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Extraction of the Active Pharmacological Ingredients from Ibuprofen, Tetracycline, Naproxen and Ketofane Drugs

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Abstract— ***This study aimed to determine the extraction of active pharmaceutical ingredients from ibuprofen, tetracycline, naproxen and Ketofane. These experiments were conducted in the laboratories of the International University of Cyrene The concept of drug recycling is demonstrated by recovering active pharmaceutical ingredients from unused tablets and capsules. The process included liquid-solid extraction, filtration, and crystallization. The active pharmaceutical ingredients were up to standard. In the experiment a mortar and pestle was used to crush 3 tablet of Naproxen , Ibuprofen , Tetracycline , Ketofane the used 35ml of Acetone , Ethyl-acetate , Diethyl-ether and 10ml of distilled water (1:1) as solvent , stirrer to enhance solubility and separatory funnel for extraction process then dried at room temperature 25°C for 7-10 days . melting point or solubility apparatus was used to confirm identification of the pure sample of Naproxen , Ibuprofen , Tetracycline , Ketofane and Acetone , Ethyl-acetate , Diethyl-ether titration to determine Separation of the active substance of it . The results presented showed a formed crystal of pure Naproxen , Ibuprofen , Tetracycline , Ketofane after 7-10 days , for purity identification separation apparatus was used . in the last measurement viewed change in drug solution values Ibuprofen (85%,70%,75%) , Tetracycline (51%,36%,49%), Naproxen (no-pain)(80%,65%,70%) , Ketofane(79% ,64%,69%) where use as solvents Acetone , Ethyl-acetate , Diethyl-ether .***

Keywords- ***Ibuprofen, Tetracycline, Naproxen and Ketofane Drugs***

I. INTRODUCTION

A. Green chemistry:

The current raise of living standard leads to the demand for more intricate and numerous consumer products, which in turn generates more wastes over time. Circular economy has gained traction recently as the answer to this challenge. Waste materials or part of them is recycled back as the raw materials to make the same or different products, forming a closed-loop system. A term of urban mining was coined, which refers to the huge amount of waste in the cities containing a lot of unseen valuable substances ready to be mined. Usually, this concept refers to the scrap metals in daily utensils, rare earth metals in electronics, plastics, papers, glass, and many more. One of the probably forgotten waste is the unused, unwanted, or expired drugs. They often end up being disposed as household trash, flushed down the toilet, or thrown out into an incinerator.

A.1 Previous attempts toward the drug recovery:

Pharmaceutical pollution has already occurred in the surface,3−8 ground,5,9−11 and drinking water,12 among which some of these problems may be attributed to the improper disposal practices. Even worse, resistant bacteria may also emerge because of the presence of antibiotics in waste water.13 There were several attempts to overcome the waste drug problem. For the unexpired drugs, some drug collecting and reusing programs have already been initiated in several places.1,2 However, no known attempt has been put forth to recycle expired medications. It has been reported that many drugs still retain their potency years after their expiration dates.14,15 Despite that, almost all of the expired drugs ended up being destroyed in reality.16 The US Food and Drug Administration (FDA) recommends the proper disposal of expired drugs because of the concern of health concern risks and drug abuse.17 Apparently, the best way to deal with drug waste is by isolating the active pharmaceutical ingredient (API) from the excipients in unused drug products such as drug tablets and capsules. The API is the most valuable component in a drug product and often causes greater environmental impact than the excipients do. Recycling the unused drugs will recover the APIs in their pure forms, which can later be reformulated into new drug products. In addition, recovering APIs is economically more attractive than synthesizing APIs from scratch because of the former having

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less-tedious and less-expensive chemical steps. A previous study in drug recycling was conducted by recovering an undisclosed API from tablets with known excipient contents and compositions by solid−liquid extraction, membrane separation, and anti-solvent crystallization.18 The process outlined in this study could give high recovery yield (>91%) and purity (>99%). Unfortunately, the feasibility of using this process to recover other types of APIs was not being explored.

In other research work, (R, S) -(±)-ibuprofen was recovered from commercial tablets with known excipient contents but unknown compositions by solid−liquid extraction using ionic liquid and citrate buffer followed by anti-solvent crystallization.19 A very good extraction performance was achieved owing to the use of an ionic liquid−water citrate buffer mixture, resulting in a remarkably high recovery value (~98%). Unfortunately, this process suffered from low purity (70−80%).

These aforementioned research studies either dealt with the drugs with known excipient compositions18 or the drugs of only one brand.19In reality, almost all of the medications sold in the market are often manufactured by different manufacturers and formulated under different brands and each brand comes with different excipient contents and compositions.

Usually, the label in the drug product mentions the API content and its dose, but the information about its excipients is often obscure. Sometimes, manufacturers only mention the name of the excipients in the label without their compositions being mentioned, but in some cases, no excipients were listed at all. These inconsistencies among manufacturers have made API recovery from drug products challenging. Dhanang. E. P et. al established a protocol for recovering APIs from unused tablets and capsules irrespective of their excipient contents and compositions. The developed process was mainly based on solid−liquid extraction, filtration, and crystallization. Because of the importance of product safety, all of the solvents used for the API recovery belong to the class 3 (solvents with low toxicity) and class 2 (solvents for limited use) solvents according to the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) classification.20

Three model drugs were selected: (1) acetaminophen, an analgesic and fever reducer; (2) tetracycline Hcl, an antibiotic; (3) (R,S)-(±)-ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID). The molecular structures of the APIs are depicted in Figure I.

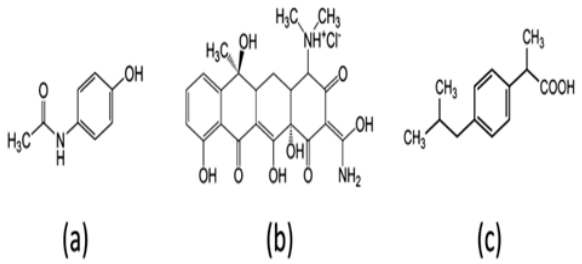

FIGURE I. *Molecular structure of the APIs recovered in this study: (a) acetaminophen, (b) tetracycline HCl, and (c) (R,S)-(±)-ibuprofen*

All of the experiments used mixtures of two or more brands at once. All the drug products that used had clear labels. If not, the recovery yield will be impossible to determine. Overview of the API Recovery Process. The API recovery process comprised three core unit operations: solid−liquid extraction, filtration, and crystallization, with comminution and rinsing as additional unit operations that could be employed if necessary, depending on the nature of the drug waste. The schematic diagram of the API recovery from solid dosage forms is shown in Figure II

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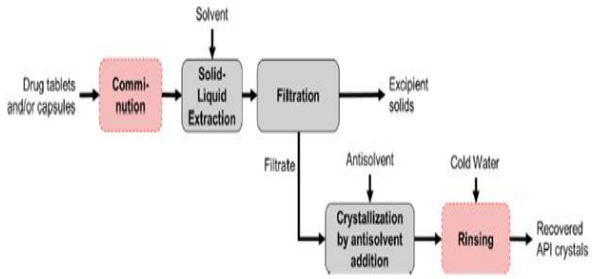

FIGURE II. *Flowchart of the API recovery process from solid dosage forms drugs (gray: core unit operations, red: optional unit operations).*

In the first unit operation, the drug tablets or capsules were charged into a solvent capable of dissolving the APIs but not for most of the excipients. To find out the best solvent, initial

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solvent screening has to be performed first. The ideal solvent used for the solid−liquid extraction should act as a "good solvent" for the API and as a "bad solvent" for as many excipients as possible.

Once the solid−liquid extraction is finished, the next step is to separate the solution phase from the undissolved excipients. Both filtration and centrifugation are capable of separating the suspended particles from the mother liquor, but filtration is more scalable than centrifugation. For filtration, successive filtration from larger to lower filter pore sizes may be necessary to minimize early clogging.

The last important step is crystallization by anti-solvent addition, that is, addition of another solvent in which the API substance has a poor solubility. This second solvent can be selected among the "bad solvents" from the initial solvent screening. It is introduced slowly into the extract solution. Upon the addition of the anti-solvent, the API crystals will precipitate until the anti-solvent has reached a certain volume in which no more crystals will precipitate out. It should be noted that the extract solution might contain some amounts of dissolved excipients, especially when the solvent used for extraction was also a "good solvent" for the excipients.

Nevertheless, in almost all of the cases, the proportion of the API in a tablet or capsule is far greater than the amount of any individual excipient, and the volume of the solvent used in the solid−liquid extraction step is near the saturation of the API but at the under saturation of any individual excipient. Therefore, anti-solvent addition will only precipitate the API but not the excipients. As illustrated in Figure 3, upon the addition of the anti-solvent, the API reached the saturation point (point 1 → 2), and continual anti-solvent addition led to the precipitation of API crystals (point 2 → 3).

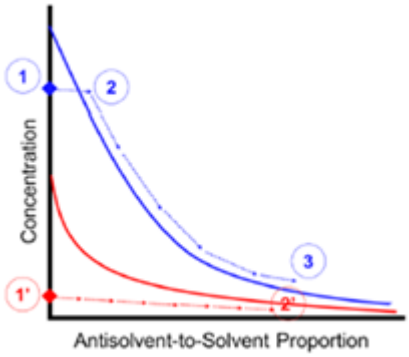

Figure III. *Solubility curves of the API (blue solid line) and the excipient (red solid line). Concentration change of the API (blue dashed arrows) and the excipient (red dashed arrows) upon the addition of the anti-solvent. Blue and red diamonds represent the initial concentrations of the API and the excipient before the addition of the b anti-solvent, respectively.*

On the other hand, the excipient started in an unsaturated concentration; as more anti-solvent was added, the excipient concentration would become more dilute and never reach the Saturation point (point 1′ → 2′).

In addition to these three core unit operations, other unit operations may also be added if necessary. For example, comminution may be performed prior to the solid−liquid extraction, by either grinding or cutting. This step may be omitted in the case of tablets because in the solid−liquid extraction process, the tablets are readily disintegrated, but for capsules, it may be important to dislodge the drug granules from the capsule matrix and expose them to the extract-ant. Rinsing the API crystals with cold water right after the anti-solvent crystallization step is capable of removing the residual solvents and some common water-soluble excipients. Rinsing should be done with caution as it may lead to the lowering of recovery yield-or, worse, the decomposition of the API.

Dhanang. E. P *et al* mapped the suitable solvent(s) for performing the API recovery, all the solubility values of the APIs and excipients were examined under the 23 selected common solvents at 25 °C and 1 atm. The sheer number of excipients and the variations in the contents and compositions among manufacturers made the solubility measurements of excipients immensely tedious. Therefore, only some of the common excipients were chosen as the representatives:

α-lactose monohydrate, α-cellulose, and starch were diluents/fillers;[21−25] α-cellulose and starch were isintegrants;[21−23,25]starch and magnesium stearate were tablet lubricants;[21,22,26]starch and hydroxypropyl cellulose were powder binders;[25,27]hydroxypropyl cellulose was a coating material;[27]ascorbic acid, butylated hydroxyanisole, and citric acid were antioxidants; [21,28,29]and anhydrous citric acid was an acidifying agent.[21]Following the criteria of Lee et al.,[30]a solvent was regarded as a "good solvent" of a material if it is capable to dissolve the material with the minimum solubility value of 5 mg/mL; otherwise, it was regarded as a "bad solvent". The results for the APIs and the selected excipients were summarized in the form space (Table I) and the detailed values are listed in Table S1.

TABLE I. *Form Space of Acetaminophen, Tetracycline Hcl, (R,S)-(±)-Ibuprofen, and the Representative Excipients, Showing the Solubility of Each Compound in 23 Common Solvents A*

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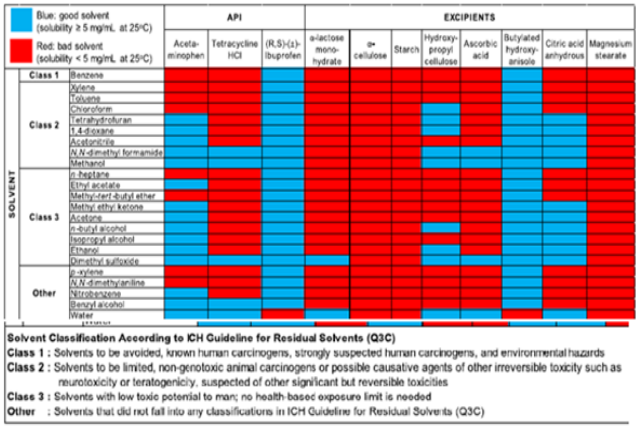

for Pharmaceuticals for Human Use (ICH) guidelines for residual solvents.[20]Ideally, all of the solvents and anti-solvents used should be class 3 solvents (i.e., solvents with no hazard for human consumption at levels normally accepted) or, if it was not possible, class 2 solvents (i.e., solvents to be limited in pharmaceutical products because of their inherent toxicity) could be considered. Class 1 solvents should be avoided at all costs.

For acetaminophen, there were 15 good solvents and eight bad solvents. Being the safest solvent, water was considered to be an excellent candidate as a good solvent, but it is also known to dissolve some polymeric binders commonly used in tablets, such as hydroxypropyl cellulose, as can be seen in Table I.

IPA was eventually chosen as the good solvent despite its ability to dissolve some excipients (i.e., butylated hydroxyanisole and citric acid anhydrous). These excipients were antioxidants, which only existed in trace amounts, and could be removed during the crystallization step, as illustrated in Figure 3. The selected anti-solvent for crystallization was n-heptane. From the solubility curve in Figure S1, the inflection was hardly distinguished. A concentration of 80% (v/v) n-heptane in IPA was decided to be the best ratio for inducing acetaminophen crystallization on one hand, without taking up too much vessel volume by the anti-solvent on the other.

There are five “good solvents” for tetracycline Hcl: DMF, methanol, MSO, benzyl alcohol, and water. Water was omitted because it could dissolve capsule shells and create problems in filtration and crystallization. DMF, DMSO, and benzyl alcohol all have a high boiling point and low volatility, making them difficult to remove by drying. Therefore, methanol was the only viable choice, and despite being a class 2 solvent, it is easy to remove by drying. For the anti-solvent for crystallization, seven relatively safe “bad solvents” were considered: ethyl acetate, MTBE, acetone, MEK, IPA, acetonitrile, and THF.

From preliminary tests, none of these anti-solvents could precipitate tetracycline HCl from its methanolic solution in a reasonable proportion except for MTBE. Although the solubility of tetracycline HCl in the methanol−MTBE co-solvent with a volume ratio of 40:60 was already low (Figure S2), the amount of tetracycline HCl precipitated was quite less. The methanol-to- MTBE volume ratio which gave the highest crystallization yield was 17:83 (Figure S2). Because of the lack of choices, this solvent−anti-solvent combination of 17:83 was used. All of the solvents acted as good solvents for (R,S)-(±)-ibuprofen, except water. Among all of the class 3 solvents, n-heptane, ethyl acetate, and MTBE seemed to be good choices, as they dissolved less amounts of excipients. However, they could not be used because of their immiscibility with the only anti-solvent for (R,S)-(±)-ibuprofen, water. Acetone was eventually selected because it was a common class 3 solvent, miscible with water, and easy to remove by drying. The optimal acetone-to-water volume ratio giving a high crystallization yield was about 45:55 (Figure S3).

In general, the use of water as an extract-ant may lead to some problems. Most of the polymeric excipients, such as binders and capsule shells, dissolve and/or get swollen in water. This type of a behavior will make the extract impure and viscous. Solution thickening is problematic for liquid−solid separation. Eventhough some polymeric excipients can be precipitated out by raising the temperature of the aqueous solution above their cloud points (e.g. hydroxypropyl cellulose has a cloud point of 45 °C18), in the case of a batch operation consisting of a mixture of drug products with many unknown excipients, the cloud points are difficult to be determined.

Furthermore, some polymeric excipients, such as methylcellulose and hydroxypropyl methylcellulose, undergo gelation upon heating.[31]More importantly, heating can sometimes decompose heat-sensitive APIs, such as tetracycline.[32]Ultrafiltration was reported to remove the dissolved known polymeric excipient in water,[18]but in our case, the overall process would have been much simpler if the problems associated with the dissolution of many types of unknown polymeric excipients in water can be avoided from the beginning.

Only eight excipients are evaluated in Table 1, even though the number of excipients is many more in reality. These eight excipients have adequately represented the other commonly used excipients. In general, there are two types of excipients in our processes: (1) insoluble in the extract-ant and (2) soluble in the extractant. The extract-ant-insoluble excipients are separated as solids during filtration, whereas the extract-ant-soluble ones are removed upon the crystallization of the API because of the relatively low concentrations of excipients as opposed to the high concentration of the API, as outlined in the concept in Figure III. Additionally, traces of impurities which may be present on the API crystal surfaces (e.g., colorants) can be adequately removed by rinsing (see Figure II). These excipient removal measures should be sufficient enough to produce the recycled API with a high purity.

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A.3 The aim of our study:

In order of getting advantage of this study, we worked on four widely used drugs in the Libyan pharmacies, ibuprofen 600, tetracycline 500, no-pain 500, and Ketofane Figure **IV.**

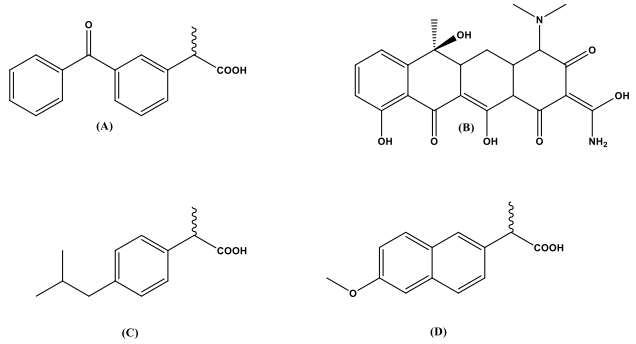

FIGURE IV*: Molecular structure of the APIs recovered in this study: (a) Ketoprofen, (b) tetracycline HCl, and (c) (R,S)-(±)-ibuprofen, (d) (R,S)-Naproxen*

A.2 Ketofane

Ketofane Tablet is a **pain-relieving medicine**. It is used to treat conditions such as painful flare-ups of rheumatism, arthritis, strained muscles and tendons, and gout. It also used to treat other painful conditions of the bone or muscle and pain and inflammation following orthopedic surgery.

A.3 Tetracycline

Tetracycline is an antibiotic that fights infection caused by bacteria. Tetracycline is used to treat many different bacterial infections of he-skin, intestines, respiratory tract, urinary tract, genitals, lymph nodes, and other body systems. It is often used in treating severe acne, or sexually transmitted

A.4 (R,S)-(±)-ibuprofen

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID). It works by reducing hormones that cause inflammation and pain in the body. Ibuprofen is used to reduce fever and treat pain or inflammation caused by many conditions such as headache, toothache, back pain, arthritis, menstrual cramps, or minor.

A.5 (R,S)-Naproxen

Naproxen may be available in the countries listed below. Ingredient matches for Naproxen Meclozine is reported as an ingredient of Naproxen in the following countries: Egypt. Pyridoxine is reported as an ingredient of Naproxen in the following countries: Egypt. The solvents that used for separation were ethyl acetate, acetone and dimethyl ether. A limited number of drugs and solvents were used, because of our inability to obtain many of the required solvents, so we were satisfied with using the aforementioned solvents. The physical properties of the chosen solvents are shown in **Table II**.

Table II: *The physical properties of the chosen solvents*:

Physical properties / Solvent	Dielectric constant (Ɛ)	**Boling point °C**	Miscibility with water
Acetone	20	56	miscible
Ethyl acetate	6.0	34	immiscible
diethyl ether	4.0	77	immiscible

The physical properties of the three solvents exhibited that; acetone is the only solvent among others that is miscible with water. This property may cause the decreasing of the API recovery. The dielectric constant for acetone is the highest which my lead to extra solubility for the API in acetone.

II. METHODS AND MATERIALS

A. The experiment:

1-The weight of the pill or capsule. 2-Weigh 3 pills before grinding or 3 capsules before emptying. 3-Grind 3 grains or empty 3 capsules. 4- Weighing after grinding or unloading.
5-We add 30 ml of solvent to the sample the mixture for stir 5min and add stirm. 6-If there is a precipitate, add 5ml of sample and stir for another 5 min, so that the total amount of solvent added become 35ml. 7-Filtration or filtering the mixture to separate the insoluble substance in the solvent from the active substance dissolved in the solvent.
8-We add 10 ml of distilled water after filtering to the mixture. 9- We calculate (%) of the sample from following equation: (Test percentage = taste weight (Fail) /Weight after grinding * 100). .

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III. RESULTS AND DISCUSSION

The separated percent of the four drugs are shown in Table 3 and illustrated in Figure V, VI

Table III: *The extraction percent of the three drugs:*

Medicine / solvent	Ibuprofen 600	Tetracycline 500(Turkey)	Nopain 500(UK)	Ketofan50 (Egypt)
Ethyl acetate	85%	51%	80%	79%
Acetone	70%	36%	65%	64%
ether	75%	49	70%	69%

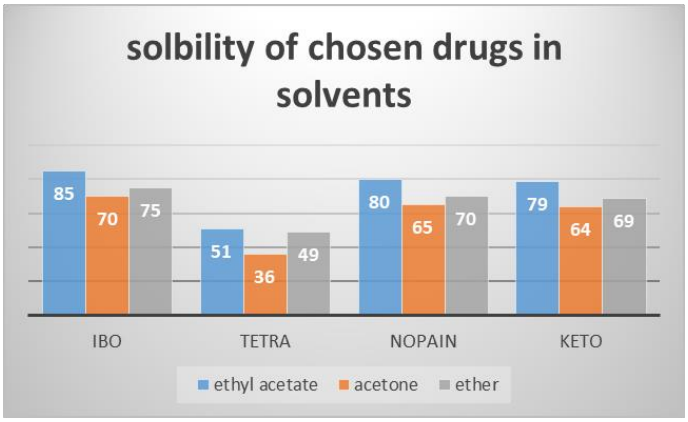

Figure V: *The percent of the three drugs*

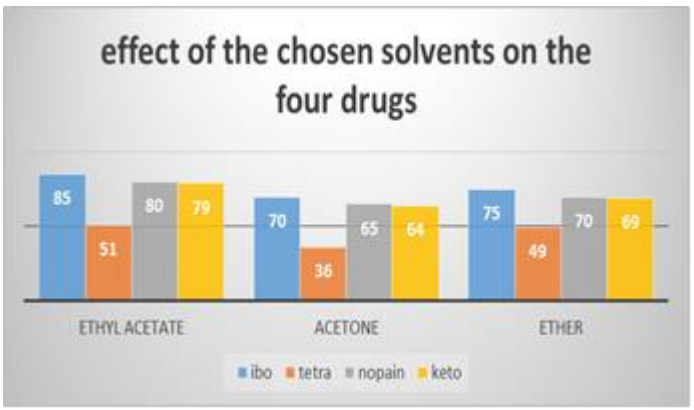

Figure VI: *The solvents extraction*

Based on the results shown in **Table III** and **Figures V, VI** which illustrate the following:

As for the ibuprofen compound, the highest separation percent was with the ethyl acetate and the lowest with acetone. The reasons are due to several factors, ibuprofen contains some polarity on the carboxylic acid side, which helped it dissolve in ethyl acetate, which has dialectical constant of six. This makes the solubility of ibuprofen higher in ethyl acetate than in ether. However, what makes the percentage of ibuprofen in ethyl acetate higher than that of acetone, although the dielectric value of acetone twenty, which is higher than ethyl acetate as shown in the table? Acetone has a high solubility in water, which reduced its ability to extract the active substance from water.

Tetracycline is isolated mostly by ethyl acetate. As shown in figure 3, the percent of tetracycline that isolated by the three solvents are 51,36 and 49% by Ethel acetate, acetone and ether respectively. The differences in percent is for the same reasons that explained in ibuprofen. The same dissolving behavior will be observed with both naproxen and Ketofane, which were further extracted by ethyl acetate, then ether, and finally acetone, as shown in the two figures.

IV. CONCLUSION

The four drugs were extracted with different percentages from excipients by three different solvents such as ethyl acetate, acetone and ether. The results showed that the best separation occurs with ethyl acetate, although the electronic separation of acetone is the highest, but the high solubility of acetone in water reduced the percentage of its separation of the active substances.

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