in the number of serious and potentially fatal cardiovascular events, such as myocardial infarctions and strokes.[25] high dose Naproxen induced near complete suppression of platelet thromboxane throughout the dosing interval and appeared not to induce cardiovascular disease risk.

1.1.10. Interactions of Naproxen:

1.1.10.1. Interaction of Naproxen with drugs:

Table (3): Interactions of Naproxen with drugs.

Drugs interact with naproxen	Interaction
Steroid	Naproxen may interfere with and reduce the efficacy of drugs and [26] may interact with steroid medicines such as prednisone.[5]
Anticoagulant	When naproxen and anticoagulants are used together, there is a higher chance of severe bleeding than when either medication is used alone.
Antihypertensive	may reduce the effectiveness of beta-blockers(including propranolol), angiotensin receptor blockers (ARBs), or angiotensin converting enzyme (ACE) inhibitors in lowering blood pressure.
Diuretics	decreased the natriuretic impact of thiazide diuretics and loop diuretics (such as furosemide) in certain people..
SSRI antidepressants	Reduce the efficacy. [27]
Digoxin.	Increase the serum concentration and prolong the half-life of digoxin
Lithium	caused decreases in renal lithium clearance and increases in plasma lithium levels.
Methotrexate	naproxen increases the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).
Antacids.	When sucralfate and certain antacids (such as magnesium oxide or aluminum hydroxide) are used together, the absorption of naproxen may be delayed..[28]

1.1.10.2. Drug–food interactions:

Alcohol consumption higher the risk of gastrointestinal bleeding when combined with NSAIDs like naproxen.[29] Pregnancy and lactation :Small amounts of Naproxen are excreted in breast milk.[5] However, side effects are uncommon in infants breastfed from mother taking Naproxen.[30] Pregnancy category C.

1.1.11. Dosage form and strength:

Table (4): Dosage form and strength: Adult and pediatric .

Dosage form Dosage form and strength: Adult and pediatric .[31,32,33]‖	
Tablet.	220 mg (over the counter),250 mg,275 mg ,375 mg, 500 mg ,550 mg.
Tablet, delayed release.	375 mg,500 mg.
Tablet, extended release.	375 mg,500 mg,750 mg.
Capsule.	220 mg.
Oral Suspension.	25 mg/ml.

1.1.12. Administration:

Naproxen can be applied topically, taken orally, orally, or as immediate- and extended-release tablets or suspensions.. Naproxen may be taken orally with food, milk, antacids

(preferably aluminum and magnesium antacids), proton pump inhibitors or misoprostol to reduce the incidence of GI side effects.[34] Naproxen sodium is the form that is most readily available, and it has been shown to have a faster absorption compared to naproxen. Specific dosing recommendations and treatment durations:

- Mild to moderate arthritis (osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis):220—550 mg PO every 12 hours Take with food if GI upset occurs Max: 1650 mg daily for up to 6 months.
- Acute gouty arthritis:825 mg PO once, followed by 275 mg PO every 8 hours until symptom resolution Take with food if GI upset occurs.
- Acute severe headache or migraine: Controversial with respect to isolated Naproxen sodium use in patients suffering from acute migraines Naproxen sodium has a longer half life compared to other NSAID options, but The recommended dosage for naproxen sodium is 550 mg every 12 hours; if necessary, this can be increased to 825 mg PO; nevertheless, the daily maximum should not be exceeded at 1375 mg..
- Children aged 12 and up should take no more than 20 mg/kg per day orally, with a daily maximum of 1000 mg. mg/day by mouth; for nonprescription use,660 mg/day by mouth2 to 12 years 20 mg/kg/day by mouth not to exceed 1000 mg/day by mouth.
- Nonprescription use is not recommended Less than 2 years. Utilize the lowest recommended dosing regimen initially Patients with Renal Impairment Dosing If creatinine clearance is higher than or equal to 30 mL/min no dosage adjustment is needed.

1.1.13. Contraindication:

- Absolute: Documented hypersensitivity to NSAID medications [37], Perioperative use for coronary artery bypass graft surgery.
- Pregnancy (caution against use in 1st trimester, absolute contraindication at 30 weeks' gestation).
- Relative: Bleeding disorder, peptic ulcer, renal impairment, stomatitis.

1.1.14. Effect of Naproxen on the environment:

Naproxen can affect the organisms' inhabiting ecosystems either through it is toxicity to an organism or via the toxicity of its metabolites. [38] [39] The basic changes that Naproxen undergoes in surface waters are via its direct photochemical degradation and indirect photochemical pathways [40]. The intensity of photo degradation is affected by the intensity of light and the presence of nonorganic ions such as carbonate, nitrate, ferrous and ferric ions as well as organic matter. It is indirect photochemical degradation occurs when dissolved organic matter absorbs sunlight، which produces reactive oxygen species such as singlet oxygen، hydroxyl radicals and other reactive species. [40] [41] [42] [43] Unfortunately، lead to the formation of products that may be more persistent and more toxic. It was also shown may affect the mRNA expression and cause gastrointestinal and renal effects in zebrafish [44]

1.2. Analytical, measuring and separation methods of Active Pharmaceutical Ingredient:

- **High performance liquid chromatography (HPLC):** Is technique used to separate, identify and quantify each component in mixture. It relies on pump to pass a pressurized liquid solvent containing the sample mixture through a column filled with adsorbent liquid material. known to be the most common used method for separation [45].
- **Filtration:** is a physical, biological, or chemical process that uses a filter media with a complex structure that only allows fluid to flow through to separate solid particles and fluid from a mixture.. [46]
- Distillation: is the method of employing selective boiling and condensation to extract the constituents or compounds from a liquid combination. [47]
- **Centrifugation:** Is a mechanical process which involves the use of the centrifugal force to separate particles from a solution based on their rotor speed, density, size, form, and medium viscosity. [48]
- Thin layer chromatography: Is a widely employed laboratory technique used to separate different biochemical on the basis of their relative attractions to the stationary and mobile phases. There's also an enhanced form of thin layer chromatography (TLC) known as High-performance thin layer chromatography (HPTLC). [49]
- **Extraction:** Is a separation process consisting in the separation of a substance from a matrix. Common examples include liquid-liquid extraction, and solid phase extraction. [50]
- **Gas chromatography (GC):** Also, sometimes known as **gas-liquid chromatography**, (GLC), is a separation technique in which the mobile phase is a gas. Gas chromatographic separation is always carried out in a column, which is typically "packed" or "capillary".
- **Spectrophotometry (Microbiological assay):** Spectrophotometry is the quantitative measurement of the

reflection or transmission properties of a material as a function of wavelength. It should be noted that colorimetric techniques are frequently employed in bulk material assays. For instance, corticosteroid drug compositions are determined using the blue tetrazolium assay. [51] [52]

- **Nuclear magnetic resonance (NMR) spectroscopy:** Is a spectroscopic technique to note the local magnetic fields around atomic nuclei. Recently finds it is application in quantitative analysis in order to determine the impurity of the drug [53], and in quantitation of drugs in pharmaceutical formulations and biological fluids [54]; [55].
- **Near-infrared spectroscopy (NIRS):** Is a spectroscopic method that uses the near-infrared region of the electromagnetic spectrum (from 780 nm to 2500 nm). There have been several articles that describe quantitative NIR assessments of the active component in intact tablets. [56][57][58][59]
- **Fluorimetry and Phosphorimetry:** Fluorescence spectrometry is one of the techniques that serve the purpose of high sensitivity without the loss of specificity or precision. [60] [61]and phosphorimetry [62] [63] used in quantitative analysis of various drugs in dosage forms.
- Electrochemical methods: It is studying an analyte by measuring the potential (volts) or current (amperes) in an electrochemical cell containing the analyte [64][65][66][67] large number of electro analytical methods are available for quantification of pharmaceuticals. An amber lite XAD-2 and titanium dioxide nanoparticles modified glassy carbon paste was developed for the determination of imipramine, trimipramine and desipramine [68].
- **Flow injection analysis (FIA):** It is injecting a plug of sample into a flowing carrier stream [69][70][71] has lent a significant contribution to the advancement of automation in pharmaceutical analysis a second generation of flow analysis was offered by [72], who titled it as sequential injection analysis (SIA) [73][74], the majority of the applications are dedicated to the determination of active ingredients for quality control in pharmaceutical formulations.
- **Capillary electrophoresis (CE):** Is a relatively new analytical technique based on the separation of charged analytes through a small capillary under the impact of an electric field which separated according to charge and size. [75][76][77][78][79] Have been applied to pharmaceutical purity testing, separation and in bio analysis of drugs.

1.3. Acid base titration:

1.3.1. Definition and history:

Is a method of quantitative analysis for determining the concentration of an acid or base known as **analyte** by absolutely neutralizing it with a standard solution of base or acid having known concentration known as titrant or reagent. Consider one of the oldest tools of analytical. Litmus paper, indicators, or, most precisely, a glass electrode and pH meter can all be used to determine a solution's pH level. The method was first described by Glauber (1658). Potash, or potassium carbonate made from wood ashes, was supposed to be added to nitric acid until the gas stopped evolving. Since then, a lot of work has gone into improving the methods for measuring H3O+ ions and the utility of acid-base titrations. Acidimetry is the specialized analytic use of acid-base titration to determine the concentration of a basic substances using standard acid. Alkalimetry, it is also specialized analytic acid base titration, but for an acidic substance using standard base.[80]

1.3.2. Uses of acid base titration:

- For biodiesel fuel and [81] and assay of benzoic acid. [82]
- Determination of barbiturates, nicotine, amino acid and aspirin.

1.3.3. pH indicators:

Is a halo chromic chemical substance that is applied in trace amounts to a solution to visually set its pH (acidity or basicity). Used to monitor the progress of reaction. If the acid dissociation constant (pKa) of the acid or base dissociation constant (pKb) of base in the analyte solution is known, its solution concentration (molarity) can be determined, or vice versa. A suitable pH indicator must be chosen in order to observe the end point of the titration. The color change should occur close to the equivalence point of the reaction so that the experimenter can exactly determine when that point is reached. The following guidelines can be used to estimate the pH of the equivalency point::

- A strong acid will react with a strong base to form a neutral (pH = 7) solution.
- A strong acid will react with a weak base to form an acidic (pH < 7) solution.
- A weak acid will react with a strong base to form a basic (pH > 7) solution.

The equivalency point solution of a reaction between a weak acid and a weak base will be basic if the base is stronger and acidic if the acid is stronger. The equivalency pH will be neutral if both are equally strong. However, because the indicator's color shift is frequently rapid, weak acids are rarely titrated against weak bases.

Table (5): Different types of indicators used in acid base titration.

Indicator	Color on acidic side	Range of color change (pH)	Color on basic side
Methyl violet	Yellow	0.0–1.6	Violet
Bromophenol blue	Yellow	3.0–4.6	Blue
Methyl orange	Red	3.1–4.4	Yellow
Methyl red	Red	4.4–6.3	Yellow
Litmus	Red	5.0–8.0	Blue
Bromothymol blue	Yellow	6.0–7.6	Blue
Phenolphthalein	Colorless	8.3–10.0	Pink
Alizarin yellow	Yellow	10.1–12.0	Red

1.3.4. Titration curve:

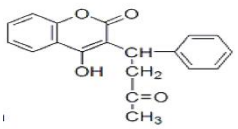
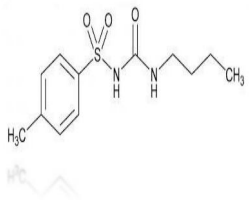
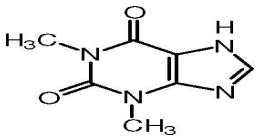
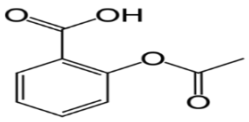
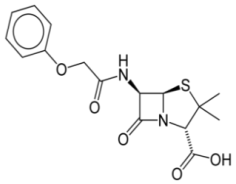
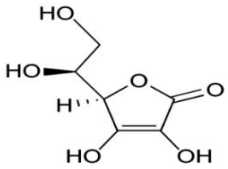
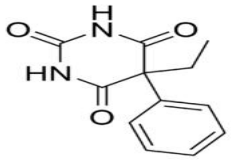
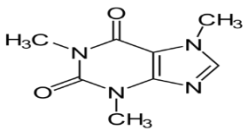
Is a curve in graph the x-coordinate of which represents the volume of titrant added since the beginning of the titration, and the y-coordinate of which represents the concentration of the analyte at the corresponding stage of the titration (in an acid–base titration, the y-coordinate usually represents the pH of the solution).[83]

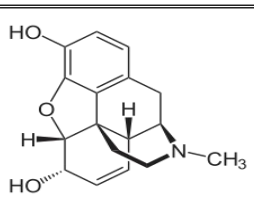
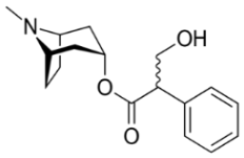
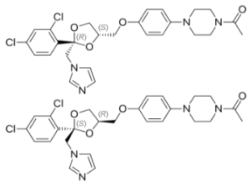
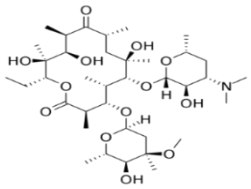
1.3.5. The endpoint and the equivalence point:

The end point: refers to the point at which the indicator changes color in an acid base titration. The equivalence point or stoichiometric point: is the point at which chemically equivalent quantities of reactants have been mixed. In other words, the moles of acid are equivalent to the moles of base [84]. A pH meter or a conductance meter are employed when more accurate readings are needed or when the reagents are a weak acid and a weak base..

1.4. Example of some Acidic and basic drug in Libya:

Table (6): Acidic and basic drugs in Libyan market.

Drug	PH	Structure
Warfarin	**Weak acid**	
Tolbutamide	**Weak acid**	
Theophylline	**Acid**	
Acetylsalicylic Acid (aspirin)	**Acid**	
Penicillin V	**Acid**	
Ascorbic Acid (vitamin C)	**Acid**	
Phenobarbital	**Acid**	
Caffeine	**Basic**	

Morphine	**Basic**	
Atropine	**Basic**	
ketoconazole	**Basic**	
Erythromycin	**Basic**	

1.5. Conductivity:

The flow of charged particles is known as electrical current, and it is measured in amps (A). The ease with which those charge particles flow through a substance or solution is known as conductance, and it is measured in Siemens, S.

1.5.1 Electrical conductivity:

Is the rate of flow of electric charge and also is the conductance (S) measured across a specified distance through a material/solution (measured in Siemens per centimeter, S/cm), the size of the current depends on:[85][86]

- Nature of the ions: charge, size, mobility and temperature.
- Solvent characteristics: viscosity and dielectric constant
- Ion concentration: conductivity can be used as a gauge of concentration because the more ions present, the higher the conductivity.
- Concentration and Total Dissolved Solids (TDS): Conductivity can be used to measure solution concentration and provide a value for Total Dissolved Solids (TDS), which is measured in parts per million (PPM), due to the link between conductivity and the number of ions in solution.[85]
- Measuring conductivity: can be achieved in a variety of ways. Using a conductivity probe is the most used technique. These directly test the conductivity using two or more platinum electrodes.
- More advanced conductivity cell uses four electrodes. These probes use current through the outer electrodes and measures the voltage across the inner electrodes, [86] gives a lower current and so has less charge transfer at the metal-liquid interface. This allows a much large dynamic range to be measured than a two-electrode sensor.
- Replatinization: is required If a probe is treated poorly or when measurements become slow, erratic or inconsistent or when the cell constant shifts more than 10% from the nominal cell constant. [85] [86]
- Storage: The probe can be stored in the deionised water between measurements; however, for overnight storage, or longer-term storage, the probe should be rinsed and stored dry. The proper tissue can be used to carefully dry the probe.

II. OBJECTIVES

The aims of the present study were:

- To determine an appropriate separation method for active ingredient (Naproxen) from tablet solid dosage form.
- For maintaining the environment, through separation of an active pharmaceutical ingredient from expired drug.
- To discover the effect of sunlight on active ingredient (Naproxen) by expose it to an ultraviolet lamp.
- To know and determine the pH of active ingredient (Naproxen) and put it in curve.
- To measure the EC and TDS of the drug to determine the quality of it and study the ability of reuse of expired drugs.

III. MATERIAL AND METHODS

3.1. Materials and equipment:

3.1.1. Chemical material:

Naproxen tablets Bristol company [Each tablet contains 500mg Naproxen**,** excipients also contain 98.979 mg of lactose and 0.027 mg of sunset yellow (E110)], diethyl ether, ethanol, sodium hydroxide, distilled water.

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Figure (2): Naproxen Bristol company (UK).

Figure (3): Ethanol.

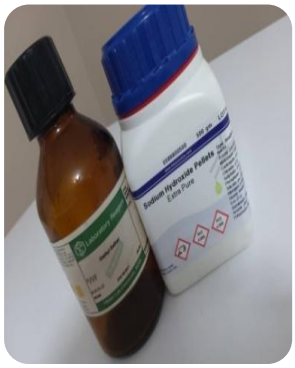

Figure (4): Ether and NaOH

3.1.2. Equipment:

Separatory funnel 125ml (borosilicate glass), beaker 250ml (borosilicate glass), Erlenmeyer flask 250ml (borosilicate glass), measuring Cylinder10ml, capillary melting point tubes, automatic Burret, spatula, mortar and pestle, stand.

Figure (5): Stand and (mortar and pestle).

Figure (6): Separatory funnel 125 ml.

Figure (7): Glass wear.

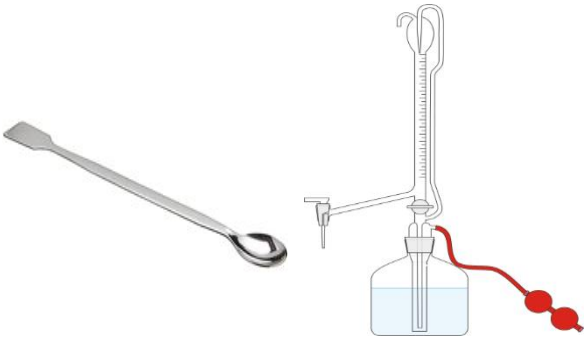

Figure (8): Spatula (stainless steel) and automatic burette.

3.1.3. Devices:

- Stuart Bibby Hotplate Stirrer CB162 UK.

Figure (9): Stuart Bibby Hotplate Stirrer.

- Electronic scale (Henan Lanphan Industry china).

Figure (10): Electrical balance.

- Adwa PH meter & Temperature gauge AD-11 (waterproof) Romania.

Figure (11): pH meter.

- AD31 Waterproof Conductivity-TDS-TEMP Pocket Testers with replaceable electrode Romania.

Figure (12):EC and TDS meter.

- Ultraviolet lamp mode UVGL -58 /wave length for short wave 254 nm, longwave 365nm USA.

Figure (13): Ultraviolet lamp mode UVGL -58.

- Melting Point Apparatus, Stuart Scientific, Model SMP3, 240v Uk.

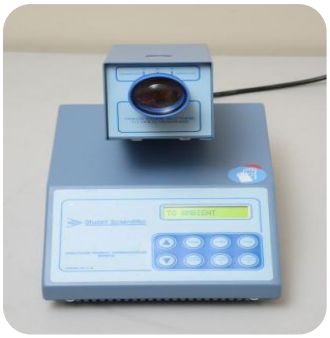

Figure (14): Melting Point Apparatus.

3.2. Methods:

3.2.1 Extraction (separation of active ingredient of Naproxen by ether):

- 5 tablet of Naproxen drug was taken, then weighted to determine an average tablet weight (3.85g).
- A mortar and pestle were used to crush the tablets and produced approximately 2g of tablet powder (was grinded precisely).
-

Figure (15): Crushed Naproxen tablet.

- The powder was transformed into labeled 250 ml Erlenmeyer flask, followed by adding 50 ml of distilled water and 30 ml ether after that was putted on the stirrer for couple of minutes until the drug powder dissolved.

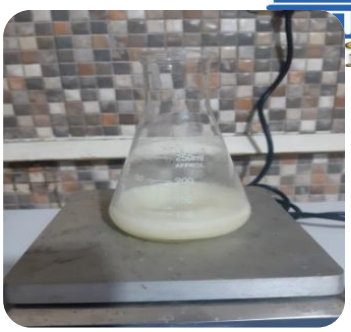

Figure (16): Mixture of Naproxen solution on stirrer.

- The separatory funnel was placed in the stand, then the mixture of drug to be extracted was added into it (make sure the stopcock closed).
- The separatory 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 separatory 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).

Figure (17): The mixture of solution separates 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.

Figure (18): Separation of the clear (ether) layer.

- The procedure was repeated by add the excipient, water mixture and add 10 ml of ether into Erlenmeyer flask then putted into the stirrer to dissolve for couple of minutes, then the mixture was transformed into the separatory 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 Naproxen 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 Naproxen 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. All that is needed is a tightly packed column of crystals in the tube that is roughly 3 mm high..
- 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 152 Ċ (melting point of Naproxen 152Ċ).

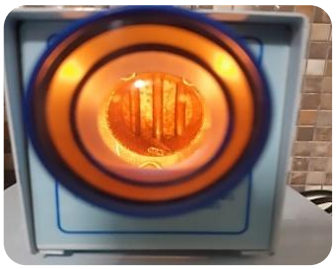

Figure (19): Sample of Naproxen in melting point apparatus.

3.2.2 Acid base titration (to determine the acidity concentration of pure Naproxen):

- A 300mg of pure Naproxen 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 Naproxen 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 4.4).
- 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 at room temperature.(fig 31).

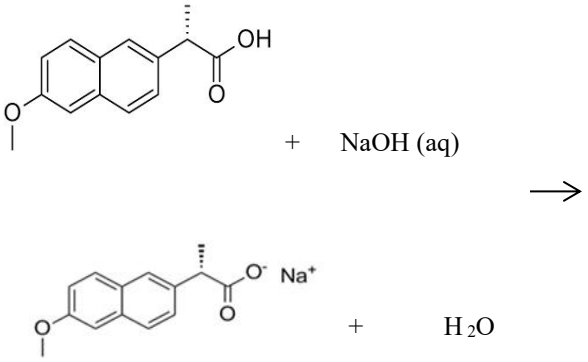

Figure (20): Reaction between Naproxen and NaOH.

- 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.

3.2.3 Measuring EC, TDS and PH of Naproxen solution after adding NaOH:

- 50ml of water and 50ml of ethanol was added into labeled 250 ml beaker.
- The pH, EC and TDS of mixture was measure by Immerse the electrode in it without adding pure Naproxen crystal and 0.1M NaOH.
- 100mg of pure Naproxen powder was weighted and added to the previous mixture then putted the on stirrer for 15 min until pure Naproxen drug was dissolved.

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Figure (21): Mixture of Naproxen solution on stirrer.

- The followed equation was used to know the amount need it from 0.1M from NaOH:

$$V \times M = Wt. / M.W.$$

$$V \times 0.1\ mol/L = 100\ mg / 230.263\ g / mol.$$

$$V \times 0.1\ mol/L = 0.1\ g \ / 230.263\ g / mol.$$

$$V \times 0.1\ mol/L \ = 0.00043\ mol.$$

$$V = 0.00043\ mol / 0.1\ mol/ L = 0.0043L.$$

$$V = 4.3\ ml.$$

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

- **Measuring PH, EC and TDS of solution after UV exposure:**

- 100mg of pure Naproxen powder was weighted, 50ml water and 50ml of ethanol all was added into labeled 250 ml beaker then putted on stirrer for 45 min until pure naproxen crystal dissolve.
- The PH, EC and TDS 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.
- Naproxen solution was exposed to ultraviolet lamp for one hour and the pH, EC and TDS was measured.

Figure (22): Solution of Naproxen under UV lamp.

- The previous step was repeated every hour until reach six hours, which was done quickly and precisely each time when measure PH, EC and TDS and recorded.

IV. RESULTS and DISSCUSSIONS

In separation experiment after 5 days was noticed formation of white crystal of pure Naproxen in the beaker as seen in figure (34) then weighted (1.880 mg), due to use of ether an aprotic solvent which has characteristic that make it the best choice for extraction process (high volatility, ability to dissolve API without been miscible with water and less density than excipient and water) make it at the top in the separation process with desired material. The melting point was 152Ċ exactly the same as noted, demonstrate a successful separation.

Figure (23): The formed crystal of pure Naproxen.

As seen from titration table (7) and figure (35) a notable increase in pH by point at each time 1ml NaOH was added until reach the equivalence point (8.7) at 17 ml of NaOH were moles of NaOH equal to mole of Naproxen, then followed by sudden increase (sudden jump) in pH values (11.2) at 18 ml of NaOH (which determine the end point of titration) followed by gradually increase in pH. The ability of determining the

acidity, concentration of Naproxen and drew the curve was due to adding of NaOH and known to be the most common base used in acid base titration.

Table (7): Acid base titration values of Naproxen solution measuring pH, EC and TDS after adding NaOH.

NAOH (ml)	pH	EC (µS/cm)	TDS(PPM)
0	4.4	18	9
1	5.1	23	16
2	5.4	48	24
3	5.6	67	34
4	5.7	93	46
5	5.8	115	57
6	5.9	137	68
7	6.0	152	76
8	6.2	175	86
9	6.2	199	100
10	6.3	218	109
11	6.5	234	117
12	6.6	254	127
13	6.7	271	136
14	6.9	292	146
15	7.2	307	154
16	7.5	325	162
17	8.7	348	174
18	11.2	385	193
19	11.6	418	209
20	11.8	457	229
21	12.1	490	245

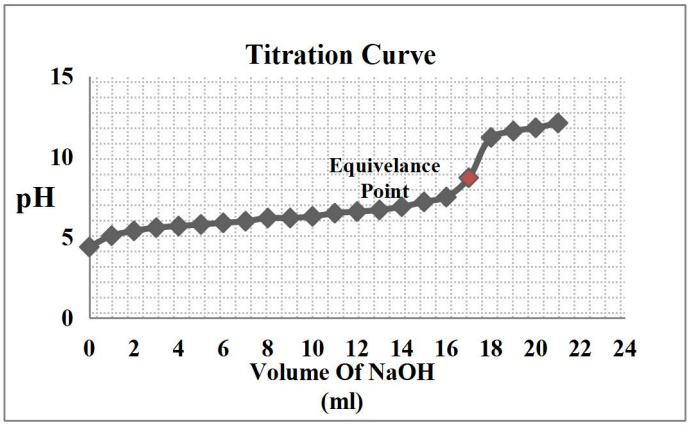

Figure (24): Titration Curve of Naproxen with NaOH.

As present in the table (8) and figures (36,37,38) the values of EC, TDS and pH increased at each time 100 mg of crystal powder of Naproxen and 4ml of NaOH was added, that's reflect direct proportional relationship between EC, TDS, pH and weight. This increase in concentration of Naproxen, increases the percentage of salts in the solution because of interaction between the acidic group in Naproxen (COOH) with NaOH results in the formation of salts ions so increase values of EC, TDS and pH. These results were compared with the conductivity and acidity between ibuprofen, ketoprofen, and found the conductivity values of these drugs also increased, but when compared to ours similarly the acidity values of ibuprofen decreased, while increasing in ketoprofen, and this difference needs to be studied.

Table (8): Values of measuring EC, TDS and pH of Naproxen solution.

N	pH	EC (µS/cm)	TDS(PPM)	Wt.(mg)
1	5.2	3	1	0
2	5.7	124	63	100
3	5.8	230	115	200
4	5.9	319	160	300
5	6.0	397	199	400
6	6.1	481	240	500
7	6.2	566	283	600
8	6.3	641	321	700
9	6.4	715	357	800

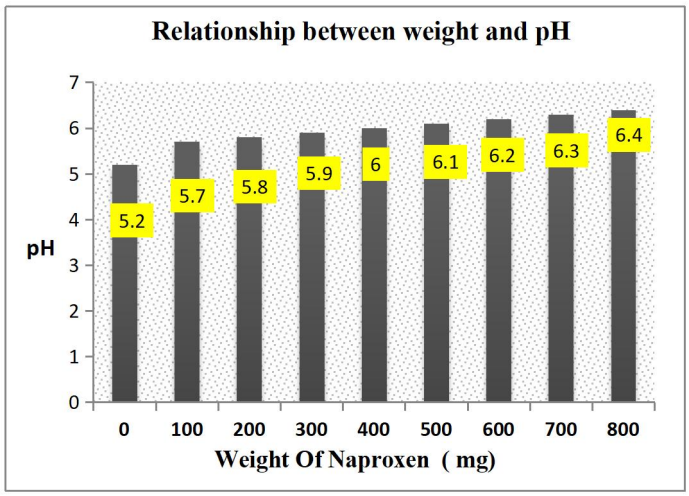

Figure (25): The relationship between weight and pH after adding NAOH.

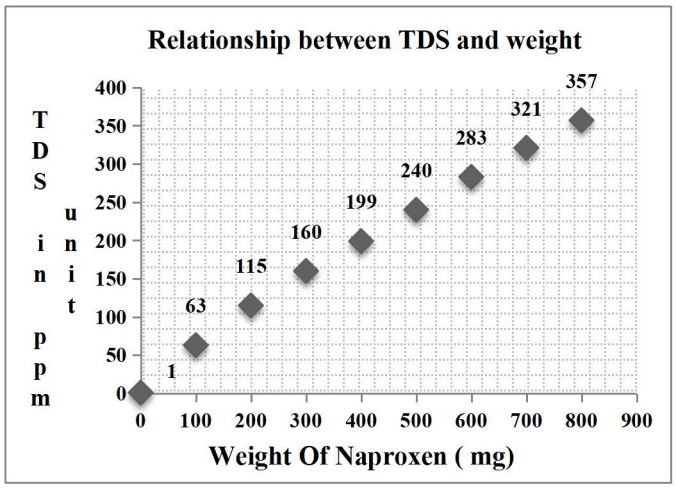

Figure (26): Electrical conductivity of Naproxen.

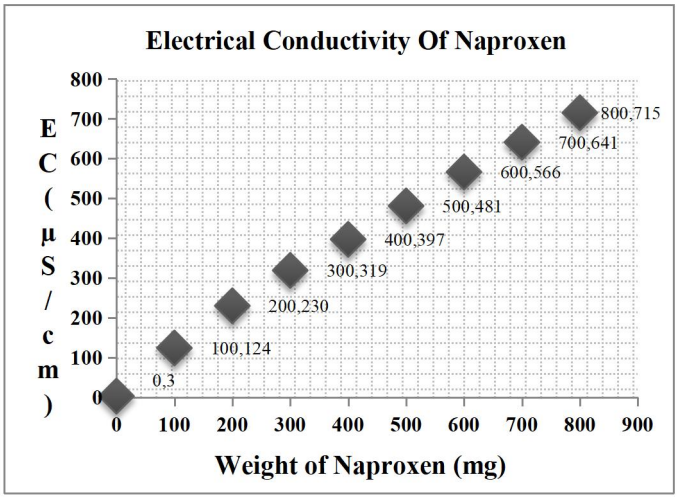

Figure (27): Relationship between weight and TDS in ppm unit.

The following law determine the relationship between weight and Concentration:

$$\mathbf{M} = \frac{n}{V(L)}, \mathbf{n} = \frac{Wt}{M.W} = \mathbf{M} = \frac{Wt}{M.W \times V\,(L)}.$$

- $\mathbf{M} = \frac{100mg}{230.263\ g/mol \times 100ml} = \frac{0.1g}{230.263\ g/mol \times 0.1L} = 0.0043 = 4.3 \times 10^{-3}$
- $\mathbf{M} = \frac{200mg}{230.263\ g/mol \times 100ml} = \frac{0.2g}{230.263\ g/mol \times 0.1L} = 0.0086 = 8.6 \times 10^{-3}$
- $\mathbf{M} = \frac{300mg}{230.263\ g/mol \times 100ml} = \frac{0.3g}{230.263\ g/mol \times 0.1L} = 0.013 = 1.3 \times 10^{-2}$
- $\mathbf{M} = \frac{400mg}{230.263\ g/mol \times 100ml} = \frac{0.4g}{230.263\ g/mol \times 0.1L} = 0.017 = 1.7 \times 10^{-2}$
- $\mathbf{M} = \frac{500mg}{230.263\ g/mol \times 100ml} = \frac{0.5g}{230.263\ g/mol \times 0.1L} = 0.021 = 2.1 \times 10^{-2}$
- $\mathbf{M} = \frac{600mg}{230.263\ g/mol \times 100ml} = \frac{0.6g}{230.263\ g/mol \times 0.1L} = 0.026 = 2.6 \times 10^{-2}$
- $\mathbf{M} = \frac{700mg}{230.263\ g/mol \times 100ml} = \frac{0.7g}{230.263\ g/mol \times 0.1L} = 0.03 = 3.0 \times 10^{-2}$
- $\mathbf{M} = \frac{800mg}{230.263\ g/mol \times 100ml} = \frac{0.8g}{230.263\ g/mol \times 0.1L} = 0.034 = 3.4 \times 10^{-2}$

In the following table (9), figure (39), the relatively high conductive value of Naproxen shows the higher concentration of ions dissolved in solution, leading to fast absorption of drug

by the body fluids where the ionic response of a drug to the body medium is a measure of the electrical conductivity of such a drug.

Table (9): Values of conductivity and relationship between EC and concentration of dissolved salt at variant weight of Naproxen.

N	pH	EC (µS/cm)	TDS (PPM)	Wt. (mg)	Concentration
0	5.2	3	1	0	0
1	5.7	124	63	100	4.3×10^{-3}
2	5.8	230	115	200	8.6×10^{-3}
3	5.9	319	160	300	1.3×10^{-2}
4	6.0	397	199	400	1.7×10^{-2}
5	6.1	481	240	500	2.1×10^{-2}
6	6.2	566	283	600	2.6×10^{-2}
7	6.3	641	321	700	3.0×10^{-2}
8	6.4	715	357	800	3.4×10^{-2}

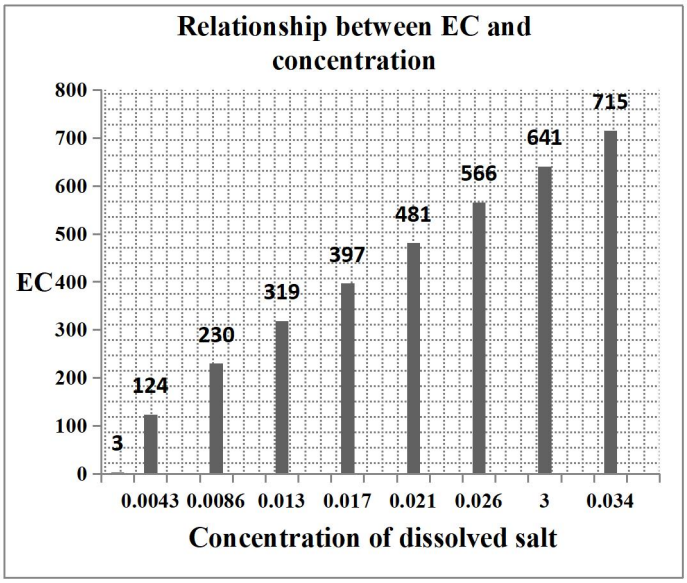

Figure (28): Relationship between EC and concentration.

As present in the figures (40,41,42) and table (10) was noticed slowly decrease in pH at each hour Naproxen salt solution was exposed under UV Lamp through six hours (inverse proportional). While for EC and TDS a little increase was noticed after exposure (direct proportional between EC, TDS and exposure under UV lamp). These variation and changes in values was result of breaks of salts particles.

Table (10): Values of pH, EC and TDS of Naproxen solution after UV exposure.

HOURS	pH	EC (µS/cm)	TDS(PPM)	Wt.(mg)
0	6.5	106	53	100
1	6.5	108	54	100
2	6.4	110	55	100
3	6.3	115	58	100
4	6.2	115	58	100
5	6.1	117	59	100
6	6.1	120	60	100

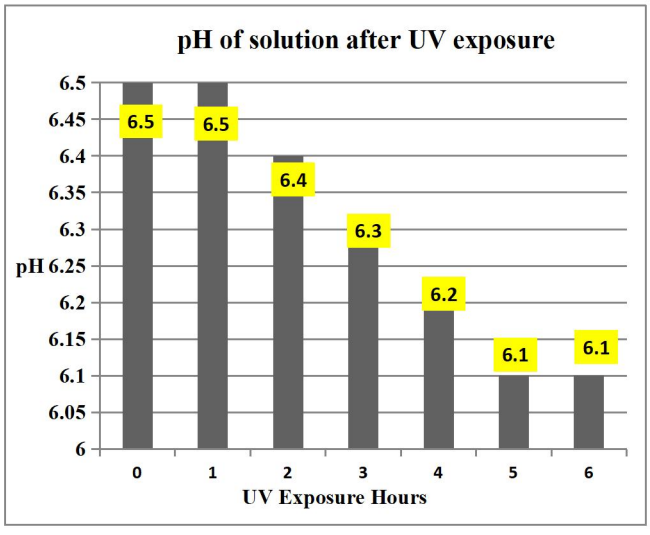

Figure (29): pH of Naproxen solution after UV exposure.

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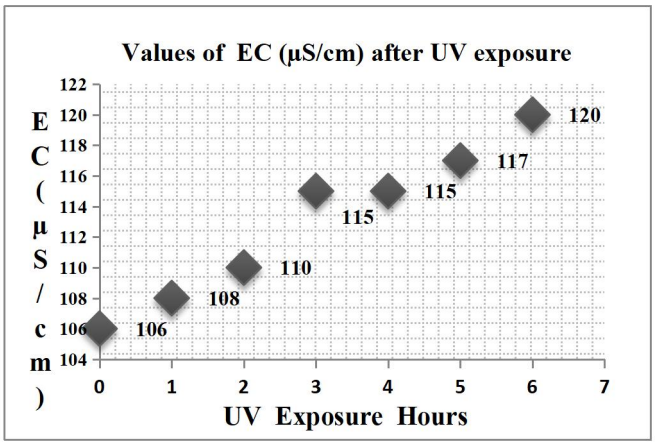

Figure (30): Values EC of Naproxen solution after UV Exposure.

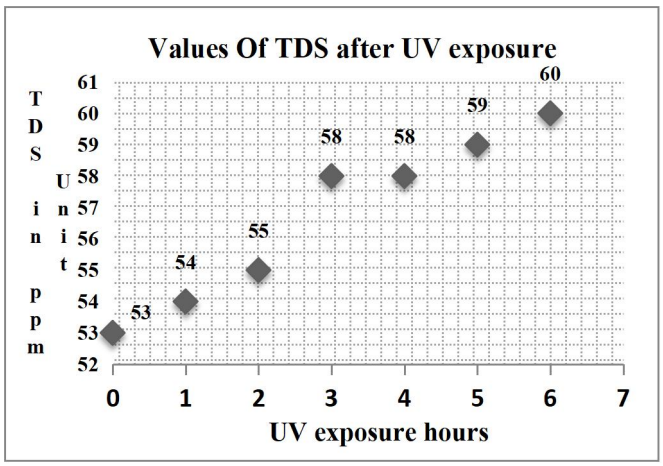

Figure (31): Values of TDS in ppm unit after UV exposure.

CONCLUSION

In this study we done four experiment, started by separation of the active ingredient (Naproxen) from tablet dosage form by using ether where concluded that the ether was best choice for separation method by using separatory funnel for its low density ,solubility of drug in it and low solubility of free Naproxen in water.2nd measuring electrical conductivity ,TDS and pH for different concentrations of pure Naproxen in solution and were conclude that the conductivity and TDS values increase with increasing drug concentration where their marked increase in linearity was found along the curve and relationship between EC and concentration was determined. 3rd measuring was determining concentration and drew the curve of pH of drug through acid bas titration between API (Naproxen) and NaOH at the end obtained the desired curve and determine the concentration of Naproxen. 4th study was focusing on the effect of UV rays on Naproxen through taking 100mg of Naproxen crystal powder with 4ml of NaOH ,50ml of water and 50ml of ethanol then exposed for different time periods at that conclude that EC, TDS and pH values change by increase time of exposure as result of breaking down of Naproxen salts. The conduct trimetric technique was helpful to understand the effect of sun rays on drug through process of shipping, which could affect the quality of drugs, the exact amount of drug available on tablet dosage form through electrical conductivity and protect the environment form expire by extracting API from it.

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 this measurement 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.

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