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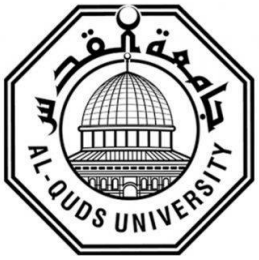

Topical Tenoxicam Microemulsion and Co-crystal

Maha Mohammad Mosa Othman

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Prepared by:

Maha Mohammad Mosa Othman

B.Sc. Chemistry and Chemical Technology Al-Quds University - Palestine

Supervisor: Prof. Ibrahim Kayali

Co-Supervisor: Dr. Mohammad Abul-Haj

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Prepared by: Maha Mohammad Mosa Othman

Registration No: 21520166

Supervisor: Prof. Ibrahim Kayali

Co-Supervisor: Dr. Mohammad Abul-Haj

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The name and signature of examining committee member are as follows:

1- Head of Committee: Prof. Ibrahim Kayali Signature: .....

2- Co-Supervisor: Dr. Mohammad Abul-Haj Signature: .....

3- Internal Examiner: Dr. Mahmod Alkhatib Signature: .....

4- External Examiner: Dr. Michel Hanania Signature: .....

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Dedication

This thesis is dedicated to my father, who has never failed in a day to help and support me, and to give me the high trust of myself, my mother, who is constantly in giving, love, and the most loyal friend to me, to my brothers, and sisters in supporting and helping me all the time to be the best in my life.

To Mr. Maher Al-Jamal, who was in the first place as a brother and a teacher to me, the person who supported me to success this work, his moral and scientific support for me.

To my dearest doctors, Dr Ibrahim Kayali, and Dr Mohammad Abul-Haj, and all doctors in "Applied Industrial Technology Program", to my best friends, my dearest colleagues, to my loved home land Palestine.

Maha Mohammad Mosa Othman

Declaration

I certify that this thesis submitted for the degree of Master, is the result of my own research, except where otherwise acknowledged, and that this study (or any part of this study) has not been submitted for a higher degree to any other university or institution

Signed: ……

Name: Maha Mohammad Mosa Othman

Date: 17 / 11 /2019

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Abstract

This research targets to form a-topical Tenoxicam microemulsion by using different combinations of lower amount of Tweens to stabilize the system. In this work, sugar surfactant is used, such as Tween 80 (Polyoxyethylene (20) sorbitan monooleate). Also, co-surfactant with short chain of alcohol like propylene glycol is used. The oil phase used is castor oil and oleic acid. The aqueous phase used is the Tenoxicam dissolved in 0.1NNaOH (water phase). Moreover, the study aims to prepare a co-crystal of Tenoxicam as the active pharmaceutical ingredient, by using different co-solvents.

In this work, we studied at various temperature 25, 37 and 45°C, the impact of adding different amounts of surfactants on the phase behaviour of the suggested system like Tween 80. On other hand, it showed the effect of co-surfactant used (propylene glycol) on the phase behaviour. Propylene glycol is used as tuning parameter for all ingredients and clearly contributes in forming the microemulsion. The phase behaviour started as clear, isotropic microemulsion upon the addition of as low as 4% water. This was analysed by visual inspection and cross polarizer and dynamic light scattering. Lastly, this study indicates a successful development of microemulsion formulations of Tenoxicam with optimum characteristics.

In this research a study of co- crystallization with different diacids in various solvents were done by using grinding techniques. The co-crystals produced here studied by using Fourier Transform Infra-Red spectroscopy (FTIR), determination of the melting point and solubility. The melting point of co-crystal changed to lower than pure Tenoxicam. The co-crystals solubility showed a wide change from practically insoluble in water to soluble.

Table of contents

List of tables:

List of figures:

List of appendices:

Abbreviations, Symbols and Terminology:

DSC	Differential Scanning Calorimeter
DMSO	Di methyl Sulfoxide
DMF	Di methyl Formamide
NSAID	Nonsteroidal Anti-Inflammatory Drugs
3D	Three Dimension
HLB	Hydrophile Lipophile Balance
L1	Spherical normal micelle
L2	Reversed micelle
CMC	Critical Micelle Concentration
O/W	Oil in Water
W/O	Water in Oil
NMR	Nuclear Magnetic Resonance
API	Active Pharmaceutical Ingredient
FTIR	Fourier Transform Infra-Red
PG	Propylene Glycol

Chapter one

Introduction

1. Introduction:

1.1 Microemulsions:

They are clear, transparent by microscope, low in viscosity, thermodynamically stable, water and oil dispersions that would be stabilized by using surfactants and co-surfactants. The term "microemulsion" means thermodynamically stable isotropically clear dispersion of two immiscible liquids, like oil and water, they are stabilized by an interfacial thin film of surfactant molecules. A microemulsion is rated to be a thermodynamically stable liquid dispersion of an oil phase and water phase, with the combination of a surfactant. The dispersed phase usually included small particles, with a size range of 5 nm-200 nm, and has very low interfacial tension of (O/W). Microemulsions are transparent, with the reason of that the droplet size is less than 25% of the wavelength of visible light. Microemulsion can be produced readily and spontaneously, sometimes without needing high-energy input [1, 2].

Three types of microemulsions could be formed according to their composition:

1- Oil in water microemulsions, the oil particles are dispersed in the continuous aqueous phase, (O/W).

2- Water in oil microemulsions, the water particles are dispersed in the continuous oil phase, (W/O).

3- Bi-continuous microemulsions, the micro ranges of oil and water are inter dispersed inside the system.

The three types of microemulsions, the interface is stabilized by using surfactants and/or co-surfactants as shown in **Figure. 1** [3]**.**

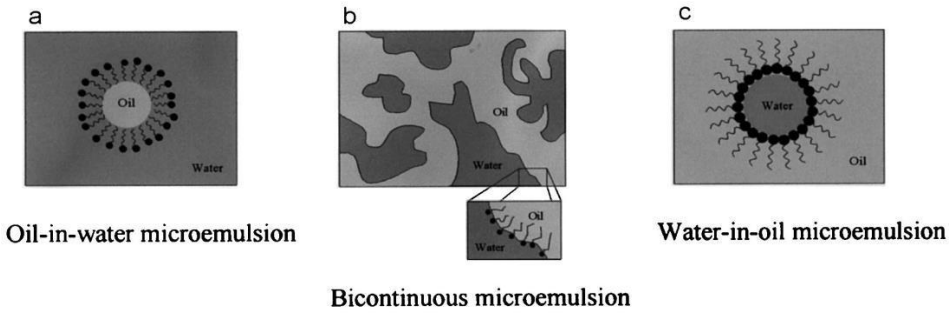

Figure. 1. emulsion micro structures:
(a) Oil-in-water, **(b)** Bi-continuous, and **(c)** Water-in-oil microemulsion

It is common that, the oil and water are not miscible together at the surrounding temperature (ambient temperature); it needs a certain quantity of surfactant to solubilize them [3]. It is known that, the **non-ionic** surfactants are selected because of their good skin tolerance, low in irritation potential and toxicity, for example Poly sorbate 80 (Tween 80). Some of co-surfactants such as ethanol, propylene glycol are being important in the formulation of microemulsions [4].

Microemulsion formulation has to be critical and strict in production, because of the high number of degrees of freedom in any practical case [5].

Benefits of microemulsion over other dosage forms:

1- Increasing the rate amount of absorption.
2- Decreasing variability in absorption.
3- Powerful in solubilizing lipophilic drug.
4- Adding an aqueous dosage form for water insoluble drugs.
5- Increasing bioavailability.
6- High effectivity in penetration of the drug moiety.
7- Powerful in taste masking.

8- Protect drugs in oil phase in O/W microemulsion from hydrolysis and oxidation.

9- Decreasing the amount of energy formulation requirement [6].

1.1.1 Microemulsion as drug carrier system:

One of the most important characters of microemulsions, they increase therapeutic efficacy of the drug and reduce the volume of the drug delivery vehicle, thus, decreasing toxicity side effects. The existence of surfactant promotes the permeability of the cell membrane, which increases the rate of absorption. Moreover, to these advantages, microemulsions could be administered to patients having problems swallowing solid dosage forms [6,7].

1.1.2 Method of drug delivery system:

The use of microemulsions as drug delivery system has a wide range area of researches because of its amazing uses and benefits. Microemulsions supply powerful carrier system for drug delivery with the reason of their stability, lower viscosity, high solubilization capacity, transparency, easy in preparation, and high rate of diffusion and absorption with the comparison to solvent without the surfactant system [8].

1.1.3 Topical drug delivery:

Topical drug delivery microemulsions could improve the transdermal drug delivery by the following effects:

Microemulsions can provide highly solubullization ability to each lipophilic and hydrophilic drugs, high quantity of drug can be loaded to the microemulsion, thus, increases the concentration through the skin. The internal phase provides a constant driving force of drug from the external phase to the skin and extends absorption. Thus, with the diffusion of the drug to the skin provided from the external phase of the microemulsion, the internal phase continuously keeps drug to the external phase which makes it saturated with the drug [9].

Applications of topical microemulsions:

Microemulsions are offering delivery systems that enhance controlled or sustained drug release for topical, per oral, percutaneous, and transdermal administration. Increasing absorption of drugs, and limited the toxicity, are several advantages in the delivery process, some of these applications:

1- Antifungal.

2- Antiviral.

3- Antioxidants [10]**.**

1.1.4 Factors impacting drug release:

1- Amount of drug:

The large amount of drug integrated in the internal phase provides the development of a concentration gradient between the internal and external phase, increasing the thermodynamics of the drug and providing the diffusion of drug from the internal phase into the skin layers [11].

2- Type and amount of surfactant:

There are different kinds of surfactants used in the topical microemulsions, for example oil in water or water in oil. The non-ionic surfactants are favorited than the anionic or cationic surfactants, because of their low irritation and toxicity on the skin. There is an inverse relationship between the amount of surfactant and drug permeation, when increasing the amount of surfactant, the thermodynamic activity of the drug system reduces [12,13].

3- Amount of alcohols:

Alcohols are used as skin penetration enhancers, and they are able to lower the microemulsion melting point and have been known to disorganize the stratum corneum lipid structure, enhancing the partitioning and permeation of drugs [14,15].

4- Amount of water:

At low water concentrations, all water molecules are used in hydrating the polar heads of the surfactant molecule leaving no free water available for hydrating the stratum corneum, thus affecting the permeation of both lipophilic as well as hydrophilic drug that provides a strong force to push the drug molecules across skin layers [16,17].

1.2 Surfactants:

They are surface active agents with organic compounds contain at least one lyophilic (solvent-loving) group and one lyophobic (grease-loving) group in the molecule. When the solvent contains surfactant is water or an aqueous solution, then it is named as hydrophilic "water loving" and as hydrophobic "grease loving". As a result, a surfactant contains at least one non-polar group and one polar (or ionic) group, as shown in **Figure. 2** [18].

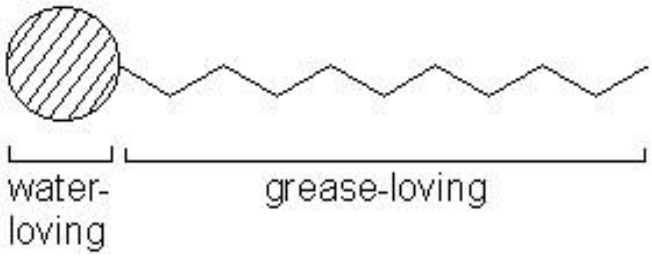

Figure. 2. Surfactant molecule

1.2.1 Surfactant film properties:

The mechanical features of a surfactant film of oil/water interface can be characterized by three constant phenomenological: tension, bending rigidity, and spontaneous curvature.

Because they depend on the restrictions sensed by the film. These parameters control the interfacial stability of the surfactant films which monitoring the thermodynamic properties of microemulsions. This study includes phase behaviour, stability, and solubilisation ability. The classification of surfactant is based on the nature of the hydrophilic part (head), and the nature of the hydrophobic part (tail) [19].

1.2.2 Types of surfactants used to stabilize drug systems:

The ionic and non-ionic surfactants combination is favourite, because of their effectivity in increasing the range of microemulsion region.

1. **Non-ionic surfactants:** the hydrophilic part with no charge, it derives its water solubility from the polar groups such as sugars.
2. **Zwitter ionic surfactants:** amphoteric groups.
3. **Cationic surfactants:** hydrophilic part is a positive charge group.
4. **Anionic surfactant:** the hydrophilic part has a negatively charged group [19].

To choose a suitable surfactant for a certain application, an empirical numbering system found to select the correct type of surfactant. This system is called the 'hydrophile–lipophile balance' (HLB). Therefore, poly sorbate 80 (Tween 80) is selected in this project preparation to achieve the drug product microemulsion formation since it has an HLB=15.0 [19].

1.2.3 Self-assembled surfactant structures:

In aqueous solution dilute concentrations of surfactant act much as normal electrolytes, but at higher concentrations very different behaviour results will be obtained. This behaviour is explained in terms of the formation of organized aggregates of large numbers of surfactant molecules called micelles as shown in **Figure. 3.** In which the lipophilic parts of the surfactants will be associated in the interior of the aggregate leaving hydrophilic parts to face the aqueous medium. Meanwhile, that happens at a specific higher surfactant concentration, known as the critical micelle concentration (CMC). Besides, the physio-chemical properties of surfactants vary markedly above and below the CMC value [20,21].

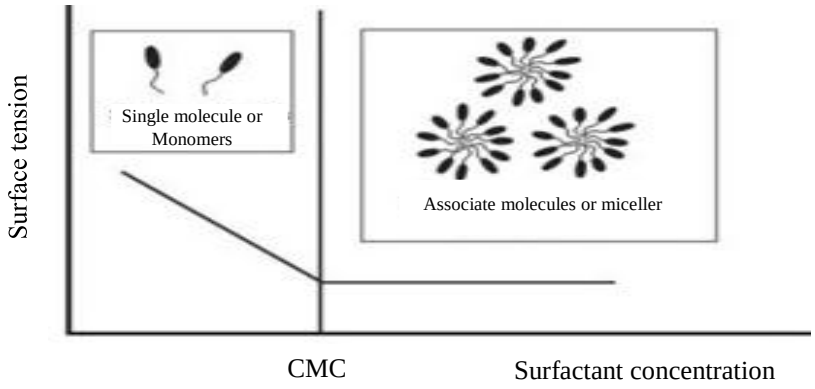

Figure. 3. Illustration of a surfactant micelle

In addition, acting surfactants at oil/water interface forms a large number of self-assembled structures depending on the type of surfactants Spherical normal micelles (L1) are formed at high water content (oil/water), while reversed micelle (L2) are formed at low water content (water/oil), between these two extremes different isotropic and anisotropic liquid crystalline phases with decreased water content or increased temperature or electrolyte concentration may be formed. The following sequence of anisotropic liquid crystalline phase may take place for the surfactant systems as shown in **Figure. 4** [22].

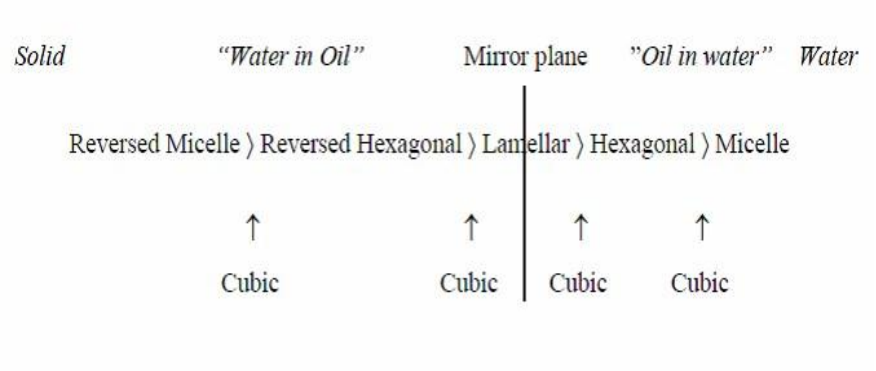

Figure. 4. The idealized sequence of association structures of surfactants

1.2.4 Sugar-based surfactants:

Sugar-based surfactants are characterized by having the hydrophilic sugar head group and the hydrophobic alkyl chain. This structural feature provides unique physicochemical properties to these surfactants. Among the characteristic properties of Sugar-based surfactants, a frequently remarked fact is that they can be produced from renewable resources and exhibit excellent environmental behaviour, certainly, there is currently a clear tendency to replace conventional surfactants with more environmentally good naturally compounds. Although interest in Sugar based surfactant was traditionally, they have recently become the object of increasing attention for many researchers. The behaviour of Sugar-based surfactants is also critically influenced by the nature of the substituent groups that are bounded to the individual monosaccharides. This substituent's can be of natural origin or semi natural quality. Whether they are natural or semi natural, the classification of Sugar-based surfactants falls into one of five categories, based primarily on the polysaccharide charge. These include: anionic, cationic, non-ionic, amphoteric, and hydrophobically modified sugar based surfactants. It is clear from an industrial perspective that only a few carbohydrates fulfill the criteria of price, quality, and availability. Today, one of the most important sugar-based surfactants is sorbitan mono oleate, which is used in pharmaceutical drugs such as polysorbate 80 (Tween 80), see **Figure. 5** [22].

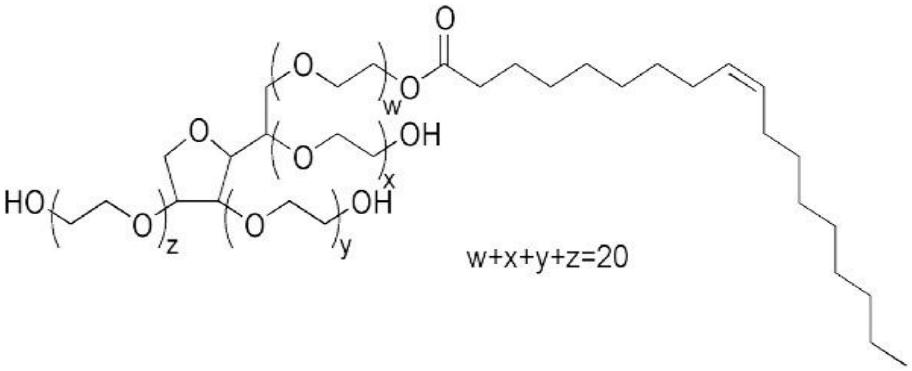

Figure. 5. Polyoxyethylene (20) sorbitan mono oleate (Tween 80)

1.2.5 Alcohol conventional effects:

There are three effects of an alcohol additive in the formulation of microemulsion. At first, it contributes to the general formulation as a co-surfactant slightly hydrophilic contribution for methanol and ethanol; lipophilic contribution for n-butanol and longer linear alcohols. Secondly, as a co-solvent. The alcohol will adsorb with the surfactant at the interface and changes the overall interaction of the amphiphilic film with the adjacent solvents. The longer alcohol chain will give the lower its tendency to act as co-surfactant, because it is partly solubilised in the oil phase. As the alcohol mostly partitions into the water or oil phase it behaves either as a co-solvent, when such alcohol co-solvents are present in small proportion, they might not mix uniformly in the bulk of the oil or water phase and they could exhibit a thirdly effect called lipophilic linker, as shown in **Figure. 5** [22].

1.2.6 Co-surfactants:

They are used in association with surfactants which enable to reduce the interface tension between oil and water to produce a microemulsion. The most used co-surfactants are the medium chain alcohols, which reduce the tension and increase the liquidity of the oil-water interface, increasing the stability of the system upon increasing the entropy for system. Also medium chain alcohols, increase the movement of the surfactants for non-polar tail region, and resulting in stabilizing the system with good formation of a microemulsion [20].

1.3 Co-crystallization:

Co-crystallization changes formation of pharmaceutical ingredients, and the interactions of molecules, it is regarded as one of the best alters to improve the drug properties. The main concept of co-crystallization is to enhance the physical properties of the API in pharmaceutical drugs, for example: solubility, stability and bioavailability, the chemical properties of the API would be the same. Several types of interactions can be constructed

by co-crystallization, like hydrogen bonding, pi-stacking, halogen bonding and Van der Waals forces. Co-crystals offer the relationship between formation and chemical structure of the conformer and API [23,24].

Sometimes solubility, poor rate of dissolution, stability and hygroscopisity have effects on the therapeutic range of many pharmaceuticals drugs, and causes decreasing the value marketing of a drug. Salts can be formed with significant design of new solids in the pharmaceutical area which produced by several component of crystals such as solvates, hydrates, and co-crystals as in **Figure. 6**. In pharmaceuticals the physiochemical properties of API can be optimized by producing co-crystals through co-crystallization method [25].

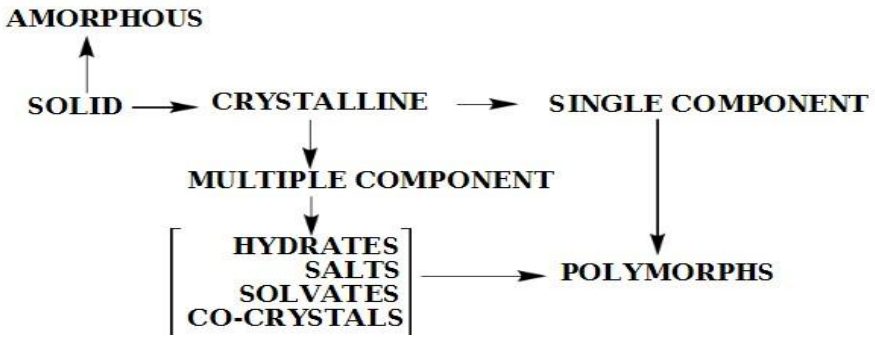

Figure. 6. API solid form classification based on structure and composition

Co-crystallization associated by the competition of molecules between the same molecules (homomers), and different molecules (heteromers). Hydrogen bonds recommended the mainly molecular attraction in the drug systems in pharmaceutical, and they are accountable for the production of networks of molecular with single component crystals and their polymorph (the ability of a solid material to exist in more than one form or crystal structure), or with multiple component crystals in the crystalline state [26].

1.3.1 Pharmaceutical co-crystallization:

Studying physical and chemical property in pharmaceutical helps in thinking to improve these properties by co-crystallization which is similar to the crystal engineering and pharmaceutical sciences [27,28].

Pharmaceutical co-crystallization is a technology used to determine and improve properties of the API in drug systems to increase the chance of producing high number forms of API in drugs. Crystal engineering studies could show that changing the physical and technical properties of a drug ingredient by pharmaceutical co-crystal production improves the performance of a drug with low solubility, increases enhancement of dissolution rate, stability, moisture up take and compressibility without changing their pharmacological configuration [29,30,31].

1.3.2 Co-crystal versus solvates:

They are different in the physical state of the isolated pure ingredients: if one ingredient is a liquid at ambient temperature (room temperature), the crystals are assigned as solvates; if both ingredients are solids at room temperature, the crystals are assigned as co-crystals [32].

1.3.3 Characterization of co-crystals:

Characterization of co-crystals contains both structure which could be analysed by (infrared spectroscopy, single crystal x-ray crystallography and powder x-ray diffraction), and physical properties can be analysed by (melting point apparatus, differential scanning calorimetry, thermogravimetric analysis and solubility test) [33,34,35].

1.4 Tenoxicam chemical structure:

Tenoxicam can be considered as nonsteroidal anti-inflammatory drug (NSAID) for inflammation [36].

It is used for treatment of inflammatory disturbances such as rheumatoid arthritis and osteoarthritis, but it is not favourite by oral route because of gastric ulcers problems that may be produced [37,38].

To remove these undesirable effects, prevent first-pass metabolism, increase patient compliance, and keep the drug plasma level more longer, it supposed to use the transdermal route, thus development of Tenoxicam microemulsion can be used in local treatment of skin inflammation and painful points of the body like bones, joints, and muscles. This development increases the satisfaction of patients through using the topical routes, and increases drug permeation by skin. There are many dermal vehicles including chemical enhancers and solvents to reach these targets [39]. The chemical structure formula of Tenoxicam is shown in **Figure.7**, and the molecular weight is 337.368 g/mol [40]. The melting point is 208-211°C with decomposition. [64].

Figure.7. Tenoxicam chemical structure formula

Chapter Two

2.1 Literature Review

2.2 Problem

2.3 Research objectives

2.4 Hypothesis

2.1 Literature Review:

Microemulsion was first discovered by Hoar and Schulman in 1943. The first microemulsion was prepared by dispersing oil to an aqueous solution containing surfactant and co-surfactant (alcohol), thus produced stable and transparent microemulsion. These microemulsions serve delivery systems which helps sustained and controlled drug release for percutaneous, oral, topical, and transdermal administration [3].

Micoemulsion in the transdermal route administration prevents first-pass metabolism, increased absorption of drugs, decreased toxicity, and increase patient satisfaction are the most goals in this drug delivery process [46, 47, 48].

The microemulsions in transdermal flow proved highly solubilization for each lipophilic and hydrophilic drugs. Thus produced highly thermodynamically stable activity through skin. These microemulsions can play an important role in efficacy of the permeability of the pharmaceutical drug into the skin, they act as transdermal permeation enhancers by changing the structure of the stratum corneum [36, 41, 42, 44, 45].

Tenoxicam is a yellow crystalline powder, practically odourless, it melts with decomposition at (208º - 211ºC) [64].

It is insoluble in water and other organic solvents. In 95% ethanol at 25ºC, its solubility is nearly 0.05 g/100 mL, at 37ºC in water the solubility is about 0.01 g/100 mL, Tenoxicam has nonsteroidal anti-inflammatory and analgesic properties pharmacological behaviour [43].

pKa1= 5.3, pKa2 =1.1, Partition coefficient (octanol/water): 0.3 (pH 7.4); 3.5 (pH 1.2) [67].

Tenoxicam is derived from piroxicam which is used to treat the inflammatory diseases, stiffness, swelling, and painful produced from osteoarthritis, rheumatoid arthritis, backache, and others .Tenoxicam could be found in different dosage forms like tablets,

suppositories and injection. Every dosage form has its limitation combined to patient satisfaction [51].

In addition, microemulsion products were found to be the best in maintaining inflammatory pain comparison to traditional topical dosage forms. On other way, they show highly efficiency equivalent to oral dosage forms. Improving formulation of microemulsion can produce a topical delivery of Tenoxicam which is effective in treatment of different inflammation requirements [51].

The dose of Tenoxicam is 20 mg / day by the oral route. It is distributed to the body tissues poorly because of the nature of low lipophilic characterization, high level in ionization and fully metabolism in liver [52].

To prevent the gastrointestinal tract irritation, decrease the toxicity of any system, easy in administration route, increase the patient compliance and to increase the range of the therapeutic effect, it is found that the skin is one of the most important approach to administrate the drug. Skin is considered the largest organ of the human body which supplies surface area of 1.5-2 m in adults body. To solve problems produced from the skin membranes which serves as barrier that avoids absorption of several drugs, chemical absorption enhancers, preparation of drug delivery systems, and microemulsions formulation are being used. Topical microemulsions were suggested for drug delivery systems for Tenoxicam [49, 50, 53, 54].

In Tenoxicam microemulsion products, which contain ethanol as co-surfactant produced more absorption and flux through the skin than the products which contain propylene glycol. On the other hand, using 10 % oleic acid displayed more flux than the 5 % oleic acid formulations [55].

All researches showed that Tenoxicam has high solubility in oleic acid (0.8 mg/ mL). Oleic acid showed high solubility and permeation capacity for Tenoxicam, which also can serve as permeation enhancer for many other drugs [56].

Microemulsions formulation of Tenoxicam showed high solubility in surfactants of Tween 20 and Tween 80, that were used together with oleic acid and isopropyl myristate (IPM) oils [57].

Surfactants are used to reduce the interfacial tension between two surfaces to a very small value, which produce easy process in dispersion of microemulsion formulations, and forming a thin film can easily deform around the droplets to give correct curvature at the interfacial site. Topical microemulsion of Tenoxicam depends on surfactants and co-surfactants which are used as emulsifying agent and stability oxidative. The nonionic surfactants such as Tween 20 and Tween 80 provide stable microemulsion with adding co-surfactant, like short to medium chain of alcohols. The using of surfactant and co-surfactant in drug delivery system produces very low interfacial tension on the surface. Therefore, spontaneously with a small droplet in diameter of microemulsion. It is predicted that, the nonionic surfactants are more favourite according to the HLB theory, thus, these two ingredients were picked up because of their antioxidant and their emulsifying properties [58].

It is important to have the drug highly soluble in oil phase in the preparation of microemulsion, the non-ionic surfactants are selected because of their less toxicity, such as Tween 80 has been selected because of its HLB value 15, which forms stable microemulsion, the addition of co-surfactant like propylene glycol makes the bending stress lower at the interface and form microemulsion [59].

In co-crystallization the modification of composition and the molecular interactions of pharmaceutical ingredients can produce new drug properties and features. It depends on the API and stoichiometric amount which could be appropriate to co-crystal former [23, 24]. Co-crystallization depends on hydrogen bonding which associate between the API of neutral molecules and other ingredient, co-crystals described of several organic substances by the years, and named as addition compounds, molecular complexes and hetero

molecular co-crystals. Moreover, co-crystals can contain one or more solvent/water molecules in the crystal network [60, 61].

Solubility plays an important role in the therapeutic activity of the drug, in the pharmaceutical industry, the poorly soluble drugs are the most important task for the formulators to increase the patients satisfaction. To solve this problem, many technologies are used to increase the solubility such as microemulsion, self-emulsifying drug delivery system and supercritical fluid strategy. Many factors can influence the solubility of drug, like co-solvent water interaction, particle size reduction, complexes inclusion, dispersion of solid, and polymorph modification. Studies showed that the melting point of 51% co-crystals have melting points between API and conformers, 39% co-crystals have melting points lower than API or conformer, 6% have higher melting points than API and conformer, and 4% have the same melting points to API or conformer [62,29].

Co-crystallization was found at the end of 19^{th} century, by means of discovering the solid state grinding as a method of preparing co-crystal, by adding few amounts of solvent through the grinding, which has been used to increase the kinetics and extends the formation of co-crystal and considering the solid-state grinding as an important method for co-crystal preparation because of its simplicity [63].

The features of co-crystals can be characterized by using: x-ray diffraction, spectroscopic methods such as FT-IR, solid state NMR spectroscopy which is used in differentiation in similar structure with achiral and racemic co-crystals. Co-crystal was formed by targeting the pyridinium NH^+ cation and enolate anion, it produced two conformers of Tenoxicam in the solid state, the co-crystals with weak phenols gives good solubility and dissolution enhancement [64].

Tenoxicam showed poor solubility in water, ethanol, methanol and propylene glycol (<1 mg/ml), the solubility increased with the less polar solvents. Some studies suggested

polyethoxylated castor oil as a good solvent for insoluble drugs. On other hand, Tenoxicam shows good solubility in DMSO with enhancement factor 985 (the ratio of Tenoxicam solubility in 1 ml of solvent / Tenoxicam solubility in 1 ml of water at 25ºCat atmospheric pressure) [67] .

2.2 Problem:

Microemulsions serve delivery systems which help sustained and controlled drug release for topical administration by increasing absorption of drugs, decreased toxicity, and increase patient satisfaction .Thus produced highly thermodynamically stable activity through skin. Moreover, to these advantages, microemulsions could be administrated to patients who have problems with swallowing solid dosage forms. When we develop a process to enhance the solubility of Tenoxicam such as using microemulsion which could be prepared by using a low-energy of emulsification method, based on the phase behaviour. We must use these benefits for microemulsion and work to develop productivity in order to improve the "Palestinian pharmaceutical industry" that increases the patient satisfaction and compliance. We need to find such industries support from the Palestinian ministries to adopt such these projects.

On other hand, the co-crystallization method supplies another enhancing for the solubility of the drug, to produce more stable drug and to improve the bioavailability through the skin. This engineering of co-crystal changing and adjusting the stability, bioavailability, mechanical behaviour, solubility, disintegration, and rate of dissolution of the drug. It deserves to adopt such these projects and apply in our Palestinian factories.

2.3 Research objectives:

The main goal of my research is to study the stability and phase diagram of Tenoxicam in a therapeutic product, to produce stable, biocompatible microemulsion with Tenoxicam and a sugar/nonionic surfactant like Tween 80, as well as a co-solvent such as ethanol,

propylene glycol and water. The topical microemulsion therapeutic products are important in drug delivery systems and therapy, which becomes more widespread. In addition, in this research, we aim to prepare Tenoxicam co-crystal by using different diacids in various solvents and using grinding techniques.

To obtain this formula there are many goals and objectives needed to be achieved:

1. To prepare phase diagram of the best components concentration for microemulsion preparation.
2. To determine the surfactant ratios which have highly solublization capacity as well as highly surfactant efficiency.
3. To identify and characterize the prepared microemulsion output results by these instruments: dynamic light scattering, crossed polarizers and polarizing microscope.
4. To identify the co-crystal output by using these instruments: FTIR, Differential Scanning Calorimeter (DSC), Melting Point apparatus and solubility test.

2.4 Hypothesis:

All studies aimed to develop topical microemulsion therapeutic products that increase the patient compliance. Studies show that the Tenoxicam used for the treatment of rheumatoid arthritis, backache and pain, prolonged oral use of this drug is linked with gastrointestinal adverse actions like peptic ulceration, thus needing the development as topical formulation that could avoid the adverse effects and increase the patient compliance. The present study aimed to develop microemulsion formulations of Tenoxicam for topical delivery at the affected site. Microemulsion formulations were found to be the best in controlling inflammation comparing to other topical dosage forms and showed efficacy compared to oral formulation. Results suggest that the developed of microemulsion formulations may

be used for effective topical delivery of Tenoxicam to treat different inflammatory conditions [65].

Co-crystals have stable crystalline form, and no need to produce or break covalent bonds. A pharmaceutical co-crystal can be prepared by crystal engineering with the purpose to get better of the solid-state properties of an active ingredient pharmaceutical without destroying its intrinsic structure. Crystal engineering aimed to be the design and growth of crystalline molecular solids with the aim of influencing material properties [66].

Chapter Three

Instrumentation and Methodology

3. Instrumentation & Methodology:

3.1 Instrumentation:

Analytical balance (Precisa125-A), Vortex (VELP), culture tubes sealed with Viton lined screw caps, sonicator, crossed polarizers, polarizer microscope, FTIR (AVATAR 320), Melting point apparatus (BUCHI B-545).

3.2 Materials:

Tenoxicam (Sigma, Deal engineers), Ethanol 96% (shitzer), Acetone (Merck), Acetonitrile (J.T.Baker), Isopropyl alcohol (Bio lab), Polysorbate 80 (Tween 80) (Seppic), Purified water (Beit Jala Pharmaceutical), Castor oil (Gustav Heess), Oleic acid (Ultra-pure), Dimethyl Sulfoxide (DMSO) (J.T.Baker), Chloroform (Merck), Dimethyl formamide (DMF) (J.T.Baker), Sodium hydroxide (Merck), and Propylene glycol (Dow). Diacids (Oxalic acid, Malonic acid, Succinic acid, L-Glutamic acid, Adipic acid, Suberic acid, Azelaic acid, Sebacic acid and Benzoic acid) (Sigma) . All components used as supplied and tested in Beit Jala Pharmaceutical Company.

3.3 Phase diagram Methodology:

3.3.1 Solubility of Tenoxicam:

Practically insoluble in water, sparingly soluble in methylene chloride, very slightly soluble in anhydrous ethanol.

3.3.2 Constructing of phase diagram:

Each phase diagram consisting of different amounts of oleic acid and (Ethanol/ Tween 80 (1:1)) where Tween 80 used as surfactant, oleic acid and (Tween 80/ Propylene glycol (1:1)) where, propylene glycol is used as co–surfactant, castor oil and (Ethanol/ Tween 80 (1:1)), castor oil and (Tween 80 / Propylene glycol (1:1)), in culture tubes sealed with Viton lined screw caps and stirred by vortex until clear solution was obtained. See **Table**

1-4 for each phase diagram tube components. These samples were titrated with the (Aqueous + Tenoxicam) which added dropwise until its solubilization limit reached. See **Table 5** for each titration percentage required amount. Stirring followed after additions on a Vortex mixer, the time for equilibration between each addition was typically, from a few minutes up to 24 hours (therefore the reading will be taken after 24 hours). Each phase diagram was investigated at three temperatures 25, 37 and 45°C and detecting the number of phases by bare eye and the anisotropy by cross polarizer. The single isotropic sample which will be dark under cross polarizer will be regarded to either cubic or micelle; which can be distinguished by its viscosity. The anisotropic Lamellar liquid crystal and hexagonal liquid crystal are determined by the cross polarizer and polarizing microscope. The boundary of single phase was detected and four phase diagrams were installed, and each phase was tested at three temperatures 25, 37 and 45 °C. Lastly, the phase diagram was drawn by using Origin program.

Each phase diagram tube components:

Table 1 Phase diagram1 components

Tube #	Oleic acid (g)	Ethanol/Tween 80(g)(1:1)
91	0.9076	0.1002
82	0.8011	0.2060
73	0.7050	0.3010
64	0.6089	0.4012
55	0.5039	0.5004
46	0.4001	0.6005
37	0.3033	0.6985
28	0.2005	0.8023
19	0.1002	0.8981

Table 2 Phase diagram 2 components

Tube #	Oleic acid (g)	Tween80/PG(g) (1:1)
91	0.9044	0.1066
82	0.8037	0.2000
73	0.7074	0.3005
64	0.6065	0.4078
55	0.5000	0.5068
46	0.4068	0.6050
37	0.3072	0.7066
28	0.2038	0.8012
19	0.1008	0.9093

Table 3 Phase diagram 3 components

Tube #	Castor oil (g)	Ethanol/Tween 80(g) (1:1)
91	0.9003	0.1035
82	0.8043	0.2148
73	0.7032	0.3002
64	0.6027	0.4071
55	0.5081	0.5094
46	0.4023	0.6103
37	0.3011	0.7011
28	0.2044	0.8059
19	0.1007	0.9037

Table 4 Phase diagram 4 components

Tube #	Castor oil (g)	Tween80/PG (g) (1:1)
91	0.9070	0.1043
82	0.8025	0.2123
73	0.7065	0.3104
64	0.6058	0.4030
55	0.5052	0.5005
46	0.4030	0.6162
37	0.3079	0.7043
28	0.2040	0.8017
19	0.0998	0.9030

Note: The tube # shows the amount of surfactant and oil components in each tube. For example, tube # 91 contains 0.9g of oil and 0.1g of surfactant and co-surfactant**.**

Titration amount required in grams for each percentage:

Table 5 Titration percentage versus weight.

%	Total added weight (g)	Net weight Each interval (g)
4	0.0417	0.0417
8	0.0870	0.0453
12	0.1364	0.0494
16	0.1905	0.0541
20	0.2500	0.0595
24	0.3158	0.0658
28	0.3890	0.0732
32	0.4707	0.0817
36	0.5626	0.0919
40	0.6668	0.1042
44	0.7859	0.1191
48	0.9233	0.1374
52	1.0836	0.1603
56	1.2730	0.1894
60	1.5003	0.2273
64	1.7776	0.2773
68	2.1249	0.3473
72	2.5715	0.4466
76	3.1670	0.5955
80	4.0007	0.8337
84	5.2077	1.207
88	7.2910	2.0833
92	11.4577	4.1667
96	23.9577	12.500

3.3.2.1 Preparation of contents for pseudo phase diagram:

- **Preparation of Tween 80:Propylene glycol (1:1):**

Mix 50 ml of Tween 80 with 50ml of propylene glycol, keep them in culture tubes sealed with Viton lined screw caps, and mixed by vortex until clear solution obtained.

- **Preparation of Tween 80:Ethanol (1:1):**

Mix 50 ml of Tween 80 with 50 ml of ethanol keep them in culture tubes sealed with Viton lined screw caps, and mixed by vortex until clear solution obtained.

- **Preparation of the aqueous phase (the titrant used in titration):**

Add 0.5 g of the API to 50 ml of water shake by stirring, adding dropwise about 20 ml of (0.1N NaOH) to dissolve it to yellow clear colour, up to volume with water to 100 ml. keep the solution in refrigerator to keep it stable.

3.3.2.2 Preparation of four microemulsion (5g) to be titrated gradually by Tenoxicam:

- **Phase 1:** Prepare microemulsion by mixing about 0.5 g of oleic acid with 4.5 g (Ethanol: Tween 80) (1:1) shake.
- **Phase 2:** Prepare microemulsion by mixing 0.5 g of oleic acid with 4.5 g (Tween 80: Propylene glycol) (1:1), shake.
- **Phase 3:** Prepare microemulsion by mixing 0.5 g of castor oil with 4.5 g (Ethanol: Tween 80) (1:1), shake.
- **Phase 4:** Prepare microemulsion by mixing 0.5 g of castor oil with 4.5 g (Tween 80: Propylene glycol) (1:1), shake.

After that, keep each phase in culture tubes sealed with Viton lined screw caps, then add gradually by weighing about 1mg of the API to each prepared phase, shake by Vortex, keep them at 25, 37,and 45°C o study their stability for 24 hrs. Keep adding gradually the API to each phase until producing saturated solution (turbid yellow solution).

3.4 Co-crystal Methodology:

Tenoxicam is considered as active pharmaceutical ingredients (API) in my work. The used co-solvents are Ethanol, Acetone, Acetonitrile, Isopropyl alcohol, Dimethyl sulfoxide (DMSO), Chloroform, Dimethyl formamide (DMF), each solvent used in the co-crystal techniques (Grinding).

There are different techniques for co-crystal formation by using grinding, supercritical fluids, and seeding methods. In mechanical co-crystal synthesis, stoichiometric ratios of

active pharmaceutical ingredients (API) are mechanically agitated (such as grinding in a mill) to induce phase transformations from a physical mixture into co-crystal. Drops of solvent, which are considered as plasticizers, have been shown to impact the crystallization outcome. Mechanical methods are often favoured due to their speed, procedural simplicity, and potential in chemistry. We tested individually FTIR spectroscopy for each pure diacids, and Tenoxicam by using KBr salt to compare them with the co-crystals we will obtain lately.

4.4.1 Grinding (mechanical) Co-crystal technique:

Weigh each diacid with the API according to **Table 6** which shows the molar ratio between the API and each diacid in mg (1:1), mixing them by stirring rod, adding few drops (about 3 drops) from each solvent used, leave them to dry, collect the dried powder into culture tubes sealed with Viton lined screw caps. After that, add from each solvent used in order to dissolve the collected dry powder, shaking by Vortex. Allow to stand, and start gradually to evaporate at room temperature, and collect the crystals to be tested individually for FTIR spectroscopy by using KBr salt and compared with the pure diacids and the API spectrum that were tested before the beginning, also, testing the melting point for the produced crystals, and testing the solubility in water .

Table 6 The molar ratio between 33.74 mg API and acids weight (1:1)

#	Acid	Formula	Molar mass g/mole	For 33.74 mg API Acids weight for 1:1 molar ratio
1	Oxalic acid	$C_2H_2O_4$	90.03	9.0mg
2	Malonic acid	$C_3H_4O_4$	104.0615	10.4mg
3	Succinic acid	$C_4H_6O_4$	118.09	11.8 mg
4	L-Glutamic acid	$C_5H_9NO_4$	147.13	14.7 mg
5	Adipic acid	$C_6H_{10}O_4$	146.1412	14.6 mg
6	Suberic acid	$C_8H_{14}O_4$	174.2	17.4 mg
7	Azelaic acid	$C_9H_{16}O_4$	188.22	18.8mg
8	Sebacic acid	$C_{10}H_{18}O_4$	202.2475	20.2mg
9	Benzoic acid	$C_7H_6O_2$	122.123	12.21mg

Chapter Four

Results and Discussion

4. Results and Discussions:

4.1 Microemulsion phase diagram results:

The results of our study indicate development of successful microemulsion formulations of Tenoxicam with optimum characteristics**.**

In the preparation of the API /water (aqueous phase), we use alkali solution (NaOH), because Tenoxicam has good solubility at neutral pH, solubility decreases with decrease pH, and increases in basic pH.

4.1.1 Pseudo phase diagram # 1 at 25°C, 37°C, and 45°C:

Ethanol with Tween 80 in the ratio (1:1) and oleic acid demonstrates that the microemulsion was obtained and started as single, clear isotropic and not shiny solution by the crossed polarizers upon the addition of 4% aqueous /API solution in the tube #55 which contains 0.5g of ethanol and Tween 80 (1:1), and 0.5g oleic acid. The microemulsion remains the same with increasing temperature which refers to the fact that the nonionic surfactant used is soluble in the aqueous /API solution. Since, oleic acid is insoluble in the aqueous /API solution, therefore, Tween 80 with ethanol (1:1) is used as tuning parameter for all ingredients and contributes clearly in forming the microemulsion for the tube #55 up to 64% of the aqueous /API solution. Thus, an increase in the temperature will not effect on the nonionic surfactant micelle structure (W/O). As shown in **Figure. 8** pseudo ternary phase diagram at all studied temperature conditions.

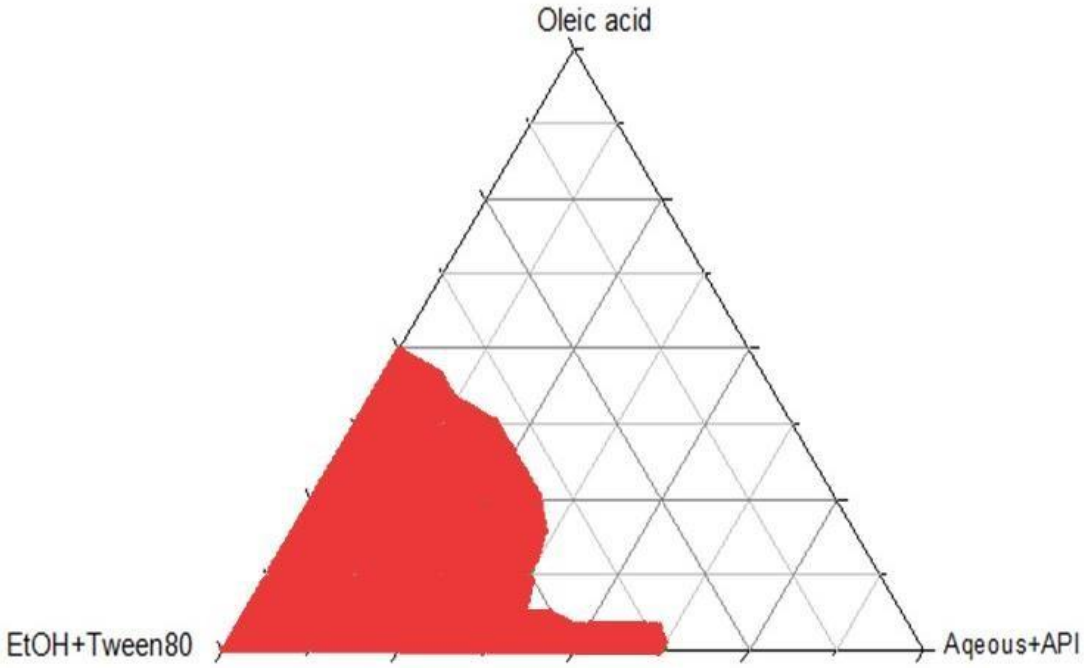

Figure. 8. Pseudo phase diagram 1

4.1.2 Pseudo phase diagram # 2 at 25°C, 37°C, and 45°C:

Propylene glycol with Tween 80 in the ratio (1:1) and oleic acid demonstrates that the microemulsion was obtained and started as single, clear isotropic and not shiny solution by the crossed polarizers upon the addition of 4% aqueous /API solution in the tube #37 which contains 0.7g Tween 80 with propylene glycol in the ratio (1:1) and 0.3 g oleic acid. The microemulsion remains the same with increasing temperature which refers to the fact that the nonionic surfactant used is soluble in the aqueous /API solution. Since, oleic acid is insoluble in the aqueous /API solution therefore, Tween80 with propylene glycol (1:1) is used as tuning parameter for all ingredients and contributes clearly in forming the microemulsion for the tube #37 up to 44% of the aqueous /API solution. Thus, an increase in the temperature will not effect on the nonionic surfactant micelle structure (W/O). As shown in **Figure. 9** pseudo ternary phase diagram at all studied temperature conditions.

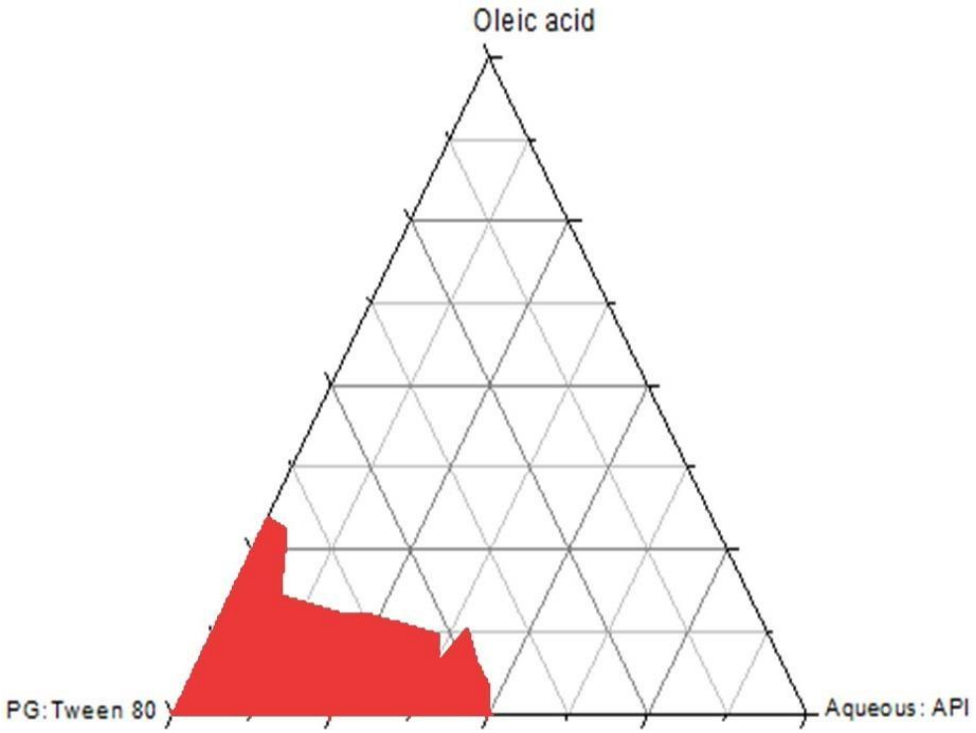

Figure. 9. Pseudo phase diagram 2

4.1.3 Pseudo phase diagram # 3 at 25°C, 37°C, and 45°C:

Ethanol with Tween 80 in the ratio (1:1) and castor oil, no microemulsion observed, castor oil is a bulk huge viscous chemical structure causing a wide turbid region, which prevents the formation of microemulsion.

4.1.4 Pseudo phase diagram # 4 at 25°C, 37°C, and 45°C:

Propylene glycol with Tween 80 in the ratio (1:1) and castor oil demonstrates that the microemulsion was obtained and started as single, clear isotropic and not shiny solution by the crossed polarizers upon the addition of 4% aqueous /API solution in the tube #19 which contains 0.9g Tween 80 with propylene glycol in the ratio (1:1) and 0.1 g castor oil. The microemulsion remains the same with increasing temperature which refers to the fact that the nonionic surfactant used is soluble in the aqueous /API solution. Since, castor oil is insoluble in the aqueous /API solution, therefore, Tween80 with propylene glycol (1:1) is used as tuning parameter for all ingredients and contributes clearly in forming the

microemulsion for the tube #19 of 4% of the aqueous /API solution .Thus, an increase in the temperature will not have an effect on the nonionic surfactant micelle structure (w/o). As shown in **Figure. 10** pseudo ternary phase diagram at all studied temperature conditions.

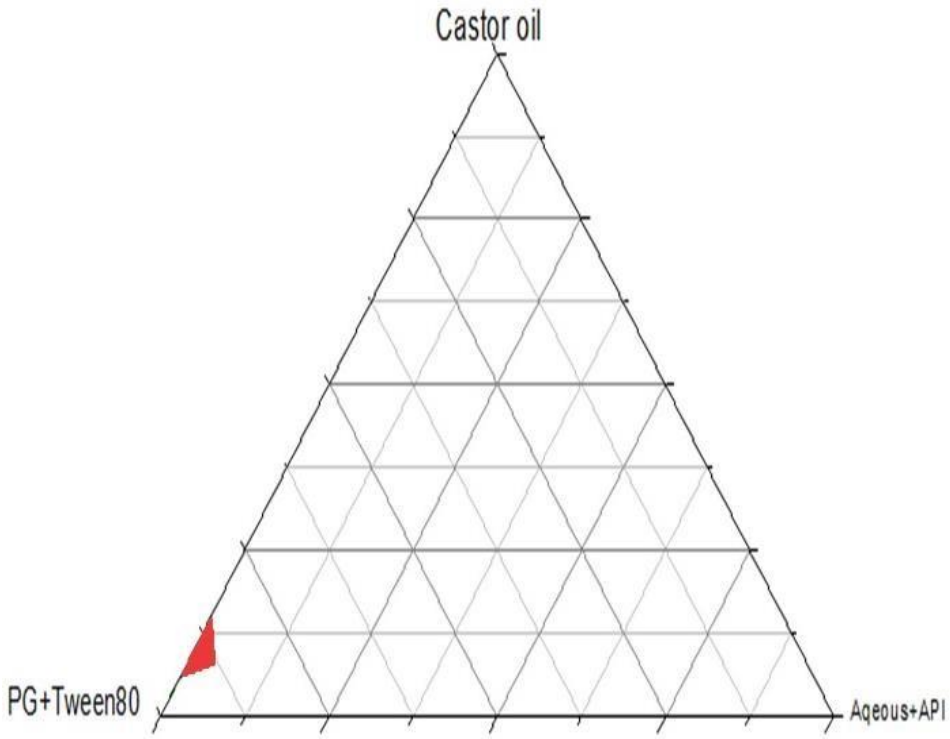

Figure. 10. Pseudo phase diagram 4

4.1.5 Titrating gradually of Tenoxicam to 5g prepared microemulsion:

Adding gradually about 40 mg of the API to each microemulsion gives transparent, clear yellow, stable, isotropic, thermodynamically stable microemulsion at temperature 25°C, 37°C, and 45°C. Each phase was viscous, but phases (2&4) were more viscous than phases (1& 3), as shown in **Figure. 11** because they are contain propylene glycol which gives thickness and increase the viscosity.

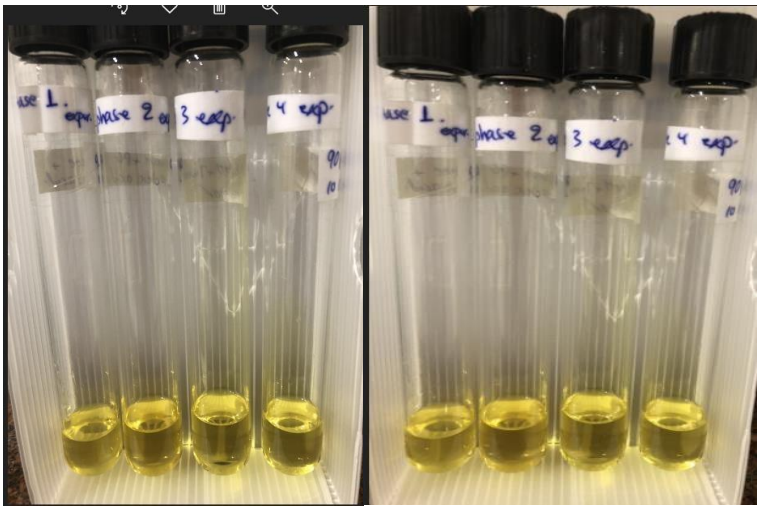

Figure. 11. The clarity of microemulsion (containing 40 mg of the API) 0.8 % (w/w).

The best concentration obtained from these microemulsions is 0.8% (about 0.04g API/5g microemulsion) and pH about 6.0, as shown in the following **Table 7.**

Table 7 pH and concentration % (by weight).

Phase #	pH	Concentration %(by weight)
Phase #1	5.727	0.818%
Phase #2	5.880	0.852%
Phase #3	6.218	0.812%
Phase #4	6.408	0.824%

Adding further quantity of Tenoxicam (about 5mg) to the 0.8% for each microemulsion, it became turbid yellow solution and produced yellow precipitate, as shown in **Figure. 12**.

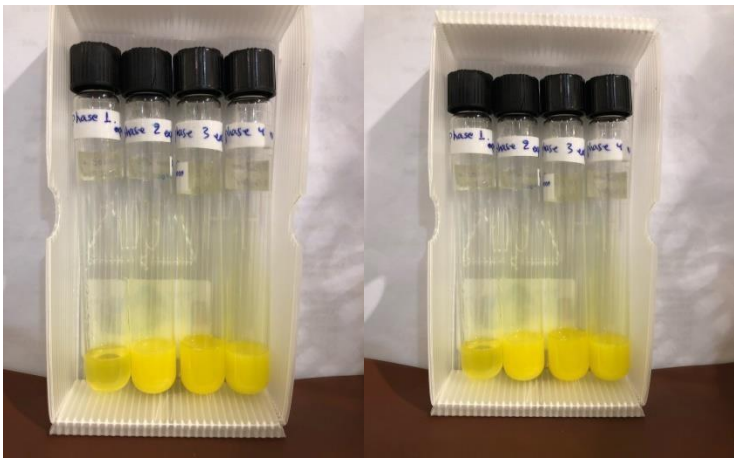

Figure. 12. Turbid yellow solutions with precipitate, when we added 5 mg of Tenoxicam to the 0.8% (0.04g/5g microemulsion).

The percentage of the API in each ternary pseudo phase diagram as the following:

1- **In phase diagram #1** in (tube #55) at the 8% addition of the aqueous phase (the titrant used is 0.5g of the API/100ml of water) gives 0.04% of concentration of the API in the microemulsion (0.5g API/100ml water × % of addition) , but in (tube #46) at 32% addition gives 0.16%, also in (tube #37) at 36% addition gives 0.18%, at the addition of 32% in (tube #28) gives 0.16%, and in (tube#19) at 64% addition gives 0.32% .

2- **In phase diagram #2** in (tube #37) at the addition of 4% gives 0.02%, but in (tube #28) at 32% addition gives 0.16%, in (tube #19) at 44% addition gives 0.22%.

3- **In phase diagram #4** in (tube #19) at 4% addition gives 0.02%.

4.2 Co-crystal results:

4.2.1 Grinding (mechanical) Co-crystal technique:

No crystals produced from the grinding (mechanical) technique with co-solvent of Ethanol, Acetonitrile, Acetone, and Isopropyl alcohol.

Also, the solutions which were prepared with co-solvent of DMSO and DMF, no evaporation happened because of their high boiling points, 189 °C for DMSO and 152 - 154°C for DMF, which shown in **Figure. 13**.

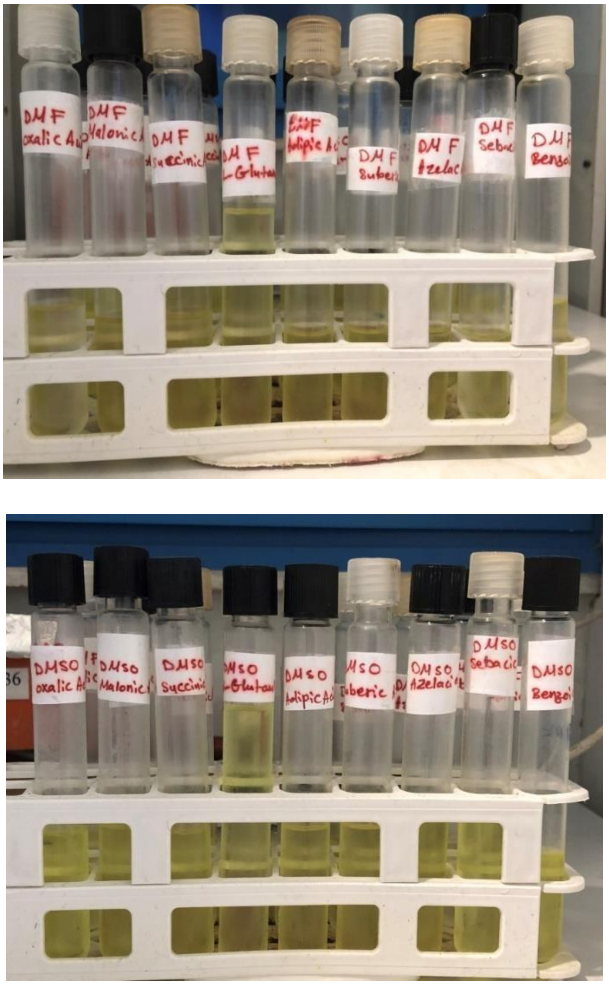

Figure. 13. Solutions with co-solvent of DMSO and DMF, no evaporation happened.

When co-solvent was used of chloroform, not all the grinded diacid with the API produced co-crystal (oxalic acid, malonic acid, succinic acid, adipic acid), as in **Figure. 14**.

In benzoic acid no co-crystal produced because the hydrogen bonding will have a high energy and will be strong, leading to weak bonding and not stable co-crystal, as in **Figure. 14**.

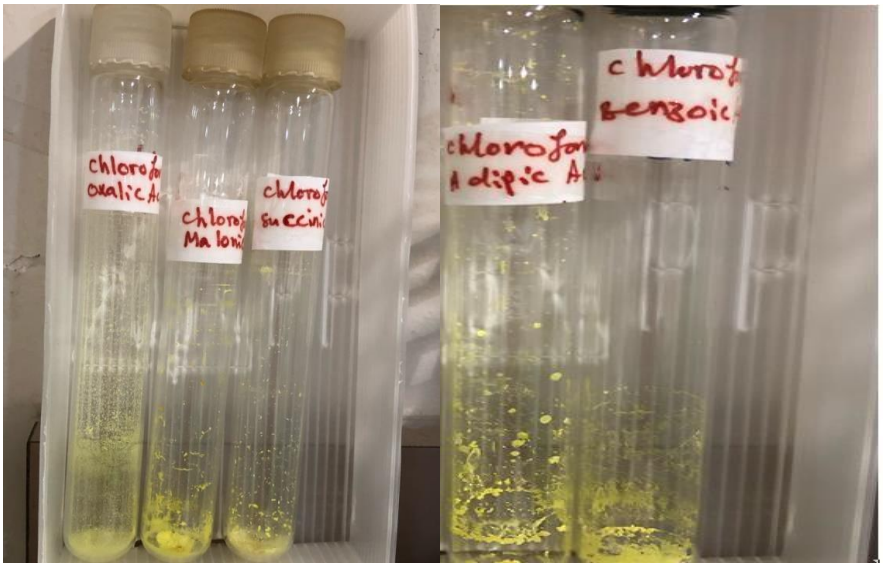

Figure. 14. No co-crystal produced with chloroform co-solvent

Only l- glutamic acid, azelaic acid, sebacic acid and suberic acid, gave yellow co-crystals with chloroform which used as co–solvent, as shown in **Figure. 15-18**, the hydroxyl group in these diacids will be differentiated and fluctuation of hydrogen bonding will invite, and leading to bonding with hydrogen bonding in the API and forming stable co-crystal. After that, we tested them individually by FTIR spectroscopy using KBr disc and compared the result with the pure samples spectrum for each diacid and Tenoxicam that was tested before the beginning of grinding**.**

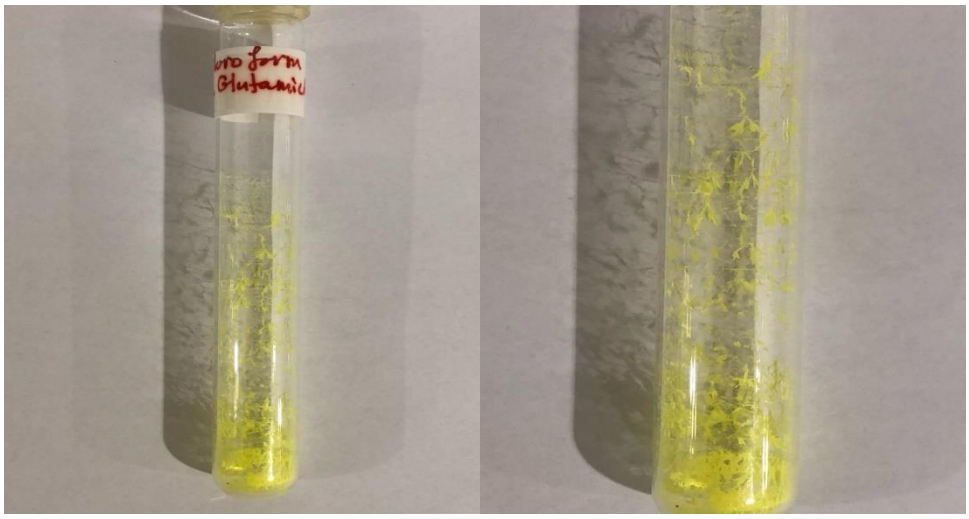

Figure. 15. L-Glutamic acid/API co-crystal in chloroform co-solvent.

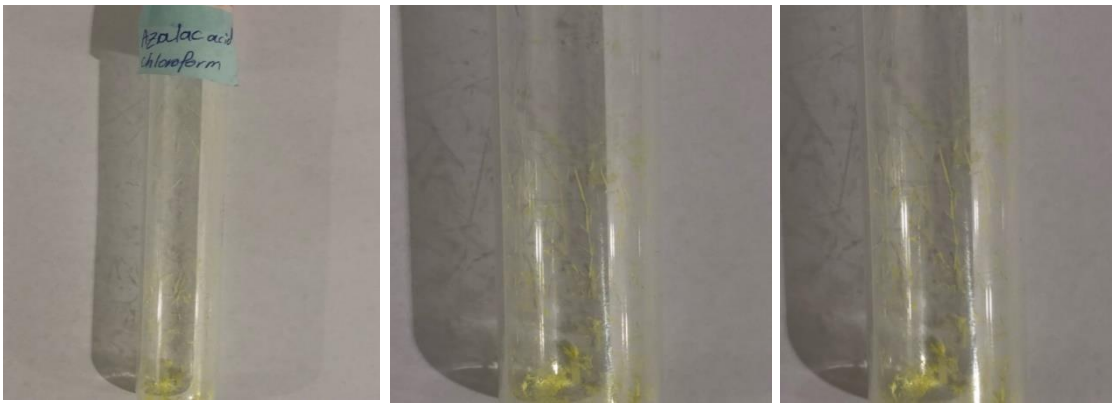

Figure. 16. Azelaic acid/API co-crystal in chloroform co-solvent.

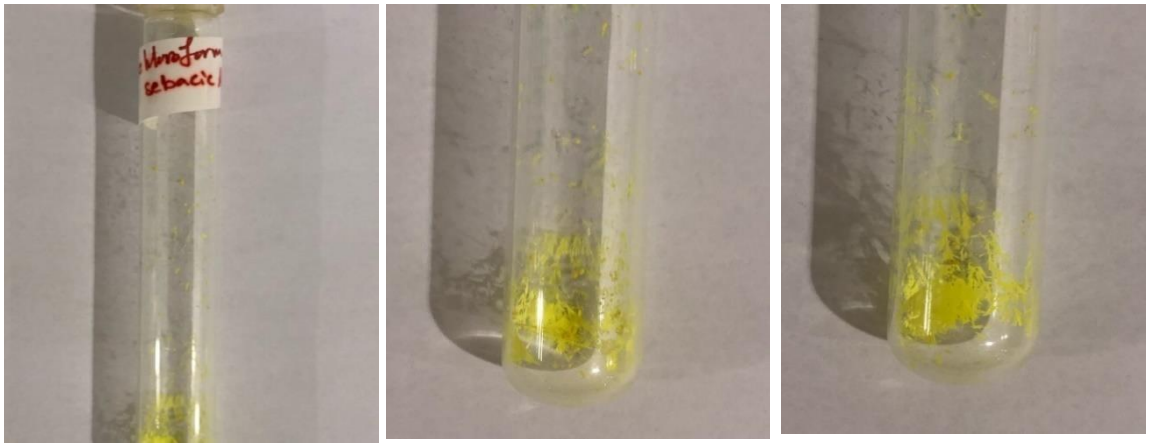

Figure. 17. Sebacic acid/API co-crystal in chloroform co-solvent.

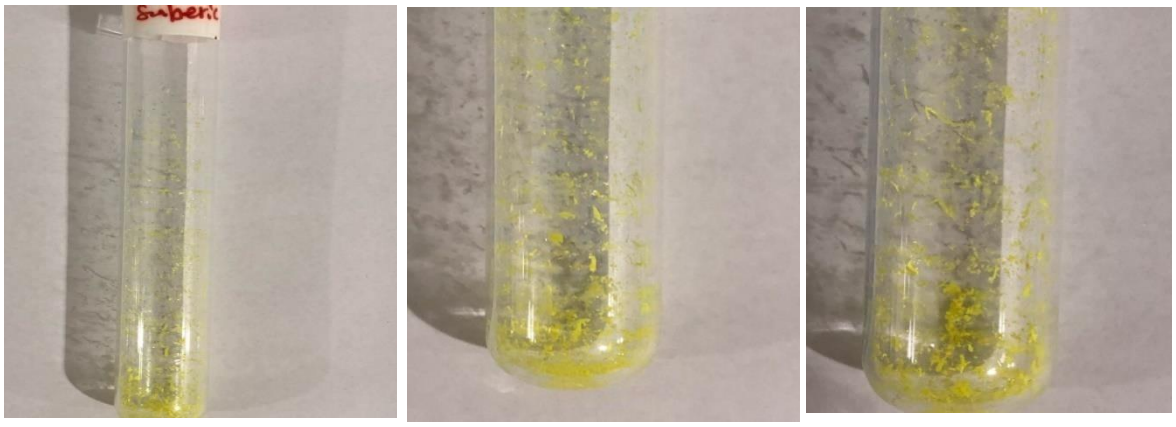

Figure. 18. Suberic acid/API co-crystal in chloroform co-solvent.

The co-crystals produced in the chloroform co-solvent tested by using FTIR showing merged API. We compared the major peaks produced with the pure API's spectrums as shown in **Figure. 19**, and the wavenumber shifted in the co-crystal spectrums as the following **Table 8**.

Table 8 Wavenumber degree shift in cm^{-1} for the major peaks

Solvent	**Chloroform co–solvent**											
	Wavenumber degree shift in cm^{-1} for major peaks											
Di acid	**1637**	**1598**	**1556**	**1495**	**1428**	**1389**	**1327**	**1292**	**1243**	**1202**	**1151**	**1043**
Azelaic acid	+7	+3	+2	-7	+6	-3	+8	+5	+2	-1	-4	-4
L-glutamic acid	+7	+3	+3	-7	+6	-3	+8	+5	+2	-1	-4	-4
Sebacic acid	+7	+4	+5	-7	-7	-3	+8	+7	+1	-1	-4	-4
Suberic acid	+6	+4	+4	-6	-7	-2	--	+5	+2	-2	-4	---

The FTIR spectrum for the pure active pharmaceutical ingredient API of Tenoxicam:

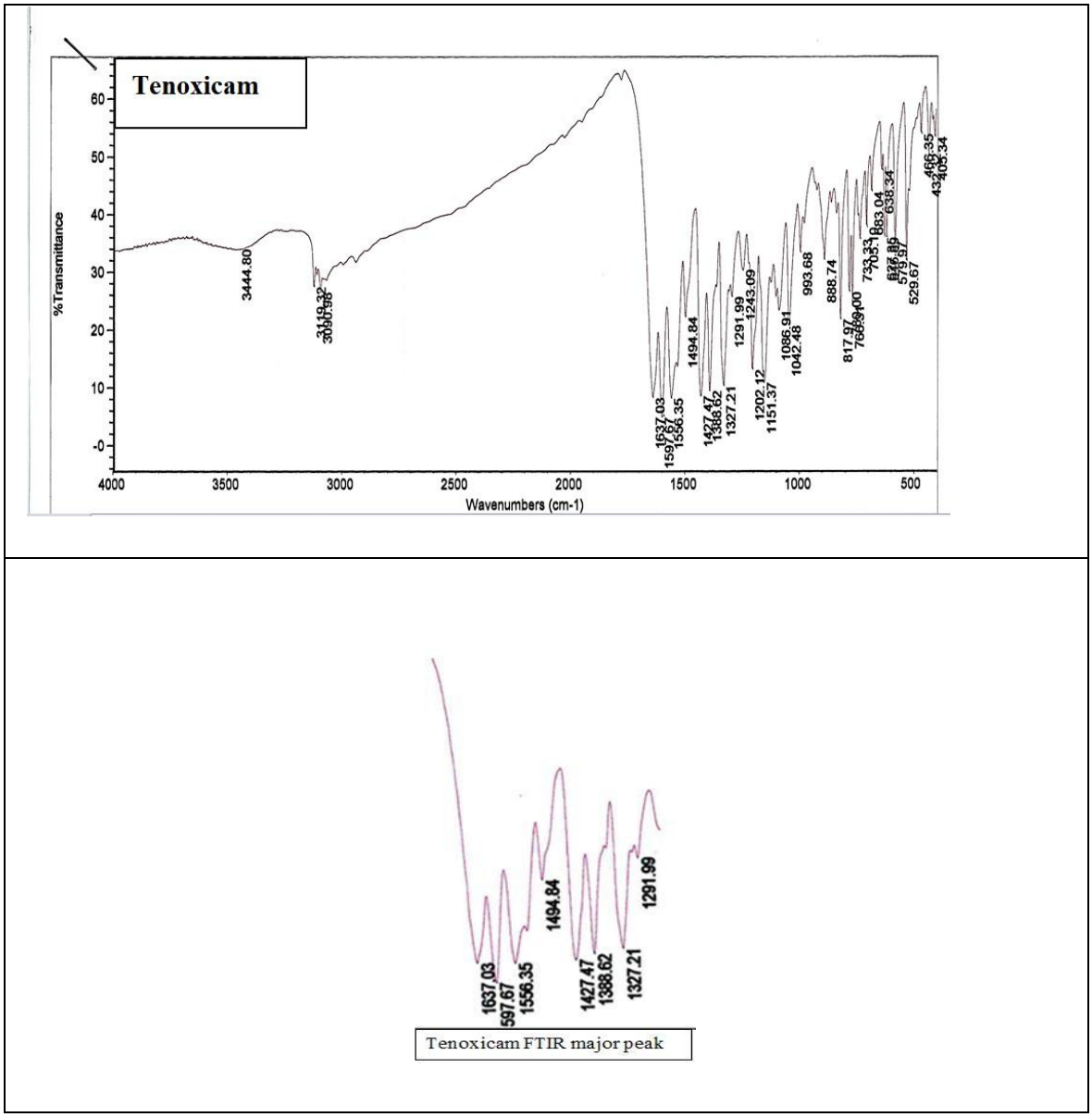

Figure. 19. Pure Tenoxicam FTIR spectrum

4.2.2 Co-crystal solubility in water:

In **Table 9** which provides the solubility requirements according to the general United State Pharmacopeia.

Table 9 United State Pharmacopeia solubility criteria

Classification	**Parts of solvent required for one part of solute (between 15˚C and 25˚C)**
Very soluble	Less than 1part
Freely soluble	1- 10 parts
Soluble	10 – 30 parts
Sparingly soluble	30 – 100 parts
Slightly soluble	100 – 1000 parts
Very slightly soluble	1000 – 10000 parts
Practically insoluble	≥10000 parts

Tenoxicam is practically insoluble in water and very slightly soluble in ethanol (96 per cent). The most important goal in co-crystallization method is to improve the solubility of the Tenoxicam in the pharmaceutical drugs. We tested the solubility in water for each co-crystal as the following result:

We weighed about 5 mg from each co-crystal into 10ml volumetric flask, adding gradually 0.1 ml of water, sonicate for 10 min, it doesn't dissolve totally. The solution was transferred to 25 ml volumetric flask, adding gradually 0.1 ml of water, sonicate another 15 min, it doesn't dissolve totally. Finally, the solution was added to 50ml volumetric flask and was added gradually 0.1 ml of water, sonicate for 15 min, it was dissolved totally to be the volume 40ml of water. They were compared to 5 mg of pure Tenoxicam dissolved in the same volume of water 40 ml.

As a result, the solubility of the Tenoxicam was 14.1mg in 1000ml of water, according to the co-crystal we obtained and tested the solubility in water, it gives solubility of 5 mg/ 40

ml in water, which gives indication a new compound is produced with new properties as shown in **Figure. 20**.

Figure. 20. The clarity of solubility of 5 mg of co-crystal/ 40 ml of water, compared to 5 mg of solubility of Tenoxicam / 40ml of water.

4.2.3 The co-crystal melting point:

Tenoxicam is a pharmaceutical API, its melting point is 208-2011˚C, the expected new co-crystal formed would have melting point to be different from the API and the diacid, which forms the co-crystals, the following **Table 10**, shows the melting points for API, diacids and the produced co-crystals:

Table 10 Melting point results:

Material name	Melting point (°C)	Description of Melting
Tenoxicam (API)	205.8-206.1	Decomposition
Azelaic acid (diacid)	105.2-108.0	Colorless liquid
Suberic acid (diacid)	141.4-141.8	Colorless liquid
L-Glutamic acid (diacid)	192.0-192.2	Colorless liquid
Sebacic acid (diacid)	133.2-133.5	Colorless liquid
Azelaic acid-Tenoxicam co-crystal	171.2-179.1	Decomposition
Suberic acid- Tenoxicam co-crystal	178.0-180.0	Decomposition
L-Glutamic acid-Tenoxicam co-crystal	176.1-183.4	Decomposition
Sebacic acid- Tenoxicam co-crystal	178.0-180.8	Decomposition

According to the previous results, there is different variation of the co-crystal melting point, which is based on the goal of the active ingredient concentration and based on the

molar ratio for each co-crystal tested. On other hand, there is a wide clear change in the melting point for the co-crystal produced, which means new form produced (consists of merging the

API with diacid), by using the co-solvent of chloroform.

Note: for data results print out refer to the **Figures. 21&22** in the list of appendices.

5. Conclusion:

My research used one of the most important sugar-based surfactants, sorbitan esters, which is used in pharmaceutical drugs such as polysorbate 80 (Tween 80), and the structural feature provides unique physicochemical properties to these surfactants. On other hand, the co-surfactant with short chain of alcohol like propylene glycol was used as tuning parameter for all ingredients and contributes clearly in forming the microemulsion. Also, the addition of different amounts of short chain of co-surfactants helps in the initiation of formation of drug product microemulsion in the formula of water, propylene glycol, and Tween 80. The microemulsion in the four phases diagram obtained gives clear isotropic, and not shiny solution upon the addition of 4% at 25, 37 and 45˚C temperatures, the microemulsion remains the same at three temperatures, and up to 100% aqueous addition, successfully, the increase in the temperature will not have an effect on the nonionic surfactant micelle structure (W/O).

The co-crystal produced from the grinding technique in the chloroform co-solvent was tested by using FTIR, melting point and the solubility in water, which gives successful results and obvious yellow co-crystal. It also showed amazing improvement in the properties of the Tenoxicam, which increases the solubility in water.

6. Future work:

- Determining the lattice structure for the obtained co-crystal of the new complex structure by using x-ray diffraction.
- Determining solid state NMR of the co- crystal and compare with solid state of pure API and diacids.

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مستحلب بجزيئات صغيرة جداً يحتوي على تينوكسيكام واستخدام طريقة البنية البلورية في دمج الأحماض المستخدمة.

إعداد الطالبة: مها محمد موسى عثمان

إشراف: البروفيسور إبراهيم كيالي

مشرف ثاني: الدكتور محمد أبو الحاج

الملخص:

تهدف هذه الدراسة إلى تحضير منتج على شكل مستحلب يحتوي على جزيئات صغيرة من (Tenoxicam) يعالج الأمراض الجلدية الموضعية (Topical) باستخدام مركبات مختلفة بكميات أقل من (Tweens). في هذا العمل، تم استخدام مركب توين 80 (البولي أوكسي إيثيلين (20) أحادية السوربيتان) (Surfactant). أيضاً، يستخدم المذيب الشريك (Co-surfactant) مع سلسلة قصيرة من الكحول مثل البروبيلين غليكول (Propylene glycol). طور الزيت المستخدم هي زيت الخروع (Castor oil) وحمض الأوليك (Oleic acid). وطور الماء المستخدم هي تينوكسيكام المذاب في محلول هيدروكسيد الصوديوم (0.1 N NaOH). وعلاوة على ذلك، تهدف هذه الدراسة إلى إعداد الكريستال المشترك من (Tenoxicam) كمكونات صيدلانية نشطة، وذلك باستخدام المذيبات المشتركة المختلفة.

في هذا العمل، تم دراسة درجات حرارة مختلفة (25، 37 و45) درجة مئوية، تأثير إضافة كميات مختلفة من المركب 80 Tween (Surfactant) على سلوك المرحلة من النظام المقترح. من ناحية أخرى، أظهرت هذه الدراسة أثر إضافة المذيب الشريك المستخدم (البروبيلين غليكول) على سلوك المرحلة في النظام المقترح، فهو يستخدم لضبط جميع المكونات الأخرى ويسهم بوضوح في تشكيل

جزيئات المستحلب الصغيرة. بدأ سلوك المرحلة في النظام واضحة، مستحلب دقيق موحد الخصائص وتم تحليلها عن طريق التفتيش البصري (visual Inspection)، وعبر الاستقطاب (cross polarizer) وتشتت الضوء الديناميكي (dynamic light scattering).

وأخيراً، تشير هذه الدراسة إلى تطور ناجح لتركيبات مستحلب صغير من (Tenoxicam) مع الخصائص المثلى.

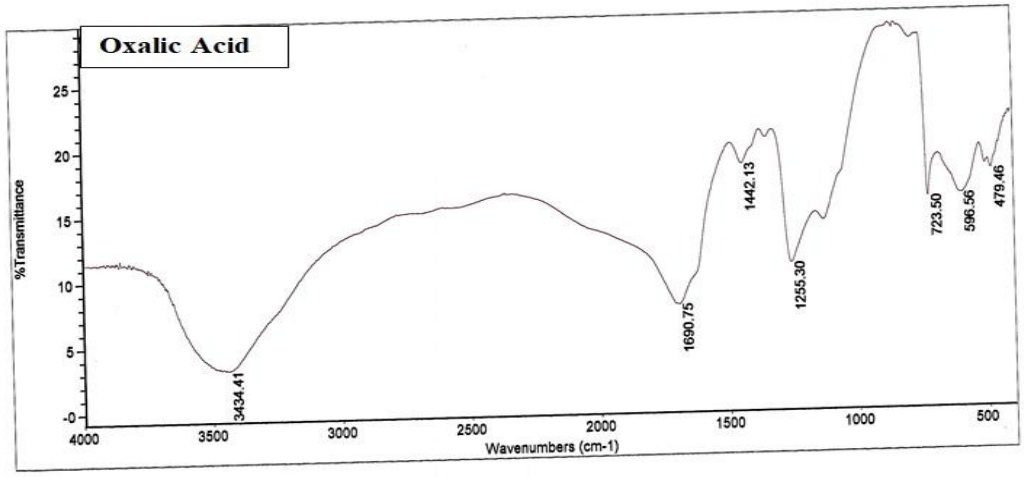
بالإضافة إلى ذلك؛ تم دراسة قوة العديد من المذيبات المشتركة المستخدمة في طريقة التبلور المشترك، مثل الكلوروفورم عن طريق استخدام تقنيات الطحن. البلورات المشتركة الناتجة تم اختبارها باستخدام مطياف الأشعة تحت الحمراء (Fourier Transform Infrared)، وقياس درجة الانصهار (Melting point)، وتغيرات الذوبان (Solubility). تم تغير درجة انصهار البلورة المشتركة لتكون أقل من تينوكسيكام النقي، وكذلك أظهرت القابلية للذوبان في البلورات المشتركة تغيراً واسعاً في قابلية الذوبان من غير قابلة للذوبان عملياً في الماء إلى قابلة للذوبان.

Appendices

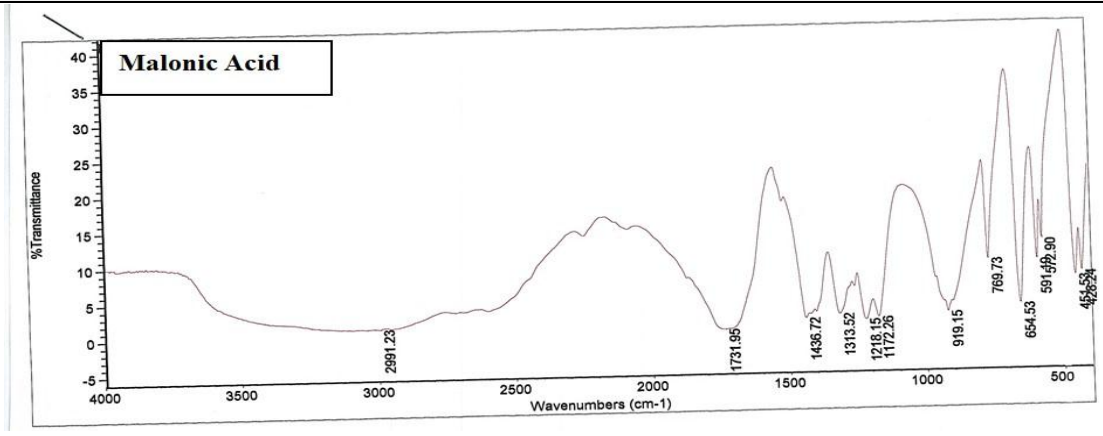
Appendix 1:

FTIR spectrum for grinding techniques for pure diacid used

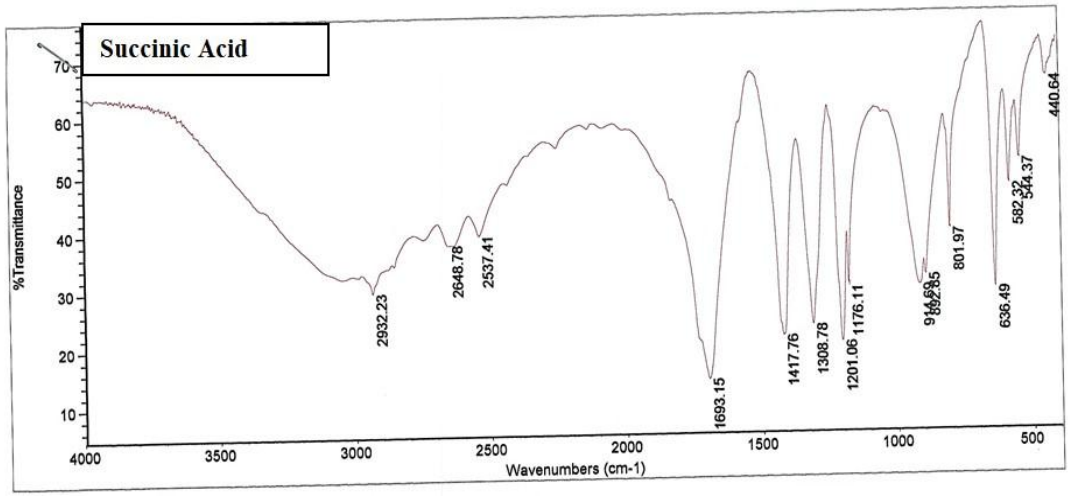
Oxalic Acid



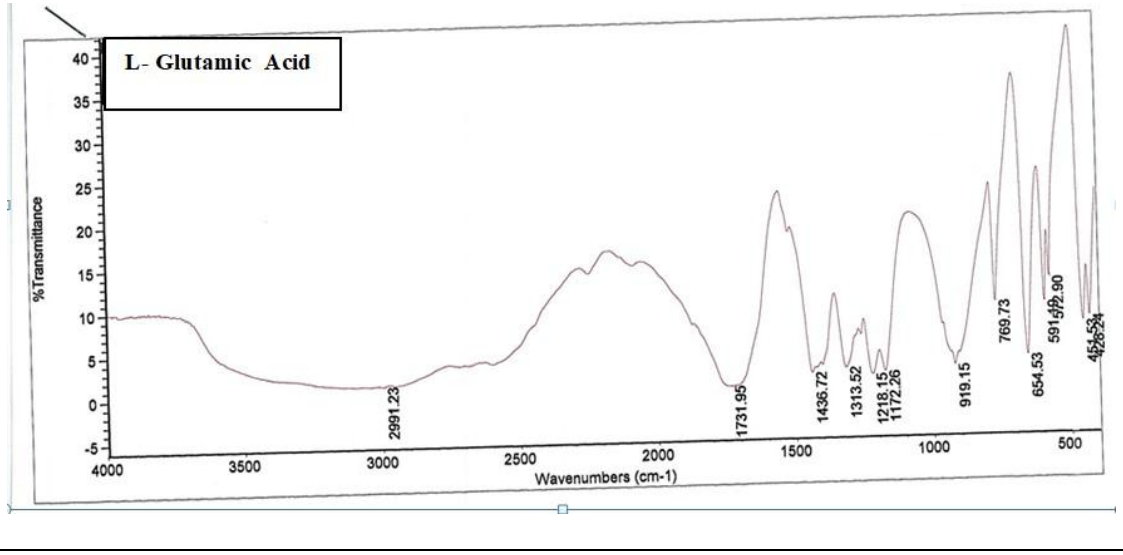
Malonic Acid



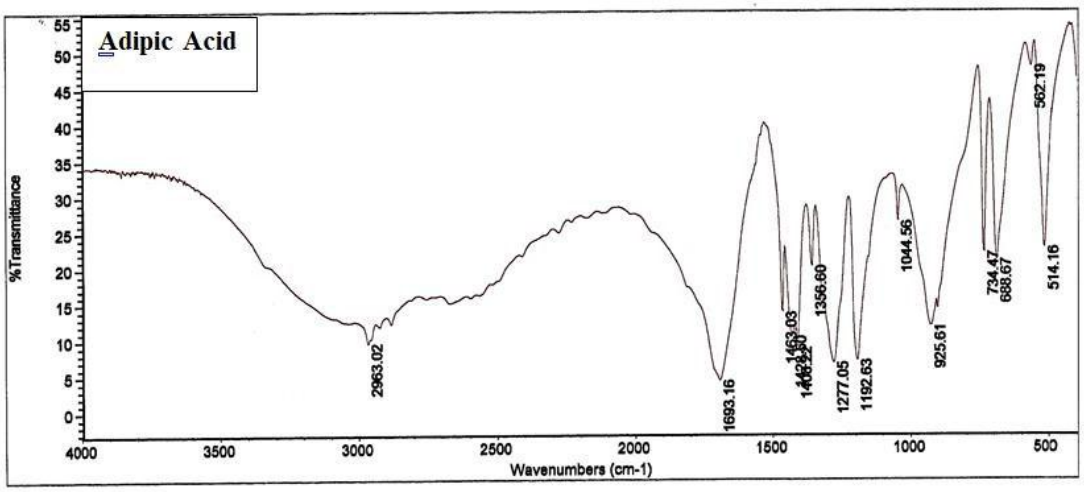
Succinic Acid



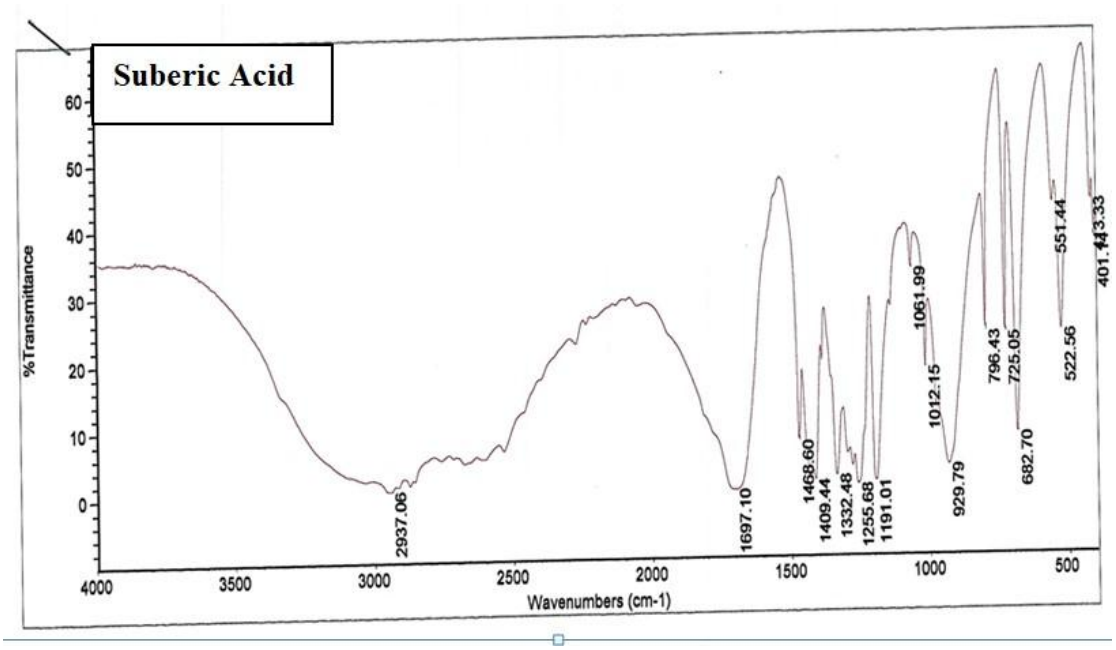
L-Glutamic Acid



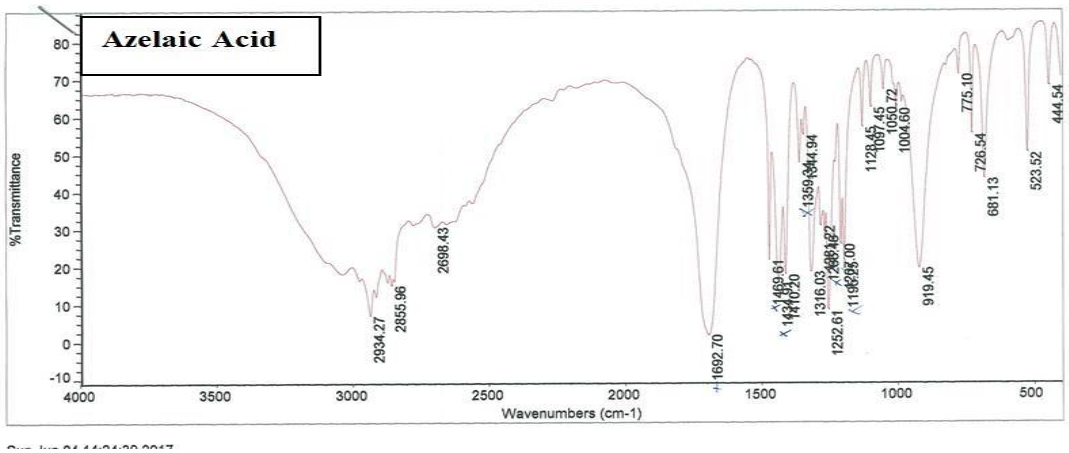
Adipic Acid



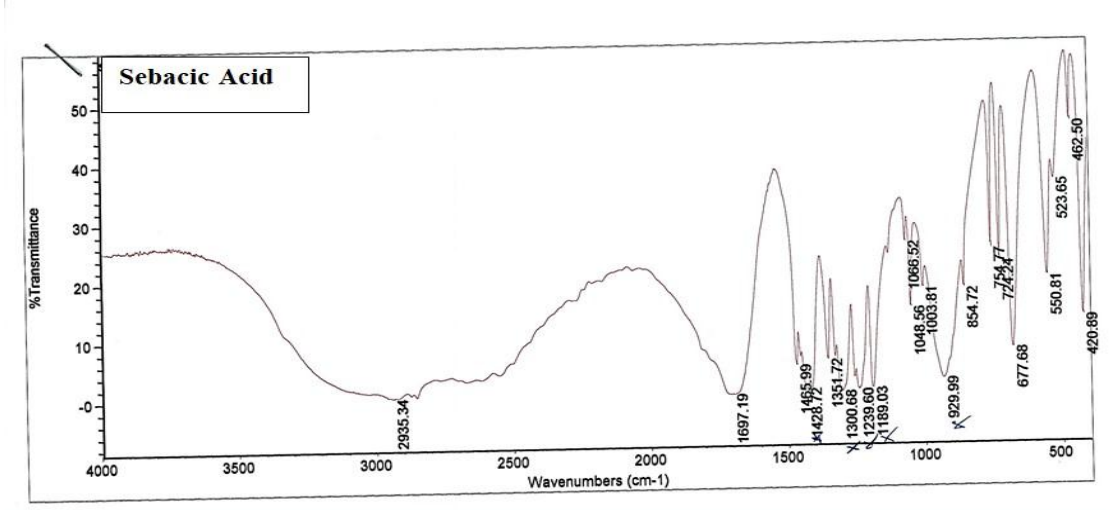
Suberic Acid



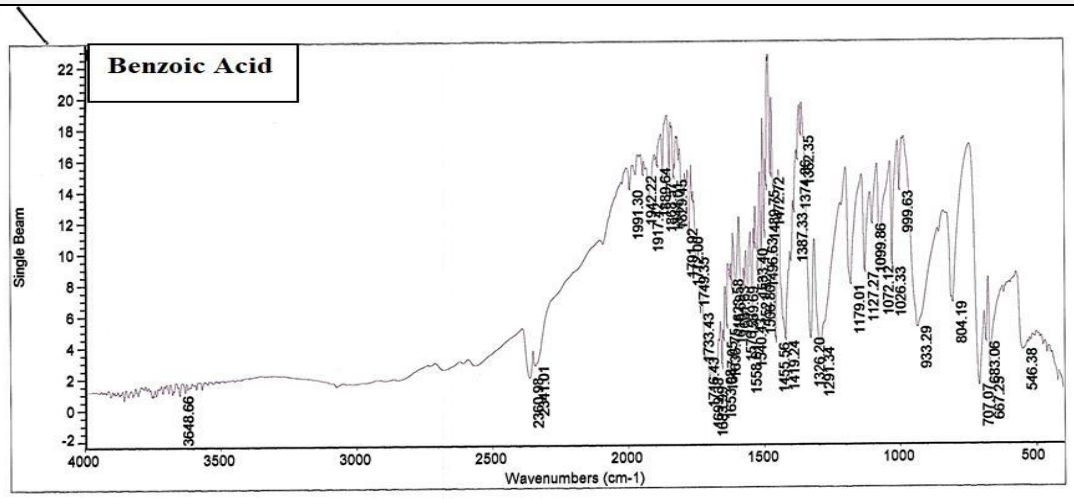
Azelaic Acid



Sebacic Acid



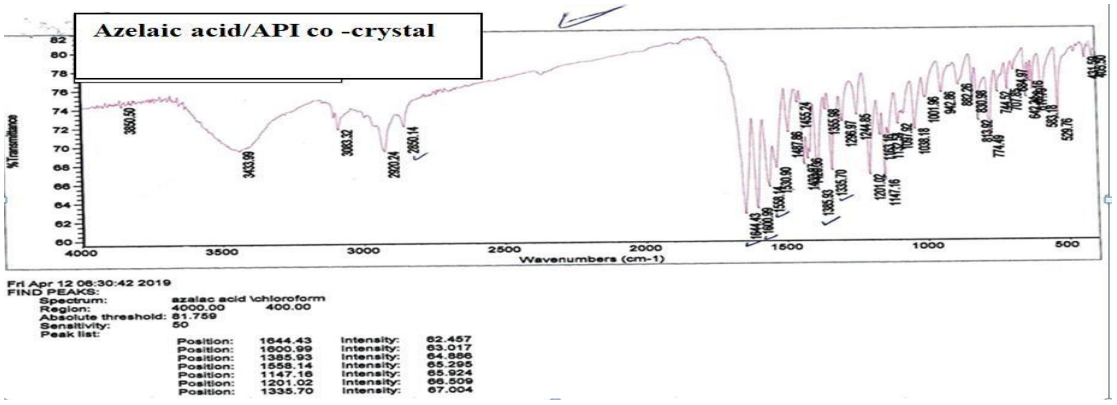
Benzoic Acid



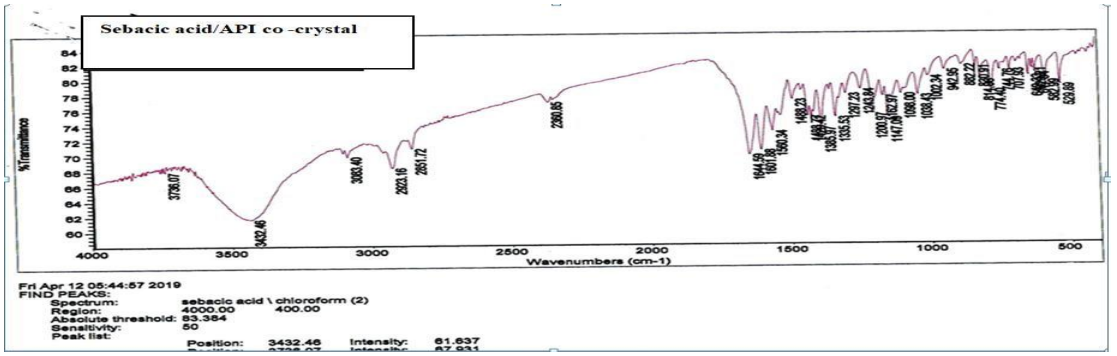
Appendix 2:

FTIR spectrum for grinding techniques in chloroform co-solvent molar ratio (1:1)

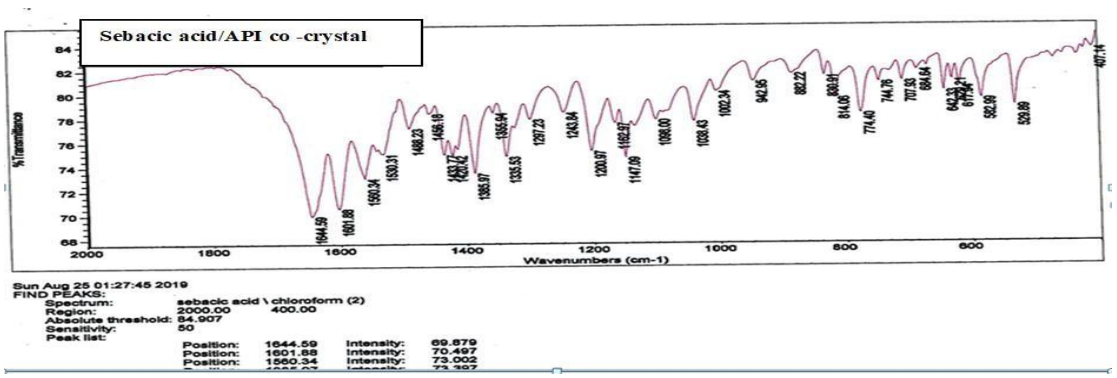
Azelaic acid/ API co-crystal



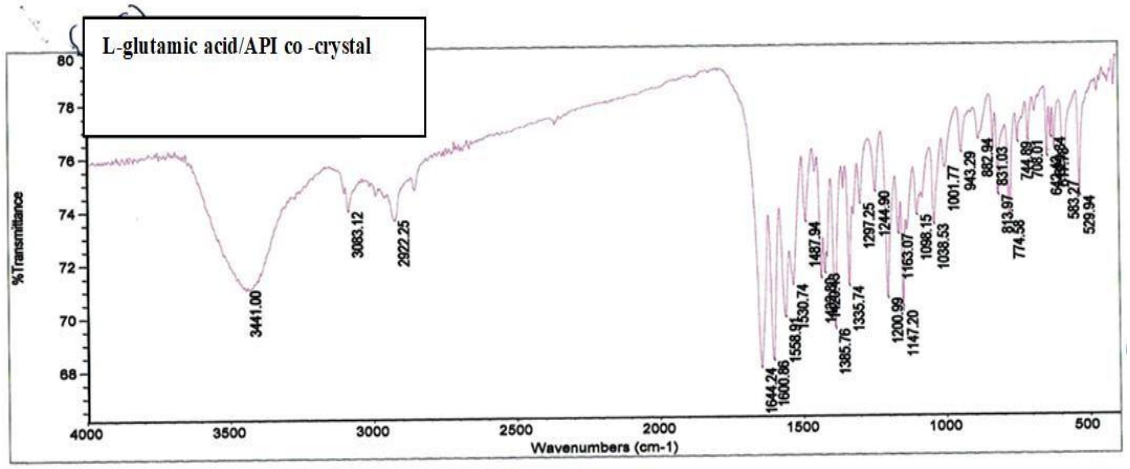
Sebacic acid/ API co-crystal



Sebacic acid/ API co-crystal



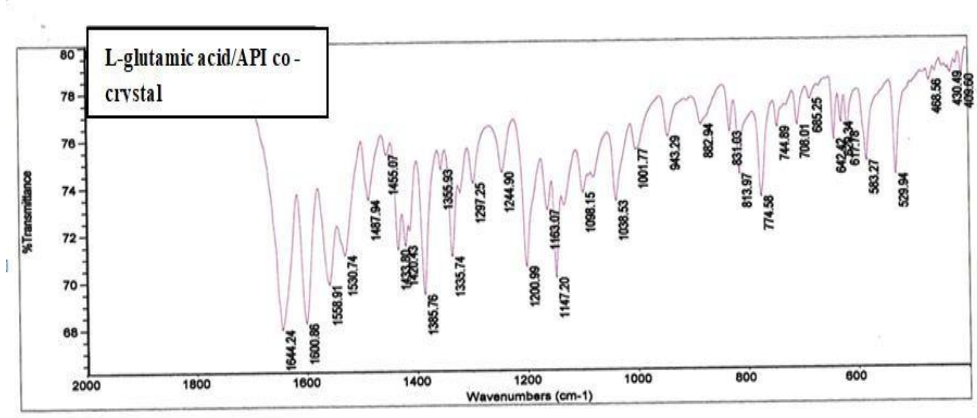
L-Glutamic acid/ API co-crystal



Sat Apr 13 18:13:46 2019
FIND PEAKS:
Spectrum: l glutamic ACID \chlor
Region: 4000.00 400.00
Absolute threshold: 79.701
Sensitivity: 34
Peak list:

Position:	1644.24	Intensity:	67.958
Position:	1600.86	Intensity:	68.231
Position:	1385.76	Intensity:	69.404

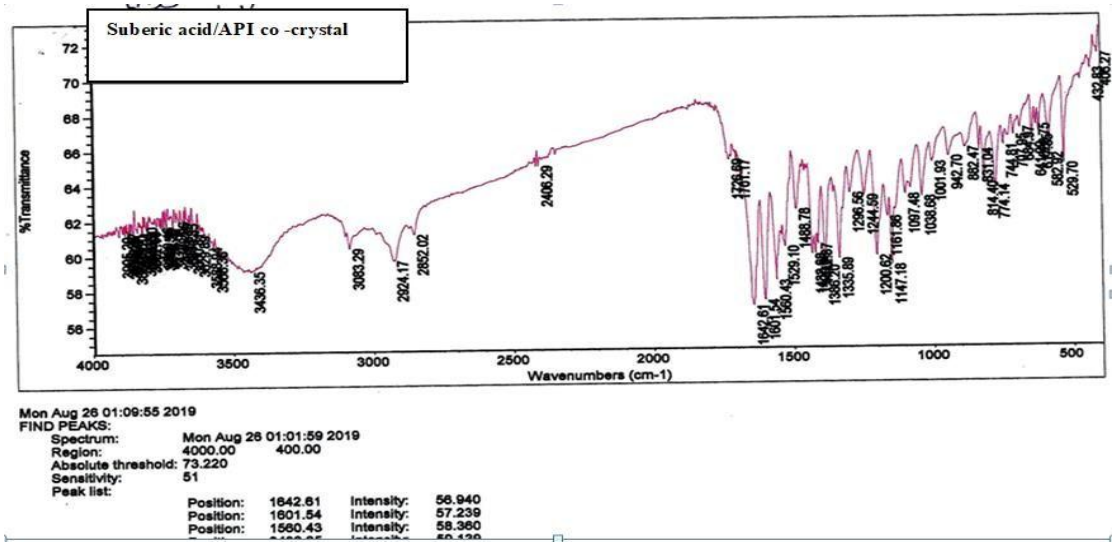
L-Glutamic acid/ API co-crystal



Tue Aug 27 02:03:18 2019
FIND PEAKS:
Spectrum: l glutamic ACID \chlor
Region: 2000.00 400.00
Absolute threshold: 79.061
Sensitivity: 50
Peak list:

Position:	1644.24	Intensity:	67.958
Position:	1600.86	Intensity:	68.231

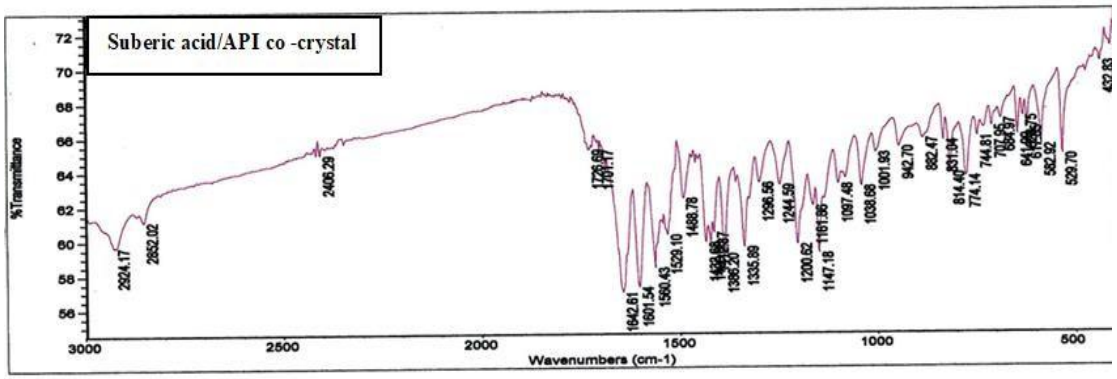
Suberic acid/ API co-crystal



Mon Aug 26 01:09:55 2019
FIND PEAKS:
Spectrum: Mon Aug 26 01:01:59 2019
Region: 4000.00 400.00
Absolute threshold: 73.220
Sensitivity: 51
Peak list:

Position:	1642.61	Intensity:	56.940
Position:	1601.54	Intensity:	57.239
Position:	1560.43	Intensity:	58.360

Suberic acid/ API co-crystal



Mon Aug 26 01:12:03 2019
FIND PEAKS:
Spectrum: Mon Aug 26 01:01:59 2019
Region: 3000.00 400.00
Absolute threshold: 73.077
Sensitivity: 51
Peak list:

Position:	1642.61	Intensity:	56.940
Position:	1601.54	Intensity:	57.239
Position:	1560.43	Intensity:	58.360

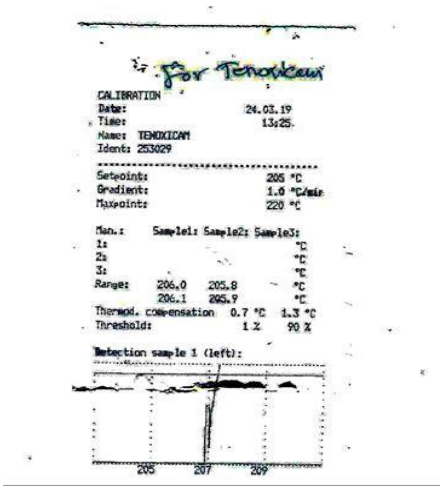
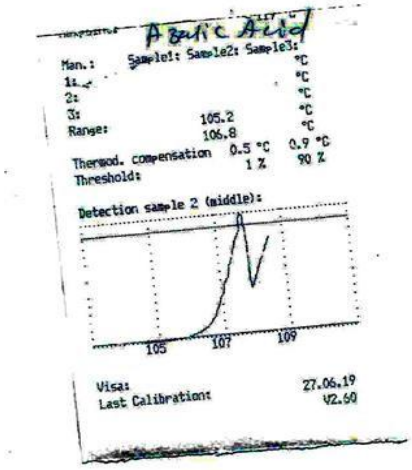
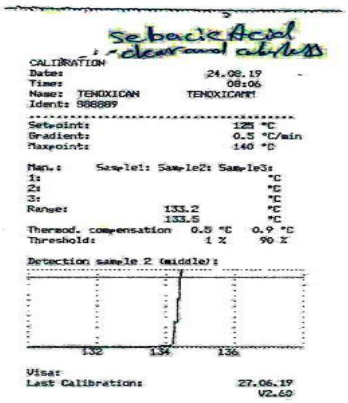
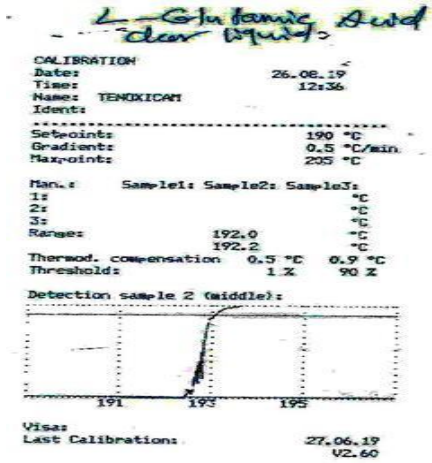
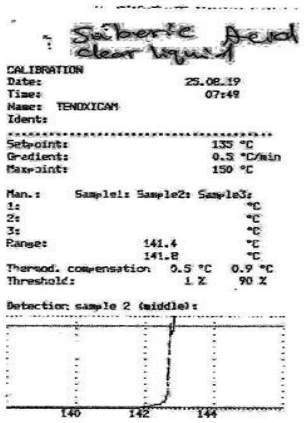
Tenoxicam:	**Azelaic acid:**
	
Sebacic acid:	**L-Glutamic acid:**
	
Suberic acid:	
	

Figure.21. Pure API & Diacids melting ranges

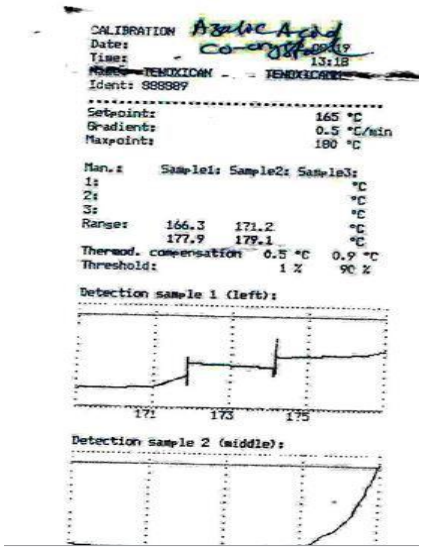
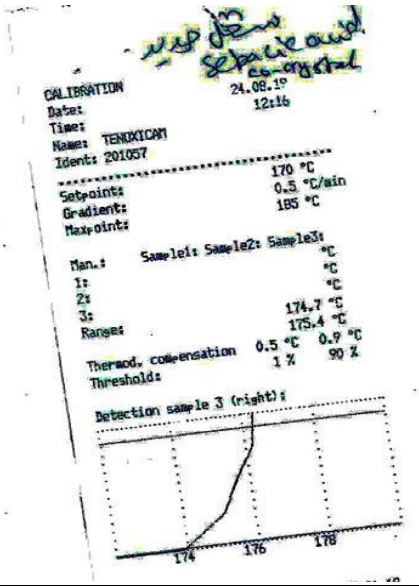
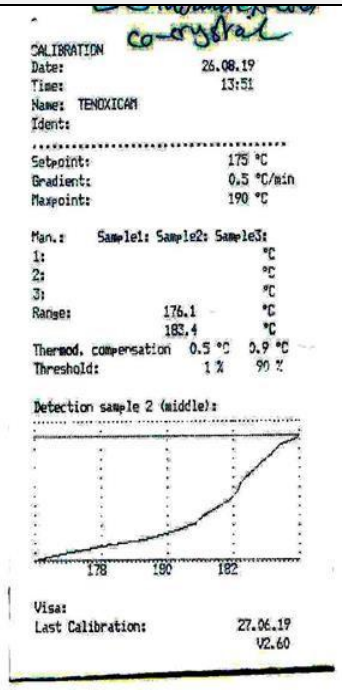
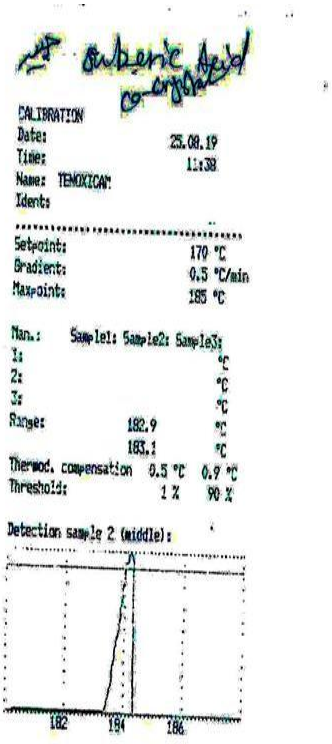
Azelaic acid-Tenoxicam co-crystal	Sebacic acid- Tenoxicam co-crystal
	
L-Glutamic acid-Tenoxicam co-crystal	**Suberic acid- Tenoxicam co-crystal**
	

Figure.22. Pure API & Diacids melting ranges