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"Mixed Nonionic Surfactant Systems: Formulation, Characterization,Cefuroxime Axetil Solubilization and Permeability Studies"

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Jerusalem-Palestine

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Dedication

I would like to dedicate this thesis to the late leaderYasser Arafat.

To my mother, may Allah bless her,who firstly helped me to reach my goals.

To my father,a Palestinian prisoner under Israeli occupation,one of the best supporters to reach my goals.

I would like also to express my deep appreciation to my supervisor, professor Monzer Fanun,who has cheerfully assisted me throughout this project.

To my beloved wife.

Moreover, I'm very grateful to my friends, family, and college for their good humor and supports throughout this project.

Declaration

I certify that this thesis submitted for the degree of master in the result of my own research, except were otherwise acknowledged, and this thesis (or many part of the same) has not been submitted for a higher degree to any other university or institution.

Signed: …………………………….

Thaer Mohammad Ahmad Al-toos

Date: 11/11/2017

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Abstract

Microemulsions containing commercial sugar ester nonionic surfactants, sucrose oleate (O1570) satisfy the quality standards for food and pharmaceutical applications, this surfactant sorted as food grade emulsifier has unique properties (nontoxic, biodegradable and of natural origin), it is capable of making temperature-insensitive microemulsion systems which are suitable for many industrial applications.

Surfactant molecules are used in microemulsion systems to bring down the interfacial tension (IFT) to a very low values, but in many research, the use of surfactant alone could not bring down the IFT to the required value and another substance must be added to ME systems to obtain the required low IFT value. These substances are co-surfactants, such co-surfactants used in this research are (ethanol, propylene glycol, propionic acid and glycerol).

Different types of oils have been used in this research, the cyclic oil, R (+)-limonene oil, linear oil isopropylmyristate and triglyceride oil caprylic-capric triglyceride. Many of these microemulsion systems including a co-surfactants; the co-surfactants used are food, cosmetic and pharmaceutical grade that include ethanol, propionic acid, glycerol and propylene glycol.

In the first part of this research, we study the effect of different types of co-surfactants and oils on the phase behavior of the systems water/ sucrose oleate/ co-surfactant/oil (W/Sur/Cos/O) at different temperatures 25, 37 and 45ºC, in the second part we examined the effect of mixed surfactants in microemulsion systems in order to explore the surfactant mixing ratio and also we explored the mixed surfactants/co-surfactants or mixed oils on the phase behavior and area of the microemulsion region A_T %. The systems where water/sucrose oleate/sorbitan monooleate/oil or mixed oils.

It was found that mixed surfactants systems extended the total monophasic area A_T% to a very high values compared to single surfactant systems, it was suggested that the synergistic effect in mixed surfactants systems play a major role in the improvement of the total monophasic area.

In the first part of single surfactant phase behavior study, we found that isopropyl myristate and caprylic-capric triglyceride oils gave the best results compared to R(+)-limonene oil, because of chain length compatibility and effective carbon number (ECN) that plays a

major role in determining the A_T % in these systems. On the contrary in the mixed surfactants systems, the main driving factor that affected the A_T % is molecular volume of oil, thus we found that R(+)-limonene oil has a higher A_T % in all systems studied. R(+)-limonene oil hasa cyclic structure and lower molecular volume than other types oils studied in this research, these properties ofR(+)-limonene oil promote the penetrating more easily into the surfactant palisade layer resultingin high values of A_T %. When the temperature was changed from 25°C to 45°C, the total monophasic region A_T % either was not affected or has little affect, indicating the formulation to be of temperature insensitive microemulsions.

Electrical conductivity measurements were used to determine the microemulsion microstructure formulated along the one phase microemulsion systems, i.e., water-in-oil, bicontinuous or oil-in-water systems.

In this research, mixed nonionic surfactants (sucrose oleate, sorbitan monooleate) were used to solubilize active pharmaceutical ingredient (cefuroxime axetil). Cefuroxime axetil is used to treat or prevent upper and lower respiratory tract infections and other infections proven to be caused by bacteria.

It was found that the solubilization capacity is structural dependent, the solubilization of cefuroxime axetil also depends on the oil type and co-surfactants used in microemulsion systems that solubilizecefuroxime axetil.

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Abbreviations, Symbols & Terminology

API: Active pharmaceutical ingredient

A_T %: Total one-phase microemulsion area (total monophasic area)

BCS: Biopharmaceutical classification system

BSO: Bansal, Shah and O'Connell equation

CCT: Caprylic-capric triglyceride oil

CFA: Cefuroxime axetil

CMC: Critical micelle concentration

Cos: Co-surfactant

ECN: Effective Carbon Number

ΔE_{con}: activation energy of conductance

EMDG: Ethoxylated Mono-Di Glyceride

EO: Ethylene Oxide

EtOH: Ethanol

N_A: Alcohol chain length

N_O: Oil chain length

N_S: Surfactant chain length

FAO: Food and agriculture organization

GLY: Glycerol

HLB: Hydrophilic-lipophilic balance

IPM: Isopropyl myristate oil

IFT: Interfacial tension

LIM: R (+)-limonene oil

MEs: Microemulsions

O1570: Sucrose oleate

T-MAZ 80: Sorbitan monooleate

ME: Microemulsion

μS: Microsiemens

O: Oil

O/W: Oil-in-water

PG: Propylene glycol

PrA: Propionic acid

ppm: part per million

PIT: Phase Inversion Temperature

SC: Solubilization capacity

SDS: Sodium Dodecyl Sulfonate

SE: Sugar ester

Sur: Surfactant

W: Water

WHO: World health organization

W/O: Water-in-oil

Winsor I: Oil-in-water microemulsion coexists with excess oil

Winsor II: Water-in-oil microemulsion coexists with excess water

Winsor III: Bicontinuous middle phase microemulsion

σ: Electrical conductivity

ϕ_c: Water volume fraction

Chapter One

Introduction

Microemulsions (MEs) are thermodynamically stable mixtures of at least two immiscible liquids (water and oil) imparted by surfactant (surface-active ingredients) forming films separate these phases. Penetration of the oil in the surfactant aggregates changes the surfactant layer curvature, and this layer becomes less positive or negative [Fanun.M, 2009].These immiscible liquids were optically clear, low viscus, macroscopically homogeneous and heterogeneous in the nanometer range [Fanun.M, 2008].

Amphiphilic molecules or so-called surfactants are these compounds or molecules that have a dual affinity, for water and oil such as phospholipids, as well as many drugs [Zana.R, 2005]. It was frequently used in microemulsion systems, because theycan bring downthe interfacial tension (IFT) to a very low value. Originally, it has negative IFT which gives their stability [Akhtar.M, 1996]. But in many instances, the amphiphiles alone do not bring down the IFT to the required very low value and another substances need to be used to obtain the desired stable microemulsions such as short chain alcohols.

In general there are three types of surfactants according to their net charge on the molecule: Ionic, that has net charge negative or positive (anionic, cationic), Nonionic, this type does not have any charge and Zwitterionic surfactants; With two parts, polar hydrophilic part with strong dipole interaction gives their hydrophilicity (water-soluble), and nonpolar part gives their hydrophobicity (Fat soluble) [Fanun. M, 2010].The use of nonionic surfactants is much favorable more than ionic one, due to the problems which can raise in the use of high levels of ionic surfactants in a combination of co-surfactants (Cos) [Fanun. M, 2009], also nonionic surfactants are less irritant and nontoxic than other types of surfactants, beside it can form MEs without the presence of co-surfactants (Cos) [Fanun. M, Papadimitriou. V, Xenakis.A, 2011].

In our study, we use sugar ester (SE) as a nonionic surfactant which is sucrose fatty acid esters consisting of sucrose as a hydrophilic group and fatty acids as a lipophilic group. SE are non-toxic and biodegradable surfactants approved by FAO, WHO as food additives [Hilda B, David. G, Aarti. N, Yogeshvar. K, Jose. B, Adriana.Q, 2003]. Sucrose contains in its structure eight hydroxyl groups (OH) that can be partially esterified to produce sucrose ester with amphiphilic properties. Mono, di and tri ester of sucrose usually used as anemulsifier in detergents, cosmetics and food applications [Garti.N, et al, 2000].

Microemulsions can be self-assembled to form a variety of structures ranging from 1-100nm. This structures changes in size and shape according to its conditions such as concentration, temperature and pressure [Sagar. G, Arunagirinathan. M, Bellare.J, 2007]. In our study, we focus on the effect of different temperatures (25, 37 and 45°C) on surfactants aggregates.

One of the important parameters that affecting the structure and shape of surfactant self-assembles is molecular packing parameter, which is defined as $P= V_0/ \alpha l_0$, where V_0, l_0 are volume and chain length of surfactant hydrophobic tail respectively, α is optimal head group area [Yan Y, Xiong. W, Li. X, Lu. T, Huang. J, Li. Z, Fu.H, 2007].Head groups occupied area (α) in surfactant molecules, the attractive force between hydrophobic tails in the interface as well as the repulsive force between neighbor head groups, these two opposing forces determine the optimal area of the head group [Hiemenz. P, Rajagopalan.R, 1997].

Another concept relating molecular structure to interfacial packing and film curvature is HLB, the hydrophilic−lipophilic balance. It is generally expressed as an empirical equation based on the relative proportions of hydrophobic and hydrophilic groups within the molecule. The concept was first introduced by [Griffin. W, 1949] who characterized a number of surfactants, and derived an empirical equation for nonionic surfactant based on the surfactant chemical composition [Griffin. W, 1954]. For bicontinuous structures, i.e., zero curvature, it was shown that $HLB \approx 10$. Then w/o microemulsions form when $HLB < 10$, and o/w microemulsion when $HLB > 10$. HLB and packing parameter describe the same basic concept, though the latter is more suitable for microemulsions [Israelachvili. J, 1994].The influence of surfactant geometry and system conditions on HLB numbers and packing parameter is illustrated in**Figure 1.1**.

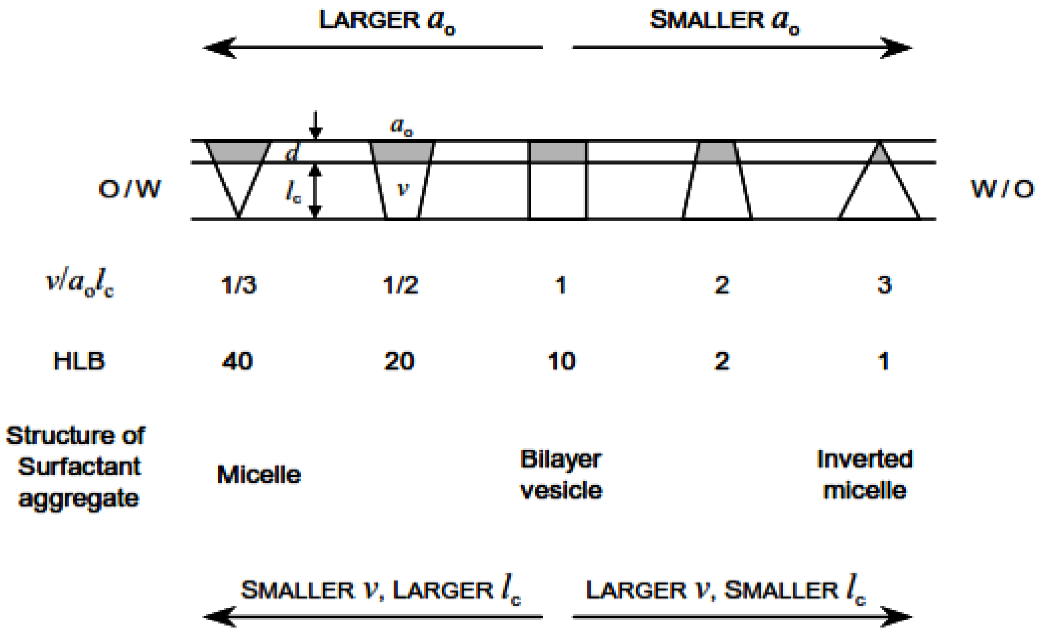


Figure 1.1: Effect of molecular geometry and system conditions on the packing parameter and HLB number (after Israelachvili. J, 1994).

Three different types of approaches have been proposed to explore the mechanisms of microemulsion formation and stability. The first approach is the mixed film theory in which the spontaneous formation of microemulsions was considered due to the formation of the complex interfacial film between oil and water by the surfactants and co-surfactants molecules. This caused to decrease the interfacial tensionto a very low values and due to the high entropy in the mixing of microemulsion droplets. [Fanun.M, 2011] [Prince.L, 1977] [Singh.P, et al, 2014]. The second approach is solubilization theories.In this approach it was proposed that the microemulsions are swollen micellar systems with oil and water solubilized in normal or reverse micelles [Shinoda. K, Kunieda. H, 1973] [Rance. D, Friberg. S, 1976], also Shinoda and Lindman was studied the solubilization behavior and thermodynamic stability of the system that have very low amount of surfactants (1 wt. %) and equal amount oil. They found that even at a low content of surfactants, it maintain microemulsion in which hydrophilic- lipophilic balance property nearly balance [Shinoda. K, Lindman. B, 1987].

The third approach was a thermodynamic theory, it was the same origin of solubilization and mixed film theories, otherwise here it considers that the free energy (ΔG) and entropy (ΔS) are the main driving forces in the formulation of microemulsions [Ruckenstein. E, CHI. J, 1974]. Accumulation of surfactants and co-surfactants at the interfacial layer causes a significant reduction in the interfacial tension, as well as a reduction in their potential in the bulk. Also, it was shown that the role of interfacial tension and presence of electrolytes such as salts in the formation of microemulsions [Ruckenstein. E, Krishnan. R, 1979] [Ruckenstein. E, Krishnan. R, 1980].

Indeed, it is estimated that 40% of approved drugs and nearly 90% of developmental drugs formulations are of poor pharmaceutical properties, low permeability, rapid metabolism, poor safety and tolerability [Kalepu. S, Nekkanti. V, 2015], thus much of work has been done in the last few years by scientists and researchers to solve the issue of slightly water soluble drugs, among of these drugs is cefuroxime axetil, which belong to slightly water soluble drugs was extensively studied. Many techniques have been taking place to enhance solubility and bioavailability of cefuroxime axetil and already enhanced the bioavailability, i.e., self-micro-emulsifying drug delivery system (SMEDDS) [Puttacharia. S, Kalyane. N, Duttagupta. S, 2016], anti-solvent precipitation using high gravity technique [Jog. R, Burgess. D, 2017], controlled nanoprecipitation method [Zhang.J, et al, 2006] and media milling technique [Patel.Y, et al, 2014]. From all of these techniques, the bioavailability of cefuroxime axetil enhanced with different ratios.

Cefuroxime axetil (CFA), is broad spectrum, β- lactame second generation cephalosporin antibiotic [Uzunovic. A Vranic.E, 2008]. it has molecular formula of $C_{20}H_{22}N_4O_{10}S$, and molecular weight of 510.5 g/mole, it is antibacterial used in the treatment of susceptible infections, such as bone and joint infections, bronchitis, other lower-respiratory-tract infections, gonorrhoea, meningitis, otitis media, peritonitis, pharyngitis, sinusitis, skin infections, and urinary tract infections. It is also used for surgical infection prophylaxis. It found in the markets as white powder capsules that slightly soluble in water and ether, soluble in chloroform, ethyl acetate, more than it freely soluble in acetone [Martindale. S, 2005]. (See **Figure 1.2**)

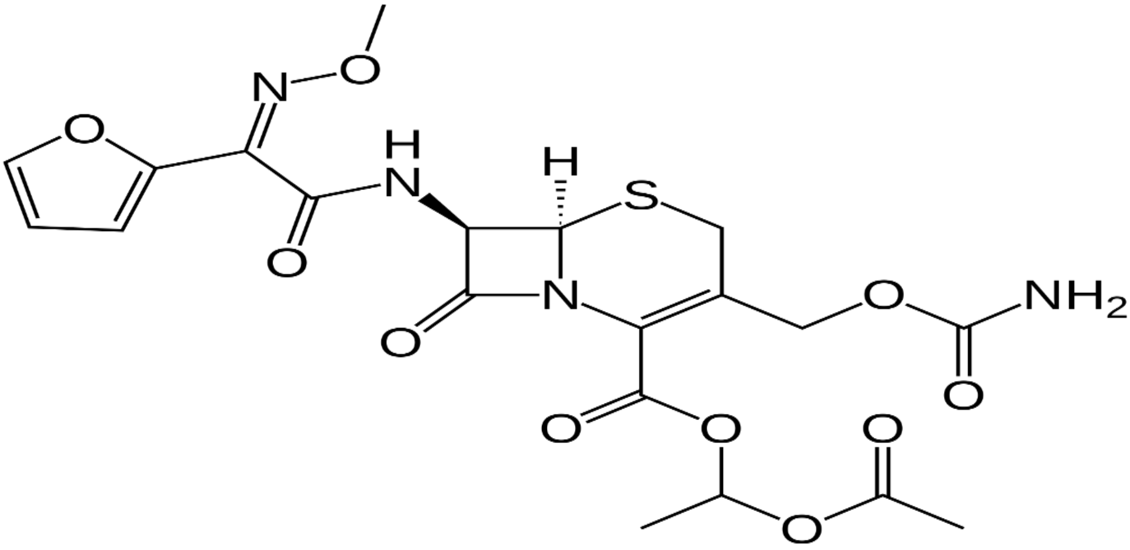


Figure 1.2: Chemical structure of cefuroxime axetil

The major problem of CFA is its low oral bioavailability, beside low aqueous solubility, according to BCS, CFA classified as class II and it needs to enhance its solubility and bioavailability [Shrinivas. P, Satish. P, Arshia. S, Thakur. R, 2014].

Other problem faceing the oral drug of CFA that it can transform into an inactive form (Δ 2-CFA) during absorption in the intestine, thus not all active ingredient converted to an active moiety of CFA [Kees. F, Lukassek. U, Naber. K, Grobecker. H, 1991].

In our study, we will try to benefit from the unique properties of MEs that include high stabilization of water and oil to increase solubility of CFA, and reduce the leaching of their active ingredients by protecting them with oil phase MEs

Chapter Two

Literature review

- Phase behavior

Kunieda. H, Harigai. F, (1990) investigate the effect of temperature (75, 77 and 79ºC) and alcohol chain length on the phase behavior of the system: W/ Ionic surfactant/ Alcohol, where surfactant is Sodium octyl sulfonate (R_8SO_3Na) and the alcohol is hexanol or pentanol. They indicated that at a lower temperature, the phase behavior is almost stable, but raising the temperature will shift the phase behavior towered high concentration of surfactant on the three phase triangle regime. Also, they observed that the solubility curves become continuous from water to the oil-rich region at a temperature above 78.3ºC.

Replacing of hexanol with pentanol, that this substitution causes a dramatic decreases in the phase behavior and solubility of surfactants from 78.3ºC in hexanol microemulsion system to 26.8ºC in pentanol microemulsion system.

Fanun.M, and Salah Al-Diyn. W, (2006) investigated the phase behavior of system water/sucrose laurate/ethoxylated mono-di-glycerides/ caprylic capric triglyceride as a function of temperature and oil content, they found that at low temperatures the mixed nonionic surfactants are soluble in water and two phases are observed, at high temperatures the mixed surfactants are soluble in oil and another two phases are observed and at low oil contents only one phase region is observed. This region extends for the range of temperatures from 7°C to 95 °C. In another study, they investigated the phase behavior of the systems water/sucrose laurate/ethoxylated mono-di-glyceride/oil as a function of temperature and the weight ratio of EMDG in the mixed surfactants. The oils were R (+)-limonene (LIM), isopropyl myristate (IPM), and caprylic capric triglyceride (CCT), they found that the phase inversion temperature (PIT) decreases and the efficiency of the mixed surfactants increase as the weight ratio of the EMDG in the mixed surfactants increases. R (+)-limonene (LIM) gave lower phase inversion temperatures and higher efficiencies compared to isopropyl myristate (IPM), and caprylic capric triglyceride (CCT). The solubilization capacity of the system water/sucrose laurate/oil increased upon the addition of ethoxylated mono-di- glyceride that stabilizes the surfactant layer and increases the interfacial area.

Fanun. M, (2010) studied the effect of surfactants mixing ratio, surfactants contents and oil/water weight ratio of the interfacial area and aggregation number of the system: W/mixed surfactants/ oil, were the mixed surfactants are Ethoxylated Mono and Di-Glyceride (EMDG), Sucrose laurate (L1695) and the oil is R (+) - Limonene (LIM). The following observation were found:

- The interfacial area increases as the EMDG content increases, so that the interfacial area increases from 0.74 to 2.8nm^2 when the EMDG content increased from 0 to 100 wt. %.

- The aggregation number (n) increases as a function of molar concentration ratio for different EMDG content increases. At 50 wt. % EMDG content the aggregation number increases to high valuesdue to a structural and shape transition.

- The aggregation number (n) increases with the increase of molar concentration ratio for mixed surfactants contents.

- The aggregation number (n) decreases with the increase in the oil/water weight ratio at fixed mixed surfactants contents.

Nursakinah. I, et al, (2015) investigated the effect of HLB and functional head group of different types of nonionic surfactant on microemulsion parameters of the systems: W/ Polyethoxylates (POE) (20), POE (20) sorbitan monooleate (or Tween 80), Fatty alcohol POE (25) and Laureth-1 / Palm methyl ester C12 – 18. They found that the Fatty alcohol POE (25) with HLB value equal 11±1 has optimum mean droplet size, stable zeta potential, and low surface tension. The second observation shows that the increase of HLB values results in increasing the droplet size and surface tension.

- Electrical conductivity

Lagues. M, Sauterey. C, (1980) studied the effect of water/surfactant molar ratio and the effect of added electrolyte (0.5M NaCl) on the electrical conductivity values of microemulsion composed of water, cyclohexane, SDS and 1- pentanol. It was showen that the different molar ratios of water/ surfactant will induce a variety in increasing of electrical conductivity values, and of different percolation threshold points according to increasing the water volume fraction. They also observed steeply increasing of electrical conductivity values when replacing the water with 0.5M NaCl solution, and the percolation threshold was increased to the highest value.

Fanun M, (2008) investigated the electrical conductivity of brine solution/ Sucrose lurate (L1695) / Ethoxylated Mono and Di-Glyceride (EMDG) / oil + ethanol. The oils were R (+) - Limonene (LIM), Isopropyl-Myristate (IPM) and caprylic capric triglyceride (CCT). The mixing ratio (w/w) of Sucrose lurate / Ethoxylated mono and diglyceride and that of oil/ ethanol equal unity.The brine solution was 0.01M aqueous sodium chloride.

No observable effect was observed on the phase boundaries by replacing pure water with brine solution in the case of LIM based MEs, on the contrary of IPM the replacing causes decrease in the one phase region, also in the case of CCT based MEs causes a significant decrease of about 30% in the total monophasic area (A_T %). On the other hand, the activation energy of the conduction was measured for the same system of different oils and found that electrical conductivity increases with increase in water volume fraction and percolation threshold were observed. LIM based MEs have a lower value of ΔE_{cond} followed by CCT, were IPM have the highest value of ΔE_{cond}. Also, it was observed that percolation threshold in MEs based on LIM and CCT are equal, and have very low value ($\Phi_c = 0.04$), while IPM hasa higher value ($\Phi_c = 0.11$).

Wang. F, et al, (2008) investigated a combination of electrical conductivity, UV- vis spectroscopy and FTIR spectra to study the diluted microemulsion system: W/ $C_{16}EO_{20}$/ n-butanol/ heptane. Fixed the mass ratio of $C_{16}EO_{20}$/ n-butanol/ heptane, then increased the water content by adding 0.1mM NaCl solution, the percolation threshold was observed at 20 wt. % water volume fraction and a complete structural inversion from water- in- oil to bicontinuous microemulsion at water volume fraction equal 40 wt. %. At low water content, the electrical conductivity has low value and increasing of electrical conductivity suggested by the hydration of polyethylene oxide in the head group of surfactant molecule after a complete hydration of EO the microemulsion system reaches a percolation threshold. Moreover the ionization of NaCl to Na^+, Cl^- induce the electric field among the system and unbounded water in the core acting as a medium for ions exchange resulting in sharply increase of electrical conductivity. They predicted that the complete inversion to bicontinuous microemulsion was occurred at water volume fraction equal to 45 wt. %.

- Drug solubility and permeability

Joshi. M, et al, (2014) studied the permeability of cefuroxime axetil (CFA) sol gel for periodontitis treatment by Franz diffusion cell technique, they used pluronic f127, pluronic f108 polymers, benzalkonium chloride and Distilled water to prepare different formulations of CFA sol gel varying with ratios of pluronic f108.

Five systems were formulated (F1 – F5) showed a varying in the permeation of CFA active pharmaceutical drugs, the formula F3 which contain 6% w/v pluronic f108 gives the highest drug release of CFA equal 97.84%. The value of drug released at the end of seven days of Franz diffusion cell permeability studies ranged from 89 – 97%, also by an antimicrobial testing of isolated strains microorganisms which caused periodontitis, the results indicated that the formulated sol gel can definitely be used for once a week treatment for periodontitis

Puttachari. S, Kalyane. N, Duttagupta. S, (2013) designed and developed self – micro emulsifying drug delivery systems (SMEDDS) with different surfactants, co-surfactants, and co-solvents to enhance solubility and bioavailability of cefuroxime axetil (CFA), were SMEDDS are thermodynamically stable MEs consisting of oil, surfactants, co-surfactants that spontaneously forming MEs when mixed with water. It was investigated saturation and solubility of CFA in different surfactants, co-surfactants, co-solvents and oils to prepare prototype formulation of SMEDDS. In the form of surfactants, Transcutol showed good solubility followed by Labrasol. Among the co-surfactants, Gelucire showed a good solubility; so it was selected as co-surfactants. According to co-solvents, PEG 400 showed good solubility; so it was selected as co-solvents. No oils showed a good solubility; hence no oils was select. From above results, S. Puttachari et al formulated 10 prototypes (F1–F10) Labrasol/ Gelucire/ PEG 400 MEs with different concentrations of all components. The drug loading capacity of formulation coded with No. F10 which contain (0.64ml PEG 400, 0.08ml Labrasol and 0.28ml Gelucire) was the highest as compared to other formulations. Beside S. Puttachari et al made comparative in-vitro dissolution profile of SMEDDS formulation, marketed formulation (Cefix 125mg tablet) and pure drug, they observed that thedissolution of SMEDDS formulation was rapid and complete within 10 minutes whereas the marketed formulation released only 70% of label claim in 60 minutes while the dissolution of pure CFA was below negligible.

Sruti. J, et al, (2013) studied the solubility and dissolution rate of cefuroxime axetil (CFA) by a combination of fusion and surface adsorption technique by means of preparing solid dispersion formulae in the presence of poloxamer 188 and neusilin (US2), were neusilin is synthetic amorphous form of magnesium alumino-metasilicate and poloxamer is polyoxyethylene-polypropylene block copolymer nonionic surfactant. They prepared different formulations with different weight ratios of CFA, poloxamer 188 and neusilin (US2).The solubility of solid dispersion by fusion and surface adsorption techniqueswas 12- 14 times more than the solubility of CFA without treatment.

Moreover, the study showed that the release of CFAin 15min and was 20-23 times degree of folding in the improvement of dissolution rate for fusion and surface adsorption technique respectively.

Patel. Y, Poddar. A, Sawant. K, (2012) investigated the effect of nanoemulsion formulation formed of capmul CMC, soya lecithin, deoxycholic acid, Pluronic F127 and distilled water on the bioavailability of cefuroxime axetil (CFA) active pharmaceutical drug. They studied a combination of drug content, diffusion study, intestinal permeability and other investigations by various way of techniques. A comparative study was performed between ordinary CFA oral suspension and a nanoemulsion formulated one, they found that the lipid nanoemulsion has 80.7% diffusion better than ordinary oral suspension that has diffusion value equal the 51.1 %, furthermore the permeability study of nanoemulsion formulation showed a higher permeability of value equal the 59.3µg/ml, whereas ordinary oral suspension has 37.3µg/ ml.

Fanun. M, (2007) studied the solubilization capacity (SC) of diclofenac sodium active pharmaceutical drug in micellar solution containing mixed surfactants and isopropyl myristate oil (IPM) at the dilution line N60, were the mixed surfactants are, sucrose laurate (L1695) and ethoxylated mono diglyceride (EMDG) micellar system at constant weight ratio of L1695/EMDG/IPM equal the 3:3:4. It was observed that the SC strongly correlated to the microemulsion microstructures, so as for at water content 0-20 wt. % were the system is a reverse micelle, the SC of diclofenac sodium decreases from 16,000 to 11,600ppm. This decrease interpreted because the reverse micelles become less hydrophilic causing less space available to penetrate the diclofenac sodium active pharmaceutical drug. From 20- 70 wt. % water content the SC remains almost unchanged suggested that the microemulsion system converted to bicontinuous, then the SC back to decrease again from 70- 90 wt. % water content to 4000ppm due to another conversion to oil- water microemulsion was formed.

Fanun also investigated the adding of co-surfactant to the previous system at a constant weight ratio of L1695/EMDG/IPM+ ethanol equal 3:3:2:2, he observed that the ethanol plays a role in enhancing the solubilization capacity of diclofenac sodium is 16,000ppm, whereas the system free of ethanol is equal to 12,800ppm.

Chapter Three

Objectives

1. Formulation of microemulsion systems using different components which include biologically compatible oil phase (cyclic oil; R (+) - limonene, linear oil; isopropyl myristate, and triglyceride oil; caprylic capric triglyceride), aqueous phase, single or mixed nonionic surfactants (sucrose oleate O1570 and sorbitan monooleate TMAZ 80) with addition of co-surfactant (ethanol, propylene glycol, propionic acid, glycerol) at different temperatures (25, 37 and 45ºC), this is accomplished by the investigation of multicomponent system phase diagrams.

2. Determination of the water solubilization capacity of the formulated microemulsion systems by evaluating the area of the one-phase microemulsion region (A_T %).

3. Exploring the microstructures of the formed microemulsion by electrical conductivity measurements (σ). This technique will be used to study how changes in the relative amounts of the surfactant and in the single or mixed surfactants, the presence of co-surfactant and the addition of water influence the microemulsion microstructure within the one-phase region.

4. Evaluation of the maximum solubilization capacity of the pharmaceutically active ingredient of cefuroxime axetil and find a relation between the microstructure of the formulated microemulsions and the quantity of solubilized material.

5. Determination of the maximum solubility and permeability of cefuroxime axetil in different microemulsion systems using Franz diffusion cell.

Chapter Four

Materials & Methods

4.1.Materials

4.1.1 Surfactants (surface active ingredients)

4.1.1.1 Sucrose Oleate (O1570)

Sucrose esters (SE) are biodegradable, biocompatible and food grade surfactants with excellent ability to be used in pharmaceutical applications. It is produced by a reaction between sucrose and fatty acids resulting in a wide variety of surfactant molecules according to the sucrose molecule.

Sucrose oleate (O1570) was obtained from Mitsubishi- Kasei Food Corp., (Mie, Japan). The purity of combined oleic acid equal 70%. The ester composition is 70% monoester and 30% di, tri and polyester with hydrophilic-lipophilic balance (HLB) equal 15. In addition, it has chemical formula $C_{30}H_{54}O_{12}$ and of molecular weight 607 g/mole(**See Figure 4.1**)

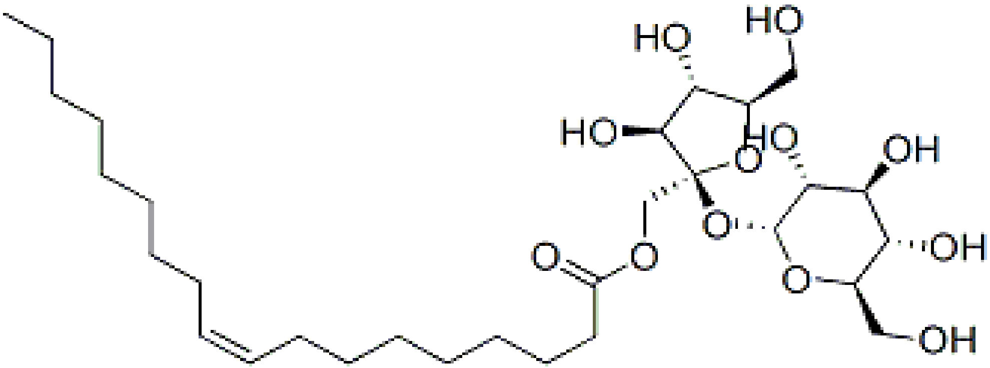


Figure 4.1: Chemical structure of sucrose oleate (O1570)

4.1.1.2 Sorbitan monooleate(T- MAZ 80)

Sorbitan monooleate (T-MAZ 80) is a nonionic surfactant and emulsifier often used in foods and cosmetics. This synthetic compound is viscous, water-soluble and yellow liquid.

It is derived from polyethoxylated sorbitan and oleic acid. The hydrophilic groups in this compound are polyethers also known as polyoxyethylene groups, which are polymers of ethylene oxide. It has been ethoxylated with approximately 20 moles of ethylene oxide to give a water soluble, oil soluble and water emulsifier, and of HLB value equal 15 with molecular formula $C_{24}H_{44}O_6$, and of molecular weight 428.6 g/mole. It is obtained from BASF corp.

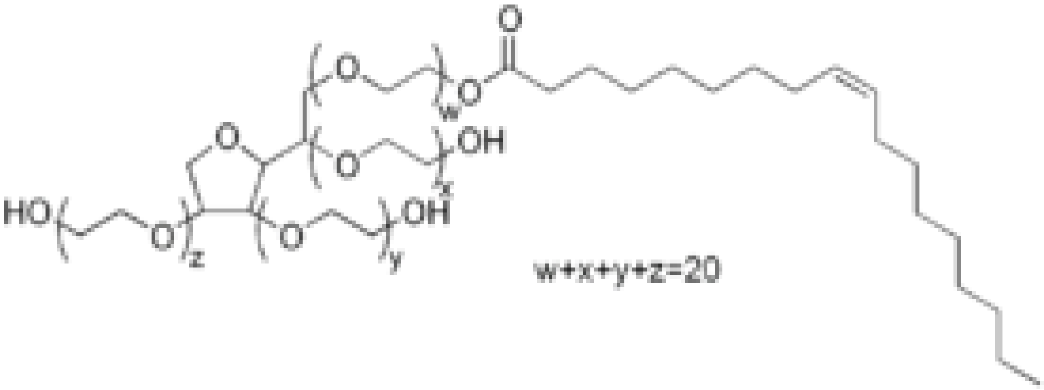


Figure 4.2: Chemical structure of Sorbitan monooleate (T-MAZ 80)

4.1.2 Co-Surfactants

4.1.2.1 Ethanol (EtOH)

Is a straight chain alcohol, it is also known as ethyl alcohol that has a clear and colorless liquid. It is chemical formula CH_3CH_2OH. Unsuitable for food uses, on the other hand, it may cause neurotoxic in the human body when takes in large quantity, but using a small amount (about 5%) of ethanol in food products is acceptable. It is obtained from frutarom (Haifa, Israel).

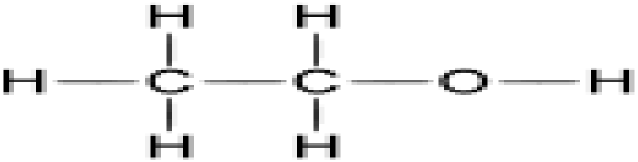


Figure 4.3: Chemical structure of ethanol

4.1.2.2 Propylene Glycol (PG)

Also called propane - 1,2 – diol, it is an organic compound with a chemical and molecular formula $CH_3H_8O_2$. 99.5% was purchased from BDH (Poole, UK).

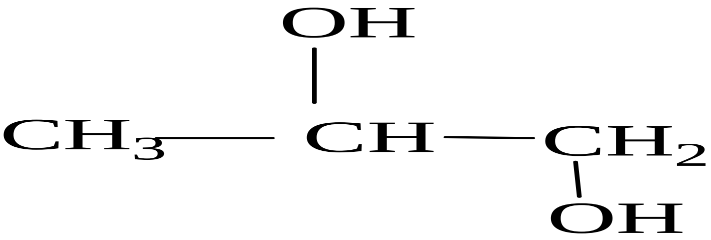


Figure 4.4: Chemical structure of Propylene glycol

4.1.2.3 Propionic Acid (PrA)

Is naturally-occurring carboxylic acid with chemical formula CH_3CH_2COOH. It is a clear liquid with the pungent and unpleasant smell, the anion $CH_3CH_2COO^-$ as well as their salts and ethers of propionic acid are known as propionates (or propanoates). (98%) was purchased from sigma chemicals Co. (St. Louis, USA).

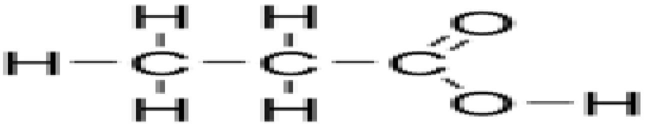


Figure 4.5: Chemical structure of Propionic acid

5.1.2.4 Glycerol (GLY)

Is a simple polyol sugar alcohol compound, or known as 1,2,3 – propanetriol. It is colorless, odorless, sweet-tasting, low toxicity and viscus liquid that widely used in pharmaceutical formulations; since it has high solubility in water, due to the presence of three hydroxyl groups (OH). Glycerol is used in drugs to improve body performance helping body replace water lost; besides it is used as a body moisturizer.

When it is dissolved in water disrupts the hydrogen bonding between water molecules, so such that mixture cannot form stable crystal structure until the temperature is significantly lowered and increase of viscosity. (99%) purchased from sigma chemical Co. (St. Louis, USA).

Figure 4.6: Chemical structure of glycerol

4.1.3 The oils

4.1.3.1 R (+) – Limonene (LIM)

Is colorless liquid hydrocarbon classified as a cyclic monoterpene, it is extracted from citrus fruits. (98%) was purchased from Sigma Chemicals Co. (St. Louis, USA).

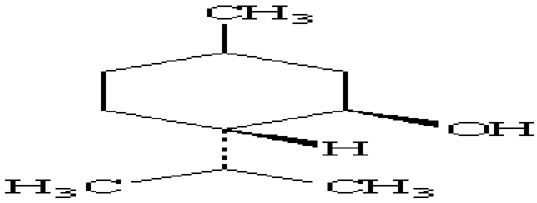
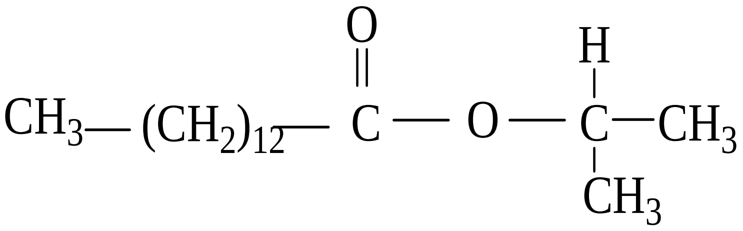


Figure 4.7: Chemical structure of R (+) – Limonene

4.1.3.2 Isopropyl myristate (IPM)

Linear oil, obtained by esterification of isopropanol and myristic acid, it has molecular formula $C_{17}H_{34}O_2$, (99%) was purchased from sigma chemicals Co. (St. Louis, USA).



$$CH_3-(CH_2)_{12}-\overset{\overset{O}{\|}}{C}-O-\underset{\underset{CH_3}{|}}{\overset{\overset{H}{|}}{C}}-CH_3$$

Figure 4.8: Chemical structure of Isopropyl myristate.

4.1.3.3 Caprylic-capric triglyceride (CCT)

Is a triglyceride oil, it is produced by the esterification of glycerol (plant sugar) with a blended of saturated capric acid (C10:0) and caprylic acid (C8:0). It is also known as fractionated coconut oil, the most popular used as emollient creams, more than it is capable of rapid penetration; thus it is used as dispersion agents. (99%) was purchased from Sigma Chemicals Co. (St. Louis, USA).

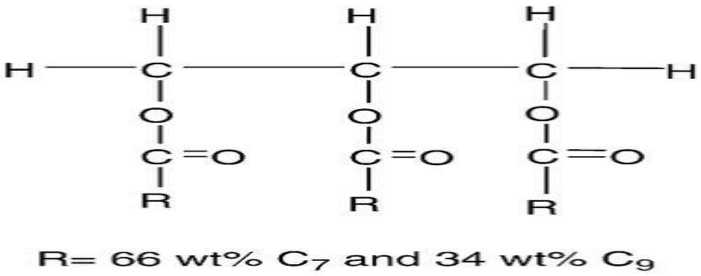


Figure 4.9: Chemical structure of Caprylic-capric triglyceride

4.1.4 Aqueous phase (water)

Aqueous solutions were prepared using deionized water supplied by a Mill-Q Water purification system (Millipore system, Al-Quds university)$\sigma < 3\ \mu S$ was used.

Table 4.1: A summary of all materials used in this research

Oil phase	Surfactants	Co-surfactant	Aqueous phase
R (+)-limonene (LIM) Isopropyl myristate (IPM) Caprylic-capric triglyceride (CCT)	Sucrose oleate (O1570) Sorbitan monooleate (T- MAZ 80)	Propionic acid (PrA) Propylene glycol (PG) Ethanol (EtOH) Glycerol(GLY)	MQ water

4.2. Methods

4.2.1 Construction of phase diagram

Phase behavior of a system containing water, surfactant, co-surfactant, and oil can be represented on ternary or pseudo-ternary phase diagram with tetrahedron whose apexes represents the pure components.

Firstly, 1g of the mixture (oil, surfactant, co-surfactant) at different weight ratios, then titrated with M.Q Water dropwise, every time added 4% water from the previous weight, followed by mixing on the vortex mixer after the equilibrium between these ingredients was reached (from few minutes up to 24 hours). We continue adding M.Q Water until the system separates into two phases,furthermore, we investigated the phase behavior of the system at different three temperatures (25, 37 and 45°C).

Table 4.2: The materials used in the construction of phase diagrams (single surfactant – single oil with co-surfactants) LIM oil

Aqueous phase	**Surfactant**	**Oil**	**Co-surfactant**	**Ratio of Sur/Cos**
W	O1570	LIM	EtOH	(1/1), (2/1)
W	O1570	LIM	PG	(1/1), (2/1)
W	O1570	LIM	PrA	(1/1), (2/1)
W	O1570	LIM	GLY	(1/1), (2/1)

Table 4.3: The materials used in the construction of phase diagrams (single surfactant – single oil with co-surfactants) IPM oil

Aqueous phase	**Surfactant**	**Oil phase**	**Co-surfactant**	**Ratio of Sur/Cos**
W	O1570	IPM	EtOH	(1/1), (2/1)
W	O1570	IPM	PG	(1/1), (2/1)
W	O1570	IPM	PrA	(1/1), (2/1)
W	O1570	IPM	GLY	(1/1), (2/1)

Table 4.4: The materials used in the construction of phase diagrams (single surfactant – single oil with co-surfactants) CCT oil

Aqueous phase	Surfactant	Oil phase	Co-surfactant	Ratio of Sur/Cos
W	O1570	CCT	EtOH	(1/1), (2/1)
W	O1570	CCT	PG	(1/1), (2/1)
W	O1570	CCT	PrA	(1/1), (2/1)
W	O1570	CCT	GLY	(1/1), (2/1)

Table 4.5: The materials used in the construction of phase diagrams (mixed surfactants – single oil) LIM oil

Aqueous phase	Mixed Surfactants	Oil phase	Ratio of O1570/T-MAZ 80
W	O1570 + T-MAZ 80	LIM	(1/1), (1/2), (2/1)
W	O1570 + T-MAZ 80	LIM	(1/1), (1/2), (2/1)
W	O1570 + T-MAZ 80	LIM	(1/1), (1/2), (2/1)
W	O1570 + T-MAZ 80	LIM	(1/1), (1/2), (2/1)

Table 4.6: The materials used in the construction of phase diagrams (mixed surfactants – single oil) IPM oil

Aqueous phase	Mixed Surfactants	Oil phase	Ratio of O1570/T-MAZ 80
W	O1570 + T-MAZ 80	IPM	(1/1), (1/2), (2/1)
W	O1570 + T-MAZ 80	IPM	(1/1), (1/2), (2/1)
W	O1570 + T-MAZ 80	IPM	(1/1), (1/2), (2/1)
W	O1570 + T-MAZ 80	IPM	(1/1), (1/2), (2/1)

Table 4.7: The materials used in the construction of phase diagrams (mixed surfactants – single oil) CCT oil

Aqueous phase	Mixed Surfactants	Oil phase	Ratio of O1570/T-MAZ 80
W	O1570 + T-MAZ 80	CCT	(1/1), (1/2), (2/1)

W	O1570 + T-MAZ 80	CCT	(1/1), (1/2), (2/1)
W	O1570 + T-MAZ 80	CCT	(1/1), (1/2), (2/1)
W	O1570 + T-MAZ 80	CCT	(1/1), (1/2), (2/1)

Table 4.8: The materials used in the construction of phase diagrams (mixed surfactants –oil with co-surfactant mixture) EtOH co-surfactant

Aqueous phase	Mixed Surfactants	Oil phase	Co-surfactant	Ratio of oil/EtOH	Ratio of O1570/T-MAZ 80
W	O1570 + T-MAZ 80	LIM	EtOH	(1/1)	(1/1)
W	O1570 + T-MAZ 80	IPM	EtOH	(1/1)	(1/1)
W	O1570 + T-MAZ 80	CCT	EtOH	(1/1)	(1/1)

Table 4.9: The materials used in the construction of phase diagrams (mixed surfactants –oil with co-surfactant mixture) PG co-surfactant

Aqueous phase	Mixed Surfactants	Oil phase	Co-surfactant	Ratio of oil/PG	Ratio of O1570/T-MAZ 80
W	O1570 + T-MAZ 80	LIM	PG	(1/1)	(1/1)
W	O1570 + T-MAZ 80	IPM	PG	(1/1)	(1/1)
W	O1570 + T-MAZ 80	CCT	PG	(1/1)	(1/1)

Table 4.10: The materials used in the construction of phase diagrams (mixed surfactants –mixed oils)

Aqueous phase	Mixed Surfactants	Oil phase	Ratio of oil/oil	Ratio of O1570/T-MAZ 80
W	O1570 + T-MAZ 80	LIM + IPM	(1/1)	(1/1)
W	O1570 + T-MAZ 80	LIM + CCT	(1/1)	(1/1)

4.2.2 Determination of maximum water solubility (A_T %)

The water solubilization capacity of different amphiphilic systems should be compared at optimal conditions. In this research, we used the one phase microemulsion region to compare the water solubilization capacity in the studied systems by evaluation the area of one phase systems under the curve. The relative error in determining of`` the A_T percentage was estimated to be ±2% for all of the systems studied. The following figure illustrated a schematic phase diagram where the one phase region and the multicomponent microemulsion regions are shown.

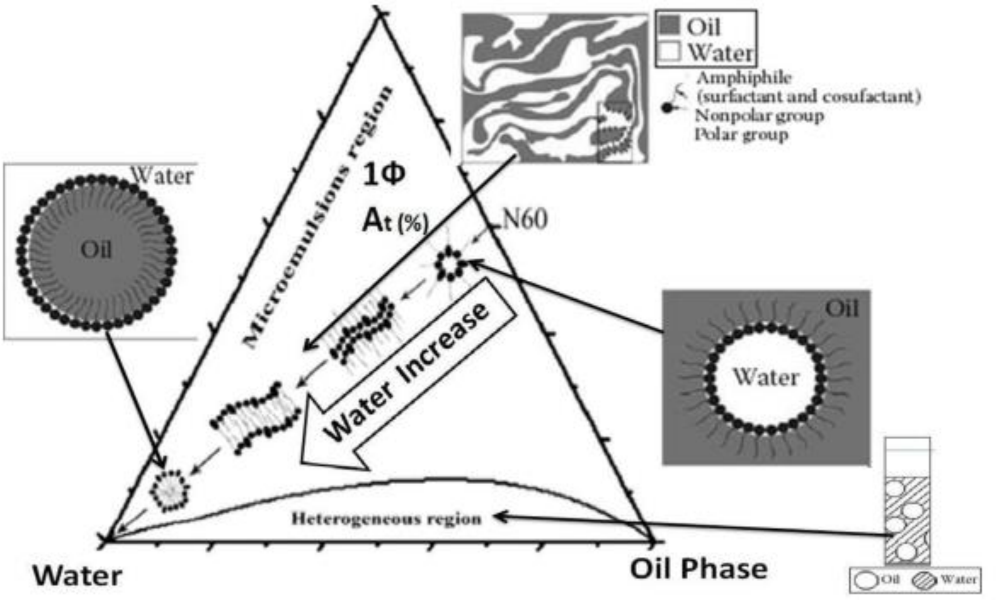


Figure 4.10: Schematic representation of the structural transitions along the dilution line N60

4.2.3 Electrical conductivity measurements

Electrical conductivity is the ability of a solution to transfer (conduct) electric current, Conductivity measurements were performed at temperature ±0.3ºC on samples the compositions of which lie along one phase channel, using conductivity meter to observe the type of microemulsion in the systems O/W, W/O or bicontinuous, the conductivity meter cell used is Tetra Con® 325, the electrode material is graphite and the cell constant is $0.475 cm^{-1}$ ±1.5%. The temperature range is from 10 to 50ºC. The electrode dipped in the microemulsion samples until equilibrium was reached and reading become stable. Sucrose ester (SE) nonionic surfactant without the addition of electrolyte was used in this study, the SE conduct electrical current because it may have impurities that carried charged ions.

Reproducibility was checked for certain samples for validation purpose. The conductivity cell was calibrated using standard KCl solutions at different time intervals or when the conductivity meter needs that.

Table 4.11: The system used for determination of electrical conductivity (Mixed surfactants- Single oil)

Aqueous phase	Mixed Surfactants	Oil phase	Ratio of O1570/T-MAZ 80
W	O1570 + T-MAZ 80	LIM	(1/1)
W	O1570 + T-MAZ 80	LIM	(1/2)
W	O1570 + T-MAZ 80	LIM	(2/1)
W	O1570 + T-MAZ 80	IPM	(1/1)
W	O1570 + T-MAZ 80	CCT	(1/1)

Table 4.12: The system used for determination of electrical conductivity (Mixed surfactants- Single oil with co-surfactant)

Aqueous phase	Mixed Surfactants	Oil phase	Co-surfactant	Ratio of Sur/Cos	Ratio of O1570/T-MAZ 80
W	O1570 + T-MAZ 80	LIM	EtOH	(1/1)	(1/1)
W	O1570 + T-MAZ 80	LIM	PG	(1/1)	(1/1)

Table 4.13: The system used for determination of electrical conductivity (Mixed surfactants- Mixed oils)

Aqueous phase	Mixed Surfactants	Oil phase	Ratio of oil/oil	Ratio of O1570/T-MAZ 80
W	O1570 + T-MAZ 80	LIM + IPM	(1/1)	(1/1)
W	O1570 + T-MAZ 80	LIM + CCT	(1/1)	(1/1)

4.2.4 Determination of drugs solubilization capacity

Solubilization of cefuroxime axetil (CFA) has been studied in different microemulsion systems, 2 g of microemulsion was prepared in a test tube and then a small amount of CFA (about 5 mg in each step) was added and dissolution was performed by mixing through a vortex in water bath at 45°C for 120 min and then stored at 25°C in water bath. Samples which remained transparent for at least 5 days were loaded step-wise with additional CFA to its maximum solubilization. The appearance of turbidity, or a precipitate, indicates that the microemulsions were drug saturated (or supersaturated). No further drug loading in such samples was done. The dissolved amount of CFA was estimated by calculating the accumulated weight of CFA which was added before the appearance of turbidity, or a precipitate after holding in a water bath at 25 °C for at least 5 days.

Table 4.14: The system used for determination of drug solubilization capacity (Mixed surfactants- Single oil)

Aqueous phase	Mixed Surfactants	Oil phase	Ratio of O1570/T-MAZ 80
W	O1570 + T-MAZ 80	LIM	(1/1)
W	O1570 + T-MAZ 80	LIM	(1/2)
W	O1570 + T-MAZ 80	LIM	(2/1)
W	O1570 + T-MAZ 80	IPM	(1/1)
W	O1570 + T-MAZ 80	CCT	(1/1)

Table 4.15: The system used for determination of drug solubilization capacity (Mixed surfactants- Single oil with co-surfactant) EtOH co-surfactant

Aqueous phase	Mixed Surfactants	Oil phase	Co-surfactant	Ratio of oil/EtOH	Ratio of O1570/T-MAZ 80
W	O1570 + T-MAZ 80	LIM	EtOH	(1/1)	(1/1)
W	O1570 + T-MAZ 80	IPM	EtOH	(1/1)	(1/1)
W	O1570 + T-MAZ 80	CCT	EtOH	(1/1)	(1/1)

Table 4.16: The system used for determination of drug solubilization capacity (Mixed surfactants- Single oil with co-surfactant) PG co-surfactant

Aqueous phase	**Mixed Surfactants**	**Oil phase**	**Co-surfactant**	**Ratio of oil/PG**	**Ratio of O1570/T-MAZ 80**
W	O1570 + T-MAZ 80	LIM	PG	(1/1)	(1/1)
W	O1570 + T-MAZ 80	IPM	PG	(1/1)	(1/1)
W	O1570 + T-MAZ 80	CCT	PG	(1/1)	(1/1)

Table 4.17: The system used for determination of drug solubilization capacity (Mixed surfactants- Mixed oils)

Aqueous phase	**Mixed Surfactants**	**Oil phase**	**Ratio of oil/oil**	**Ratio of O1570/T-MAZ 80**
W	O1570 + T-MAZ 80	LIM + IPM	(1/1)	(1/1)
W	O1570 + T-MAZ 80	LIM + CCT	(1/1)	(1/1)

5.2.5 Drug permeability study and HPLC analysis

An appropriate amount of microemulsion systems containing CFA dissolved in x% concentrationwere spreaded on the polyvinyldine difluoride (PVDF) membrane at donor site of franz diffusion cell. The receiver compartment contains methanol: phosphate buffer PH=7.4 solution in (20:80 ratio), the solution was stirred at 600rpm by magnetic stirrer atconstant temperature equal 37± 0.5ºC.

1ml samples withdrawn at different times intervals (30min, 1h, 2h and 24h) and analyzedby HPLC according to USP 39 – NF 34, 2017 guideline.

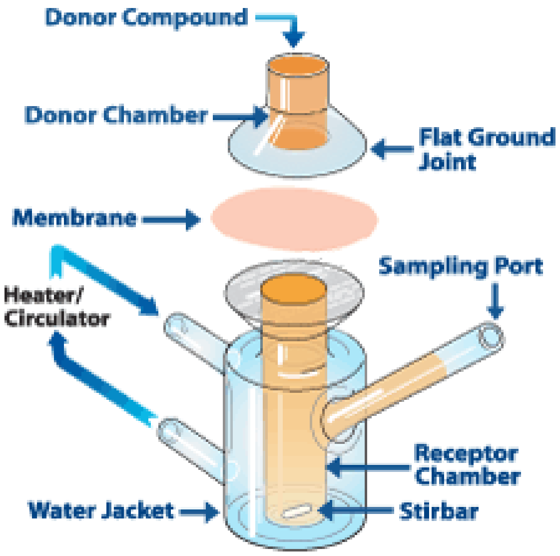


Figure 4.11: The Franz diffusion cell apparatus

Chapter five

Results and discussions

5.1 Phase behavior

It is important and necessary to determine the phase behavior of microemulsions that describe the experimental condition in which it combines the different components in order to obtain transparent, isotropic and low viscous one phase systems, it was introduced decades ago by Gillberg and co-workers [Gillberg. G, Lehtinen. H, Friberg. S, 1970].Phase behavior of microemulsion provides a valuable information about the structure of surfactants, co-surfactants, and oils that play a role in determining system properties at any point.

A number of factors that influence the phase behavior of microemulsion, among these factors the changing of temperature and/ or surfactant concentration will change the type of microemulsions formed (Winsor I, Winsor II, Winsor III) [Fanun. M, Salah Al-diyn. W, 2006], furthermore, types and concentration of surfactant can reduce the interfacial free energy and hence thermodynamic stability obtained when zero interfacial tension is achieved [Basheer. H, et al, 2013].

Alcohol's effect on the formation of microemulsion and phase behavior by decreasing the interfacial tension and interfacial energy, likewise short chain alcohol can delay the occurrence of liquid crystalline phase by increasing the fluidity of the interfacial layer separating oil and water, moreover the use of co-surfactants to reduce the surfactant concentration because of the issue of bioincompatibility of surfactants [Alany. R, et al, 2000].

Also hydrophobic chain length of surfactants, co-surfactants can influence the phase behavior of microemulsions, thereby the larger hydrophobic chain lengths of surfactants increase of penetration of the alkyl chain of the surfactant into the oil, which promote theincrease the total monophasic area of microemulsion, on the other hand, small to medium chain length of co-surfactants can enhance the total monophasic area, it is by penetrating co-surfactant molecules into the interface and destabilizing liquid crystalline phase [Zhong. F, et al, 2012].

Different types of oils affect the structure of microemulsions formed, hydrophobic ones are solubilized in the hydrophobic core while the polar molecules can be located close to the surfactant head groups, these oils influence the surfactant layer curvature in aggregates or self-organized structures when solubilized [Fanun. M, 2010], according to the types of oils being solubilized, curvature becomes less positive or negative, and the curvature is defined as positive when the surfactant film is convex toward water [Kunieda. H, et al, 2000].

Others [Kunieda. H, Harigai. F, 1990], [Mitra. R, Paul. B, 2005], [Kahlweit. M, Strey. R, Busse. G, 1991], [Lekkerker.H, et al, 1996] and [Fanun.M, 2007] studied different factors that influence the phase behavior of microemulsion.

One of the goals of this study was to incorporate a large amount of water into the microemulsions. Thus we estimated the maximum water solubilization capacity by determining the total monophasic area (A_T%) under the phase curve.

5.1.1 Single surfactant systems phase behavior

In this section, we study the phase behavior of single surfactant, sucrose oleate (O1570) with different three types of oils (LIM, IPM and CCT) and four types of co-surfactants (EtOH, PG, PrA, GLY) at two weight ratios between surfactant and co-surfactants (1:1 and 2:1 (w/w) Sur: Cos respectively) in order to determine the total monophasic area A_T% (±2%) at three different temperatures (25, 37 and 45°C).

5.1.1. a water/ sucrose oleate (O1570)/ ethanol (EtOH) / oils systems

- Ratio of O1570/EtOH of equals unity

Figure 5.1 presents the phase diagram of the system water/sucrose oleate (O1570)/ethanol (EtOH)/R (+)-limonene (LIM) at 25°C. The one phase microemulsion region extends along the different surfactant concentrations as presented in the figure below. The weight ratio (w/w) between O1570/EtOH equals unity.

O1570 + EtOH (wt%)	Maximum water solubilization (wt%)
90	100
80	15
40	15
20	10
10	19

Table 5.1: Maximum water solubilization along the different dilution lines according to figure 5.1 which is illustrated below.

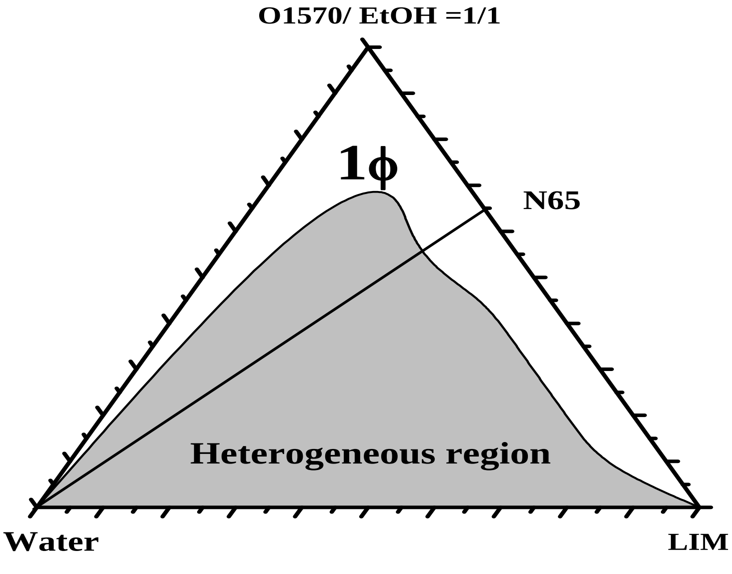


Figure 5.1: Phase diagram of the system: water/ sucrose oleate (O1570) /ethanol (EtOH)/ R(+)-limonene oil (LIM) at 25°C. The one phase region is designated by 1ϕ and the multiphase region is designated by heterogeneous region. The mixing ratio of O1570/EtOH equals unity. N65 is the dilution line where the ratio of (O1570 + EtOH)/ LIM = 65/35.

Figure 5.2 presents the phase diagram of the system water/sucrose oleate (O1570)/ethanol (EtOH)/isopropyl myristate (IPM) at 25°C. The one phase microemulsion region extends along the different surfactant concentrations as presented in the figure below. The weight ratio (w/w) between O1570/EtOH equals unity.

O1570 + EtOH (wt%)	Maximum water solubilization (wt%)
90	100
80	35
40	15
20	13
10	10

Table 5.2: Maximum water solubilization along the different dilution lines according to figure 5.2 which is illustrated below.

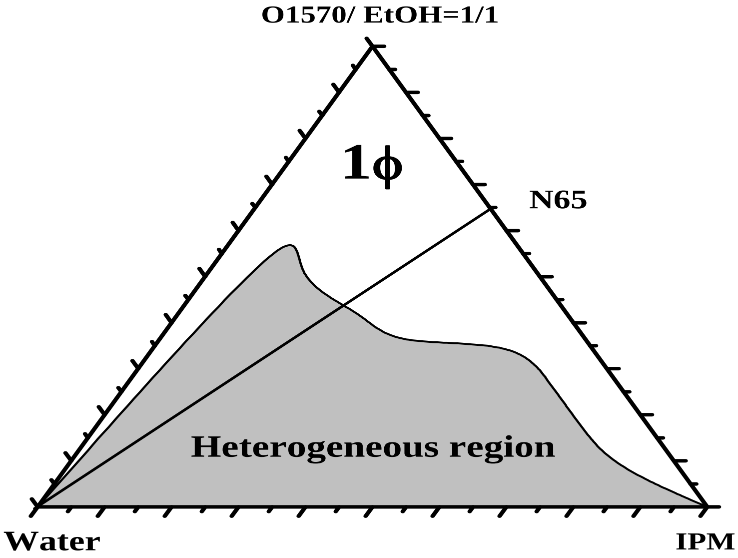


Figure 5.2: Phase diagram of the system: water/ sucrose oleate (O1570) /ethanol (EtOH)/ isopropyl myristate (IPM) at 25°C. The one phase region is designated by 1ϕ and the multiphase region is designated by heterogeneous region. The mixing ratio of O1570/EtOH equals unity. N65 is the dilution line where the ratio of (O1570 + EtOH)/ IPM = 65/35.

Figure 5.3 presents the phase diagram of the system water/sucrose oleate (O1570)/ethanol (EtOH)/caprylic-capric triglyceride (CCT) at 25°C. The one phase microemulsion region extends along the different surfactant concentrations as presented in the figure below. The weight ratio (w/w) between O1570/EtOH equals unity.

O1570 + EtOH (wt%)	Maximum water solubilization (wt%)
90	100
80	30
40	25
20	12
10	10

Table 5.3: Maximum water solubilization along the different dilution lines according to figure 5.3 which is illustrated below.

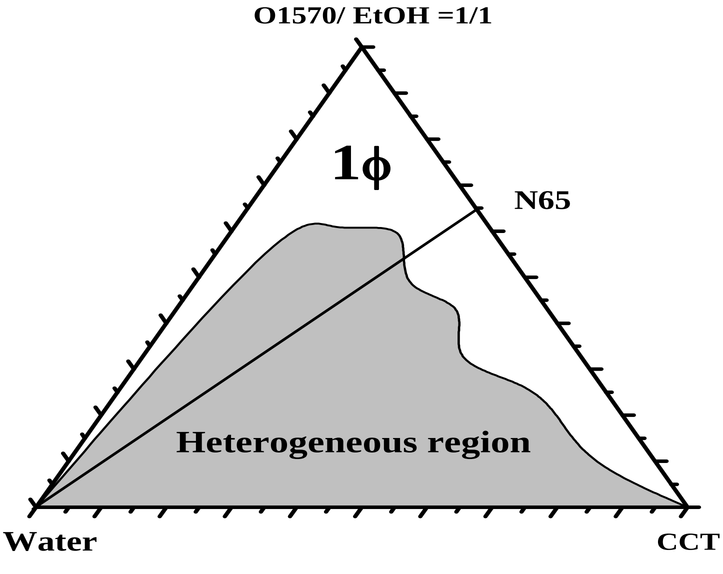


Figure 5.3: Phase diagram of the system: water/ sucrose oleate (O1570) /ethanol (EtOH)/ caprylic-capric triglyceride (CCT) at 25°C. The one phase region is designated by 1ϕ and the multiphase region is designated by heterogeneous region. The mixing ratio of

O1570/EtOH equals unity. N65 is the dilution line where the ratio of (O1570 + EtOH)/ CCT = 65/35.

Table 5.4: The total monophasic area A_T % for the system W/O1570/EtOH/oils for different oil types at different temperatures at a ratio (1/1) between O1570/EtOH.

	A_T % (Total monophasic area)		
Oil	**25°C**	**37°C**	**45°C**
LIM	31	31	31
IPM	43	44	45
CCT	36	37	38

Figure 5.4 shows the variations in the total monophasic area A_T % between three types of oils: LIM, IPM and CCT at three different temperatures (25°C, 37°C, and 45°C) for the system W/ O1570/EtOH/ oils at ratio 1/1 (w/w) between O1570/EtOH.

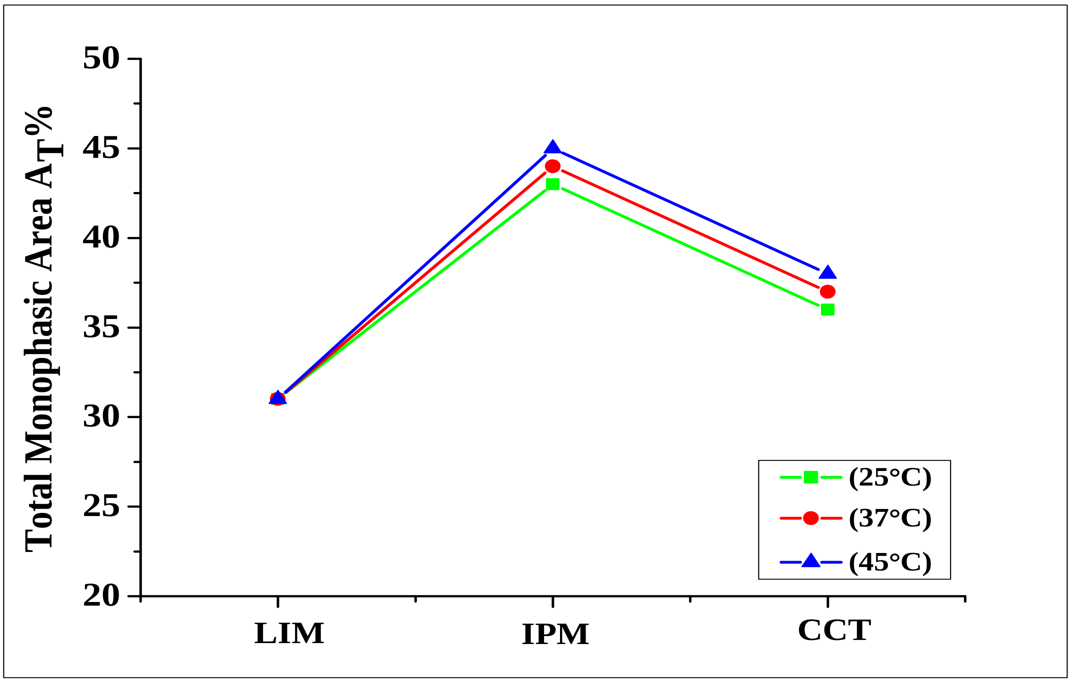


Figure 5.4: Variations in the total monophasic area A_T % of the system

W/O1570/EtOH/oils at three different temperatures (25, 37 and 45ºC) at ratio 1/1 (w/w) between O1570/EtOH.

Table 5.4 and figure 5.4 show the results of different types of oils (linear, cyclic, triglyceride oil) that being studied in microemulsion systems. IPM linear oil gave the highest total monophasic area A_T % comparing with other oils. It seems that the effective carbon number (ECN) of the oil plays the major role in determining the degree of order of the microemulsions formed. The effective carbon numbers of the oils are 7 and 14 for LIM and IPM, respectively. It is the better chain length compatibility between the IPM and the surfactant tail that improves the order in the microemulsions based on this oil.

- Ratio of O1570/EtOH equals two fold

Figure 5.5 presents the phase diagram of the system water/sucrose oleate (O1570)/ethanol (EtOH)/R (+)-limonene (LIM) at 25^{o}C. The one phase microemulsion region extends along the different surfactant concentrations as presented in the figure below. The weight ratio (w/w) between O1570/EtOH equals 2/1.

O1570 + EtOH (wt%)	Maximum water solubilization (wt%)
90	100
80	40
40	25
20	15
10	10

Table 5.5: Maximum water solubilization along the different dilution lines according to figure 5.5 which is illustrated below.

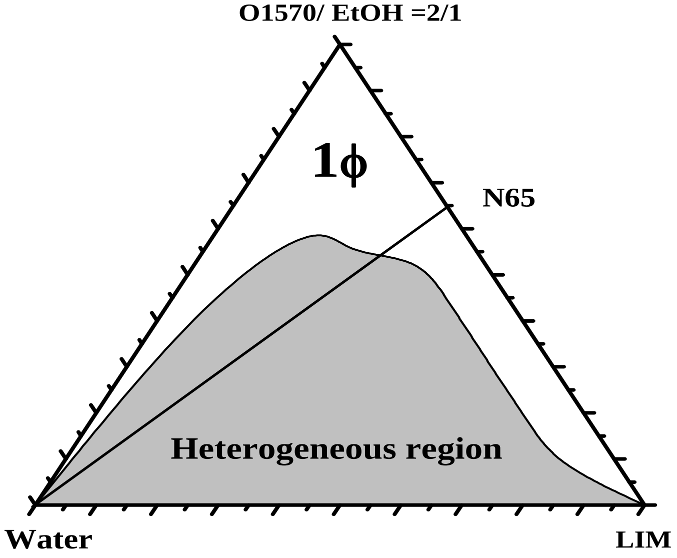


Figure 5.5: Phase diagram of the system: water/ sucrose oleate (O1570) /ethanol (EtOH)/ R(+)-limonene oil (LIM) at 25°C. The one phase region is designated by 1ϕ and the multiphase region is designated by heterogeneous region. The mixing ratio of O1570/EtOH equals 2/1. N65 is the dilution line where the ratio of (O1570 + EtOH)/ LIM = 65/35.

Figure 5.6 presents the phase diagram of the system water/sucrose oleate (O1570)/ethanol (EtOH)/isopropyl myristate (IPM) at 25°C. The one phase microemulsion region extends along the different surfactant concentrations as presented in figure the below. The weight ratio (w/w) between O1570/EtOH equals 2/1.

O1570 + EtOH (wt%)	Maximum water solubilization (wt%)
90	100
80	30
40	20
20	15
10	12

Table 5.6: Maximum water solubilization along the different dilution lines according to figure 5.6 which is illustrated below.

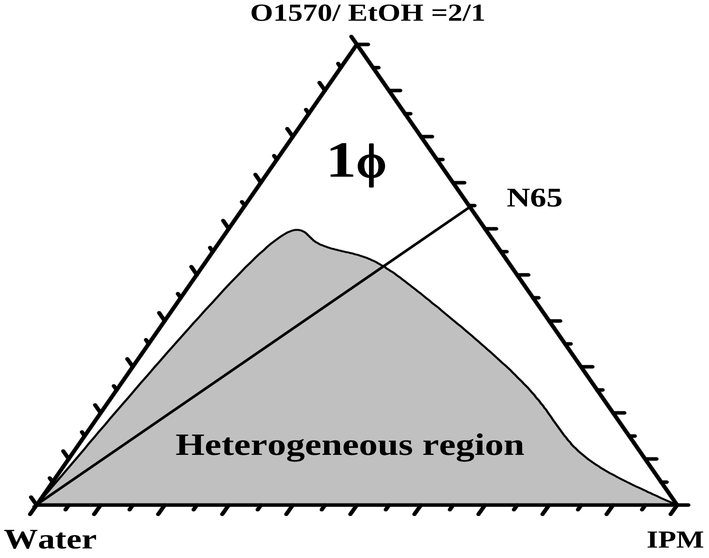


Figure 5.6: Phase diagram of the system: water/ sucrose oleate (O1570) ethanol (EtOH)/ isopropyl myristate (IPM) at 25°C. The one phase region is designated by 1ϕ and the multiphase region is designated by heterogeneous region. The mixing ratio of O1570/EtOH equals 2/1. N65 is the dilution line where the ratio of (O1570 + EtOH)/ IPM = 65/35.

Figure 5.7 presents the phase diagram of the system water/sucrose oleate (O1570)/ethanol (EtOH)/caprylic-capric triglyceride (CCT) at 25^{o}C. The one phase microemulsion region extends along the different surfactant concentrations as presented in the figure below. The weight ratio (w/w) between O1570/EtOH equals 2/1.

O1570 + EtOH (wt%)	Maximum water solubilization (wt%)
90	100
80	60
40	25
20	17
10	15

Table 5.7: Maximum water solubilization along the different dilution lines according to figure 5.7 which is illustrated below.

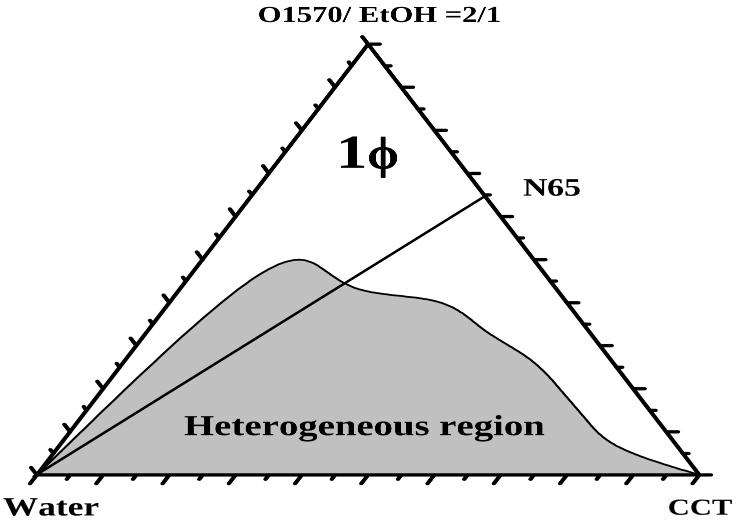


Figure 5.7: Phase diagram of the system: water/ sucrose oleate (O1570) /ethanol (EtOH)/ Caprylic-capric triglyceride (CCT) at 25°C. The one phase region is designated by 1ϕ and the multiphase region is designated by heterogeneous region. The mixing ratio of O1570/EtOH equals 2/1. N65 is the dilution line where the ratio of (O1570 + EtOH)/ CCT = 65/35.

Table 5.8: The total monophasic area A_T % for the system W/O1570/EtOH/oils for different oil types at different temperatures at a ratio (2/1) between O1570/EtOH.

	A_T % (Total monophasic area)		
Oil	**25ºC**	**37ºC**	**45ºC**
LIM	35	35	35
IPM	32	32	29
CCT	45	44	44

Figure 5.8 shows the variations in the total monophasic area A_T % between three types of oils LIM, IPM and CCT and at three different temperatures (25ºC, 37ºC, and 45ºC) for the system W/ O1570/EtOH/ oils at ratio 2/1 (w/w) between O15/70/EtOH.

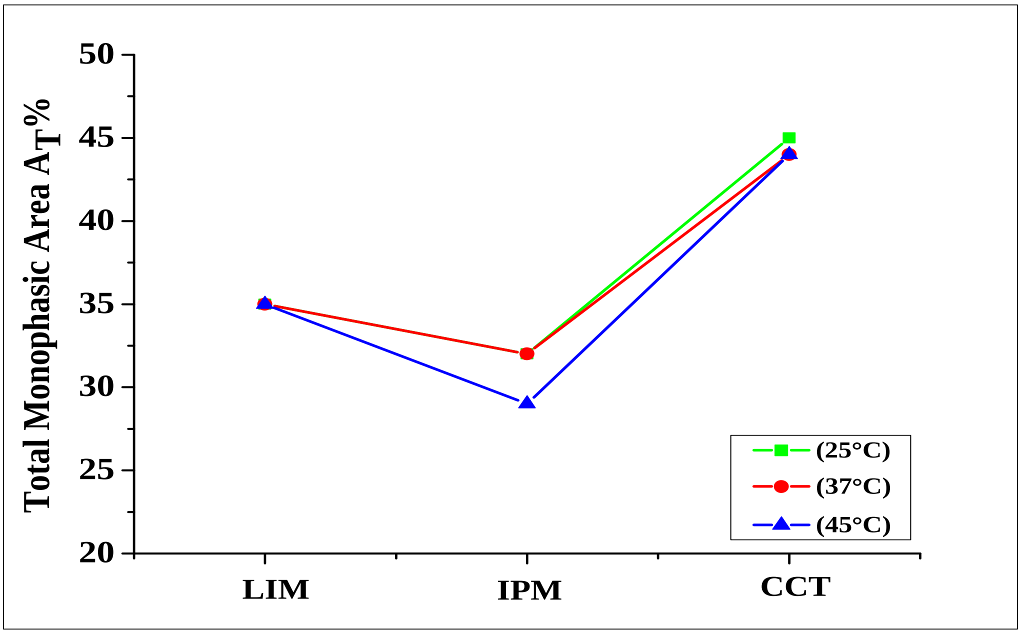


Figure 5.8: Variations in the total monophasic area A_T % of the system W/O1570/EtOH/oils at three different temperatures (25, 37 and 45ºC) at ratio 2/1 (w/w) between O1570/EtOH.

Table 5.8 and figure 5.8 shows a total monophasic area A_T % of three oils: linear, cyclic and triglyceride, respectively, and at three different temperatures 25,37 and 45ºC. Triglyceride oil (CCT) have a higher total monophasic area A_T % compared to other oils. The variation in the behavior of these oils explained in term of oil lipophilicity and penetration in the surfactant palisade layer. Solubilization and placement of polar oils will alter the surfactant layer curvature or self-organized structures, if oils have a tendency to penetrate into the surfactant palisade layer and locate near the water-lipophilic moiety, the curvature become less positive or negative, the curvature being defined as positive when the surfactant film convex toward water [Kunieda. H, et al, 2000].

Polar oils such as CCT have large tendency to penetrate in the surfactant palisade layer, thus for microemulsion system based on this oil, we observed that the total monophasic area A_T % in the system was higher than other oils studied, on the other hand, sucrose oleate (O1570) surfactant and caprylic capric triglyceride (CCT) oil have nearly homologous molecular formula that gives an ordered structure, beside nonionic sucrose ester surfactant (O1570) with high hydrophilic-lipophilic balance (HLB= 15) have water loving character tends to lower interfacial tension in combination with oil and co-surfactant, hence stable one phase (1Φ) microemulsion system was observed.

5.1.1.b water/ sucrose oleate (O1570)/ propylene glycol (PG) / oils systems

- Ratio of O1570/PG equals unity

Figure 5.9 presents the phase diagram of the system water/sucrose oleate (O1570)/propylene glycol (PG)/R (+)-limonene (LIM) at 25^{o}C. The one phase microemulsion region extends along the different surfactant concentrations as presented in the figure below. The weight ratio (w/w) between O1570/PG equals unity.

O1570 + PG (wt%)	**Maximum water solubilization (wt%)**
90	100
80	30
40	15
20	15
10	10

Table 5.9: Maximum water solubilization along the different dilution lines according to figure 5.9 whichia illustrated below.

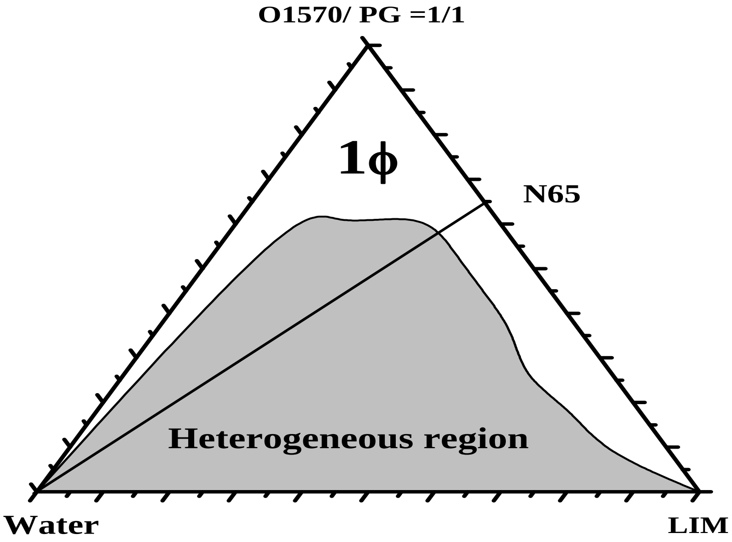


Figure 5.9: Phase diagram of the system: water/ sucrose oleate (O1570)/ propylene glycol (PG)/ R (+)-limonene oil (LIM) at 25°C. The one phase region is designated by 1ϕ and the multiphase region is designated by heterogeneous region. The mixing ratio of O1570/PG equals unity. N65 is the dilution line where the ratio of (O1570 + PG)/ LIM = 65/35.

Figure 5.10 presents the phase diagram of the system water/sucrose oleate (O1570)/propylene glycol (PG)/isopropyl myristate (IPM) at 25°C. The one phase microemulsion region extends along the different surfactant concentrations as presentedin thefigure below. The weight ratio (w/w) between O1570/PG equals unity.

O1570 + PG (wt%)	Maximum water solubilization (wt%)
90	100
80	55
40	20
20	10
10	5

Table 5.10: Maximum water solubilization along the different dilution lines according to figure 5.10 which is illustrated below.

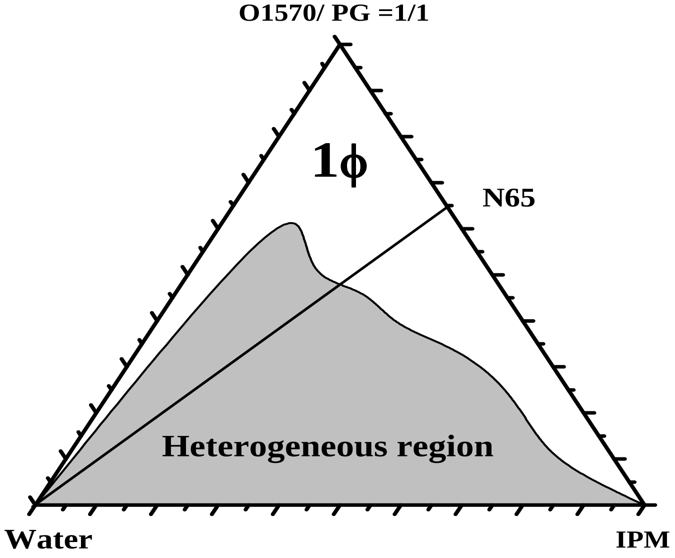


Figure 5.10: Phase diagram of the system: water/ sucrose oleate (O1570) /propylene glycol (PG)/ isopropyl myristate (IPM) at 25°C.The one phase region is designated by 1ϕ and the multiphase region is designated by heterogeneous region. The mixing ratio of O1570/PG equals unity. N65 is the dilution line where the ratio of (O1570 + PG)/ IPM = 65/35.

Figure 5.11 presents the phase diagram of the system water/sucrose oleate (O1570)/Propylene glycol (PG)/caprylic-capric triglyceride (CCT) at 25°C. The one phase microemulsion region extends along the different surfactant concentrations as presented in the figure below. The weight ratio (w/w) between O1570/PG equals unity.

O1570 + PG (wt%)	**Maximum water solubilization (wt%)**
90	100
80	60
40	20
20	15
10	5

Table 5.11: Maximum water solubilization along the different dilution lines according to figure 5.11 which is illustrated below.

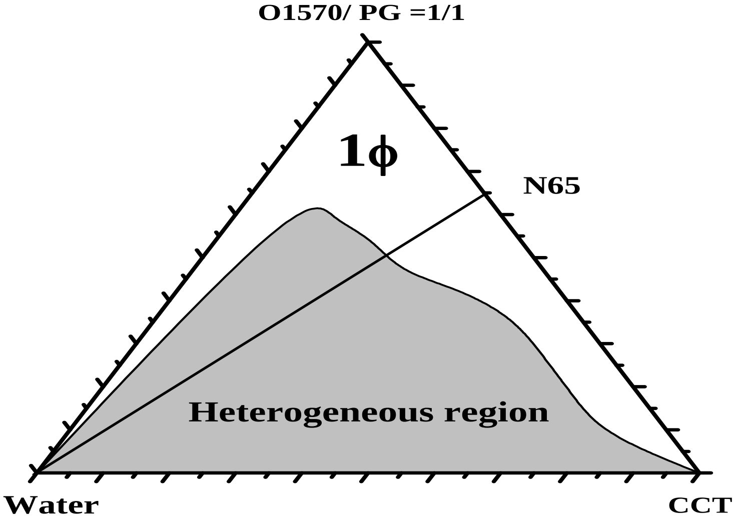


Figure 5.11: Phase diagram of the system: water/ sucrose oleate (O1570) /propylene glycol (PG)/ Caprylic-capric triglyceride (CCT) at 25°C. The one phase region is designated by 1ϕ and the multiphase region is designated by heterogeneous region. The mixing ratio of O1570/PG equals unity. N65 is the dilution line where the ratio of (O1570 + PG)/ CCT = 65/35.

Table 5.12: The total monophasic area A_T % for the system W/O1570/PG/oils for different oil types at different temperatures at a ratio (1/1) between O1570/PG.

	A_T% (Total monophasic area)		
Oil	**25ºC**	**37ºC**	**45ºC**
LIM	32	32	32
IPM	39	40	37
CCT	36	36	36

Figure 5.12 shows the variations in the total monophasic area A_T % between three types of oils: LIM, IPM and CCT at three different temperatures (25ºC, 37ºC, and 45ºC) for the system W/ O1570/PG/ oils at ratio 1/1 (w/w) between O1570/PG.

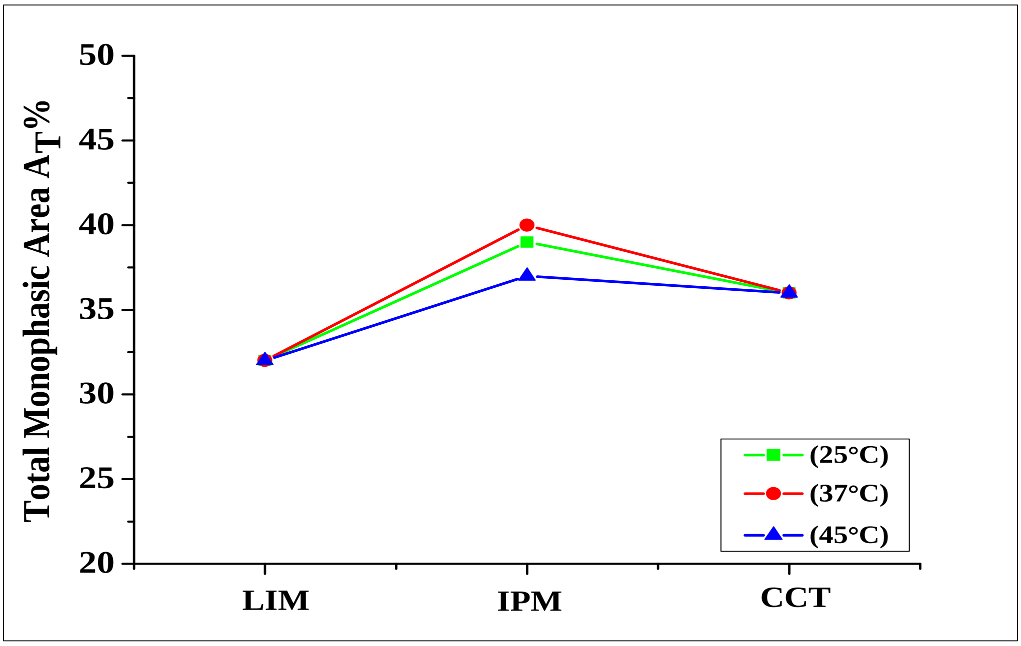


Figure 5.12: Variations in the total monophasic area A_T % of the system W/O1570/PG/oils at three different temperatures (25, 37 and 45ºC) at ratio 1/1 (w/w) between O1570/PG.

From the results presented in table 5.12, IPM oil has a higher total monophasic area A_T % comparing with other types of oils. Isopropyl myristate oil (IPM) is a polar oil that has a large tendency to penetrate in the surfactant palisade layer and therefore change the surfactant layer curvature to less positive or negative, also effective carbon number (ECN) of the oil plays an important role in determining the order of microemulsions formed, the ECN of the oils 7 and 14 for LIM and IPM, respectively. It is the better chain length compatibility between the IPM oil and the surfactant tail that improves the order in the microemulsions based on this oil.

Polyols like propylene glycol, glycerol and short chain alcohols used as tuning parameters in microemulsion systems. It penetrates into the interface and destabilizing the liquid crystalline phase by increasing interfacial fluidity of the interface and change surfactant film curvature (H_o) [Yaghmur. A, et al, 2002], hence microemulsion system based on PG/IPM have an affinity to give stable microemulsion with a higher value of the total monophasic area (A_T %) comparing to other oils studied.

- Ratio of O1570/PG equals two fold

Figure 5.13 presented the phase diagram of the system water/sucrose oleate (O1570)/propylene glycol (PG) / R (+)-limonene (LIM) at 25°C. The one phase microemulsion region extends along the different surfactant concentrations as presented in the figure below. The weight ratio (w/w) between O1570/PG equals 2/1.

O1570 + PG (wt%)	Maximum water solubilization (wt%)
90	100
80	35
40	18
20	15
10	10

Table 5.13: Maximum water solubilization along the different dilution lines according to figure 5.13 which is illustrated below.

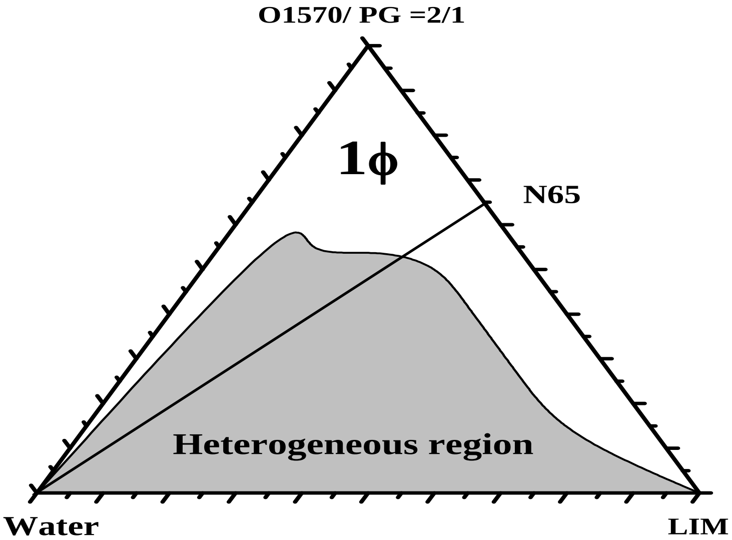


Figure 5.13: Phase diagram of the system: water/ sucrose oleate (O1570) / propylene glycol (PG) / R (+)-limonene oil LIM at 25°C. The one phase region is designated by 1ϕ and the multiphase region is designated by heterogeneous region. The mixing ratio of O1570/PG equals 2/1. N65 is the dilution line where the ratio of (O1570 + PG)/ LIM = 65/35.

Figure 5.14 presented the phase diagram of the system water/sucrose oleate (O1570)/propylene glycol (PG)/isopropyl myristate (IPM) at 25°C. The one phase microemulsion region extends along the different surfactant concentrations as presented in the figure below. The weight ratio (w/w) between O1570/PG equals 2/1.

O1570 + PG (wt%)	Maximum water solubilization (wt%)
90	100
80	55
40	30
20	15
10	5

Table 5.14: Maximum water solubilization along the different dilution lines according to figure 5.14 which is illustrated below.

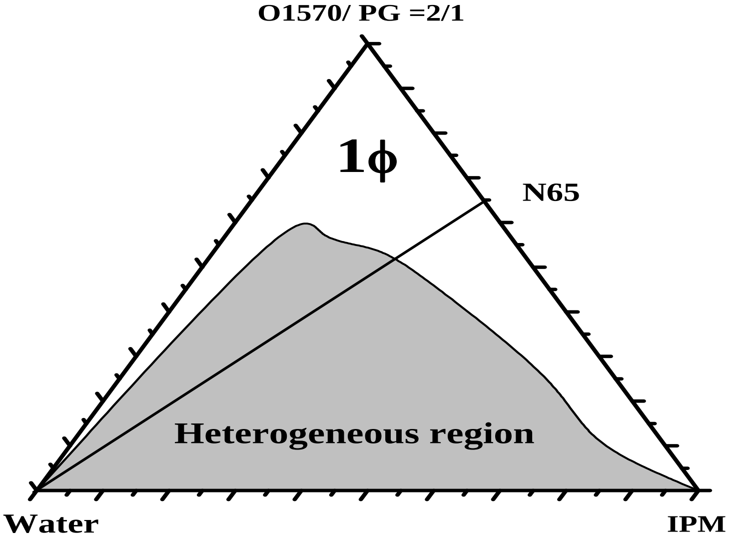


Figure 5.14: Phase diagram of the system: water/ sucrose oleate O1570 /propylene glycol PG/ isopropyl myristate IPM at 25°C.The one phase region is designated by 1ϕ and the multiphase region is designated by heterogeneous region. The mixing ratio of O1570/PG equals 2/1. N65 is the dilution line where the ratio of (O1570 + PG)/ IPM = 65/35.

Figure 5.15 presented the phase diagram of the system water/sucrose oleate (O1570) /propylene glycol (PG) /caprylic capric triglyceride (CCT) at 25°C. The one phase microemulsion region extends along the different surfactant concentrations as presented in the figure below. The weight ratio (w/w) between O1570/PG equals 2/1.

O1570 + PG (wt%)	Maximum water solubilization (wt%)
90	100
80	45
40	20
20	15
10	5

Table 5.15: Maximum water solubilization along the different dilution lines according to figure 5.15 which is illustrated below.

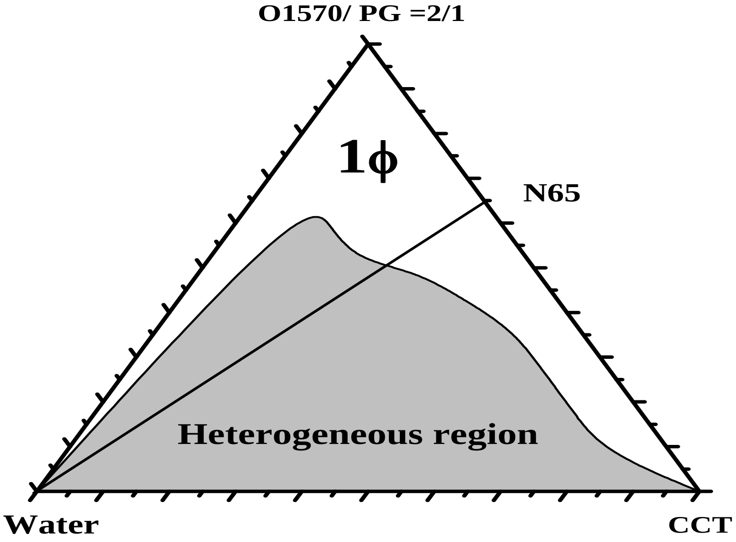


Figure 5.15: Phase diagram of the system: water/ sucrose oleate (O1570) /propylene glycol (PG) / caprylic capric triglyceride (CCT) at 25°C. The one phase region is designated by 1ϕ and the multiphase region is designated by heterogeneous region. The mixing ratio of O1570/PG equals 2/1. N65 is the dilution line where the ratio of (O1570 + PG)/CCT = 65/35.

Table 5.16: The total monophasic area A_T % for the system W/O1570/PG/oils for different oil types at different temperatures at a ratio (2/1) between O1570/PG.

	A_T % (Total monophasic area)		
Oil	**25ºC**	**37ºC**	**45ºC**
LIM	38	39	39
IPM	38	39	41
CCT	36	36	33

Figure 5.16 shows the variations in the total monophasic area A_T % between three types of oils: LIM, IPM and CCT at three different temperatures (25ºC, 37ºC, and 45ºC) for the system W/ O1570/PG/ oils at ratio 2/1 (w/w) between O1570/PG.

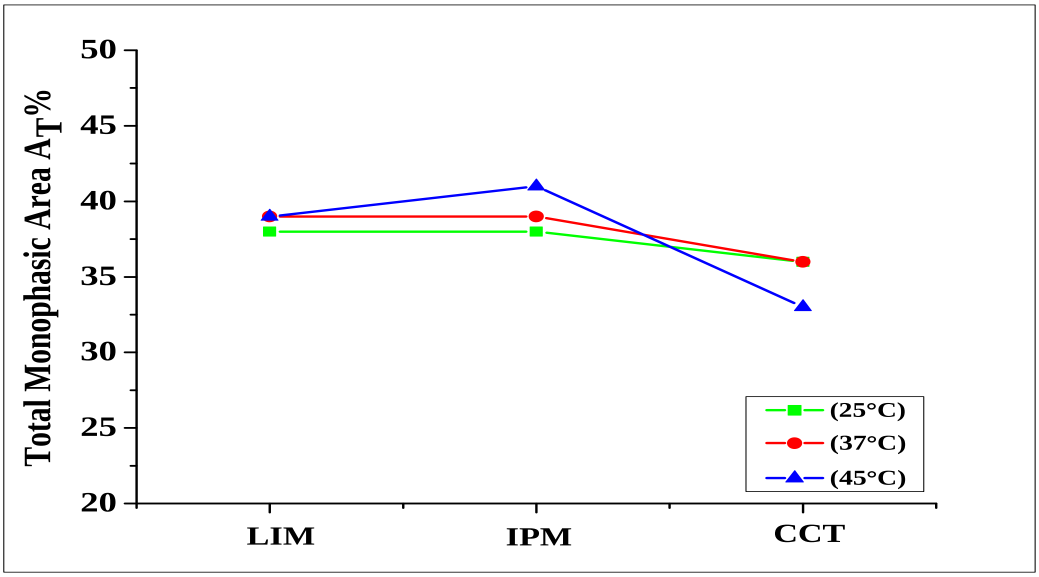


Figure 5.16: Variations in the total monophasic area A_T % of the system W/O1570/PG/oils at three different temperatures (25, 37 and 45ºC) at ratio 2/1 (w/w) between O1570/PG.

From table 5.16 which is presented above shows a comparable value of total monophasic area A_T % between R (+) - Limonene (LIM) and isopropyl myristate (IMP) with a little preference for IPM oil. R (+)- Limonene is cyclic monoterpene oil that has lower molecular volume in comparison with other oils studied, this property tends to penetrate oil in the surfactant palisade layer more easily and widen the effective cross-sectional area per surfactant, on the other hand, chain length compatibility and effective carbon number (ECN) plays an important factor in the phase behavior of microemulsions; so IPM oil that has ECN= 14 is more compatible with the surfactant tail that improved order of microemulsion system based on this oil.

5.1.1.c water/ sucrose oleate (O1570)/propionic acid (PrA) / oils systems

- Ratio of O1570/ PrA equals unity

Figure 5.17 presents the phase diagram of the system water/sucrose oleate (O1570)/propionic acid (PrA)/R (+)-limonene (LIM) at 25^{o}C. The one phase region is designated by 1ϕ and the multiphase region is designated by heterogeneous region. The mixing ratio of O1570/PrA equals 1/1. N65 is the dilution line where the ratio of (O1570 + PrA)/LIM=65/35.

O1570 + PrA (wt%)	Maximum water solubilization (wt%)
90	100
80	27
40	20
20	15
10	10

Table 5.17: Maximum water solubilization along the different dilution lines according to figure 5.17 which is illustrated below.

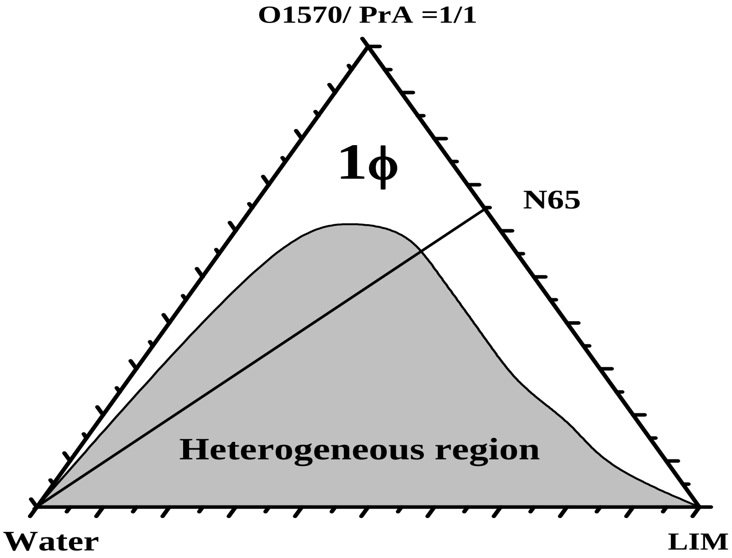


Figure 5.17: Phase diagram of the system: water/ sucrose oleate (O1570) /propionic acid (PrA)/ R (+)-limonene oil (LIM) at 25°C. The one phase region is designated by 1ϕ and the multiphase region is designated by heterogeneous region. The mixing ratio of O1570/PrA equals 1/1. N65 is the dilution line where the ratio of (O1570 + PrA)/LIM = 65/35.

Figure 5.18 presents the phase diagram of the system water/sucrose oleate (O1570)/propionic acid (PrA)/isopropyl myristate (IPM) at 25°C. The one phase region is designated by 1ϕ and the multiphase region is designated by heterogeneous region. The mixing ratio of O1570/PrA equals 1/1. N65 is the dilution line where the ratio of (O1570 + PrA)/IPM=65/35.

O1570 + PrA (wt%)	Maximum water solubilization (wt%)
90	100
80	35
40	29
20	15
10	10

Table 5.18: Maximum water solubilization along the different dilution lines according to figure 5.18 which is illustrated below.

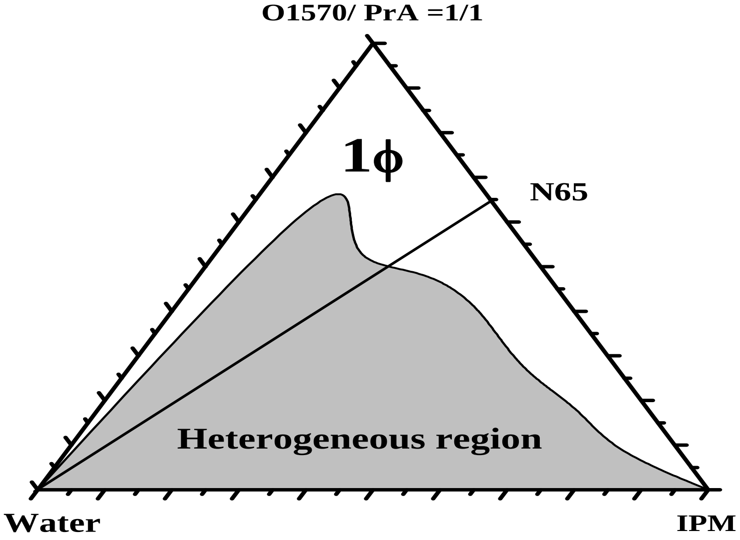


Figure 5.18: Phase diagram of the system: water/ sucrose oleate (O1570) /propionic acid (PrA)/ isopropyl myristate (IPM) at 25°C. The one phase region is designated by 1ϕ and the multiphase region is designated by heterogeneous region. The mixing ratio of O1570/PrA equals 1/1. N65 is the dilution line where the ratio of (O1570 + PrA)/IPM = 65/35.

Figure 5.19 presents the phase diagram of the system water/sucrose oleate (O1570)/Propionic acid (PrA)/caprylic capric triglyceride (CCT) at 25^{o}C. The one phase region is designated by 1ϕ and the multiphase region is designated by heterogeneous region. The mixing ratio of O1570/PrA equals 1/1. N65 is the dilution line where the ratio of (O1570 + PrA)/CCT=65/35.

O1570 + PrA (wt%)	Maximum water solubilization (wt%)
90	100
80	30
40	20
20	15
10	7

Table 5.19: Maximum water solubilization along the different dilution lines according to figure 5.19 which is illustrated below.

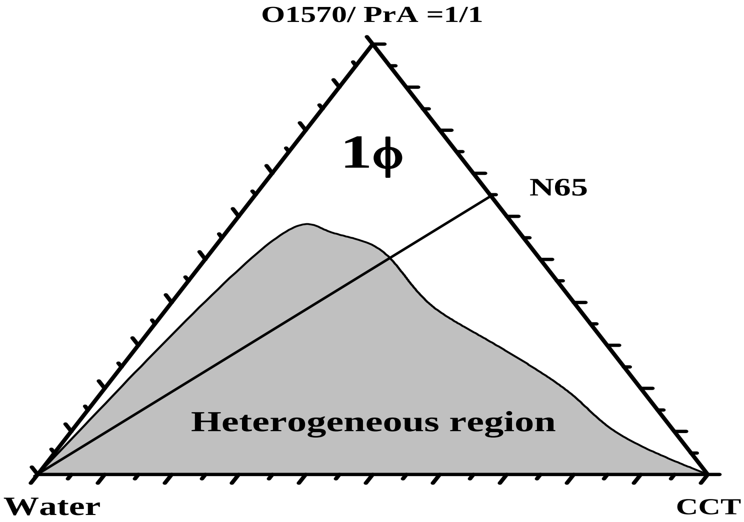


Figure 5.19: Phase diagram of the system: water/ sucrose oleate (O1570) /propionic acid (PrA)/ Caprylic capric triglyceride (CCT) at 25°C. The one phase region is designated by 1ϕ and the multiphase region is designated by heterogeneous region. The mixing ratio of O1570/PrA equals 1/1. N65 is the dilution line where the ratio of (O1570 + PrA)/CCT = 65/35.

Table 5.20: The total monophasic area A_T % for the system W/O1570/PrA/oils for different oil types at different temperatures at a ratio (1/1) between O1570/PrA.

	A_T % (Total monophasic area)		
Oil	**25ºC**	**37ºC**	**45ºC**
LIM	35	35	34
IPM	36	34	33
CCT	40	44	42

Figure 5.20 shows the variations in the total monophasic area A_T % between three types of oils: LIM, IPM and CCT at three different temperatures (25, 37, and 45ºC) for the system W/ O1570/PrA/ oils at ratio 1/1 (w/w) between O1570/PrA.

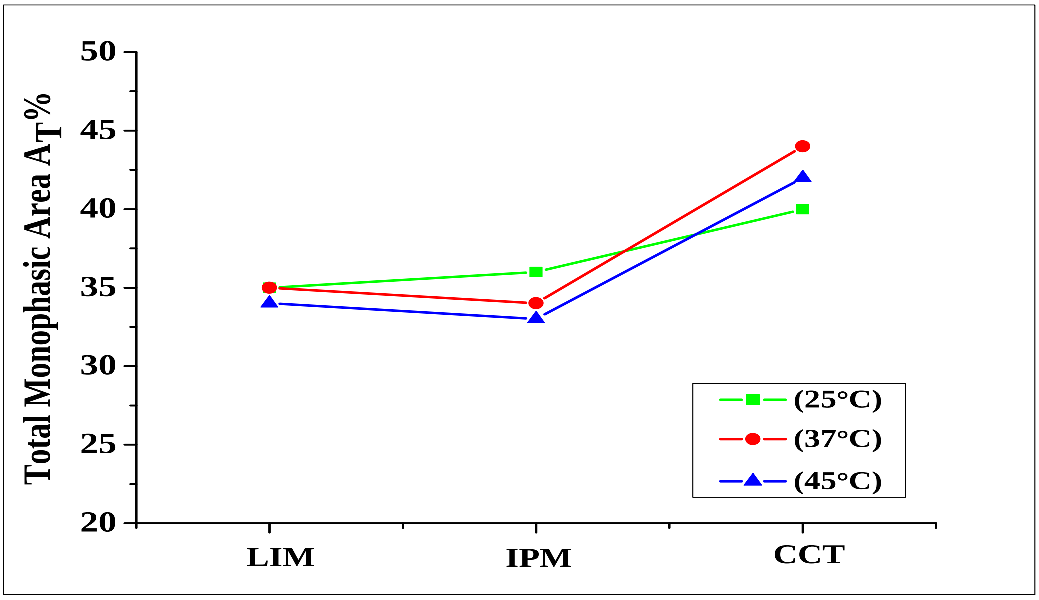


Figure 5.20: Variations in the total monophasic area A_T % of the system W/O1570/PrA/oils at three different temperatures (25, 37 and 45ºC) at ratio 1/1 (w/w) between O1570/PrA.

Table 5.20 and figure 5.20 shows a total monophasic area A_T% of three oils: cyclic, linear and triglyceride respectively at three different temperatures 25, 37 and 45ºC.Triglyceride oil (CCT) have a higher total monophasic area A_T % compared to other oils. The variation in the behavior of these oils explained in term of oil lipophilicity and penetration in the surfactant palisade layer. Solubilization and placement of polar oils would alter the surfactant layer curvature or self-organized structures, if oils have a tendency to penetrate into the surfactant palisade layer and locate near the water-lipophilic moiety, the curvature become less positive or negative, the curvature being defined as positive when the surfactant film convex toward water [Kunieda. H, et al, 2000].

Polar oils such as CCT have large tendency to penetrate in the surfactant palisade layer, thus for microemulsion system based on this oil, we observed that the total monophasic area A_T % in the system was higher than other oils studied, on the other hand, sucrose oleate (O1570) surfactant and caprylic capric triglyceride (CCT) oil have nearly homologous molecular formula that gives an ordered structure, beside nonionic sucrose ester surfactant (O1570) with high hydrophilic-lipophilic balance (HLB= 15) have water loving character tends to lower interfacial tension in combination with oil and co-surfactant, hence stable one phase (1Φ) microemulsion system was observed.

- Ratio of O1570/PrA equals two fold

Figure 5.21 presents the phase diagram of the system water/sucrose oleate (O1570)/propionic acid (PrA)/R (+)-limonene (LIM) at 25°C. The one phase region is designated by 1ϕ and the multiphase region is designated by heterogeneous region. The mixing ratio of O1570/PrA equals 2/1. N65 is the dilution line where the ratio of (O1570 + PrA)/LIM=65/35.

O1570 + PrA (wt%)	Maximum water solubilization (wt%)
90	100
80	30
40	25
20	15
10	10

Table 5.21: Maximum water solubilization along the different dilution lines according to figure 5.21 which is illustrated below.

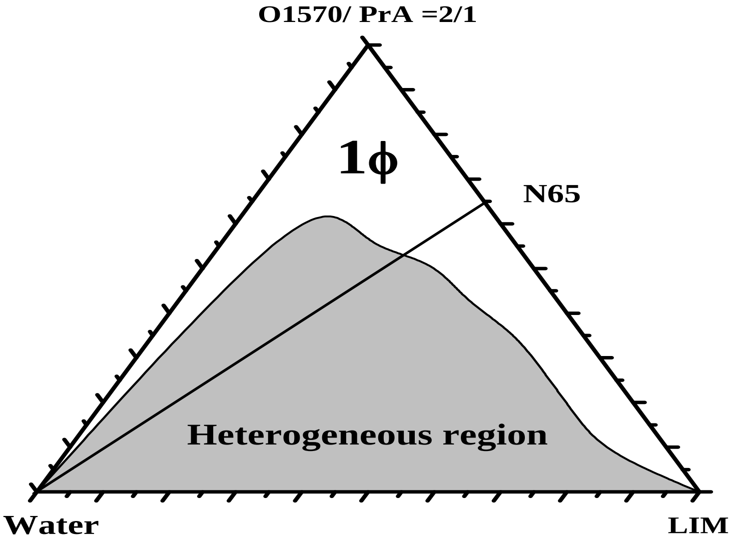


Figure 5.21: Phase diagram of the system: water/ sucrose oleate (O1570) /propionic acid

(PrA)/ R (+)-limonene (LIM) at 25°C. The mixing ratio of O1570/PrA equals 2/1. N65 is the dilution line where the ratio of (O1570 + PrA)/LIM = 65/35.

Figure 5.22 presents the phase diagram of the system water/sucrose oleate (O1570)/propionic acid (PrA)/isopropyl myristate (IPM) at 25°C. The one phase region is designated by 1ϕ and the multiphase region is designated by heterogeneous region. The mixing ratio of O1570/PrA equals 2/1. N65 is the dilution line where the ratio of (O1570 + PrA)/IPM=65/35.

O1570 + PrA (wt%)	Maximum water solubilization (wt%)
90	100
80	40
40	25
20	15
10	10

Table 5.22: Maximum water solubilization along the different dilution lines according to figure 5.22 which is illustrated below.

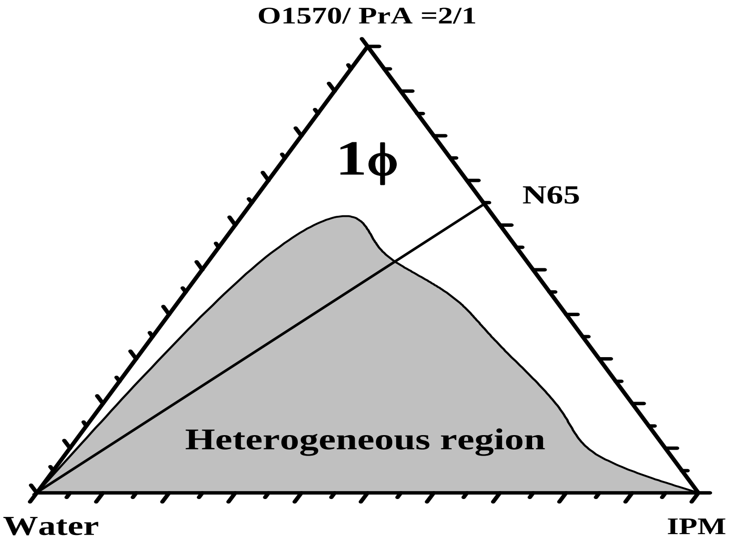


Figure 5.22: Phase diagram of the system: water/ sucrose oleate (O1570) /propionic acid (PrA)/ isopropyl myristate (IPM) at 25°C.The mixing ratio of O1570/PrA equals 2/1. N65 is the dilution line where the ratio of (O1570 + PrA)/IPM = 65/35.

Figure 5.23 presents the phase diagram of the system water/sucrose oleate (O15700/propionic acid (PrA)/caprylic-capric triglyceride (CCT) at 25°C. The one phase region is designated by 1ϕ and the multiphase region is designated by heterogeneous region. The mixing ratio of O1570/PrA equals 2/1. N65 is the dilution line where the ratio of (O1570 + PrA)/CCT=65/35.

O1570 + PrA (wt%)	**Maximum water solubilization (wt%)**
90	100
80	35
40	20
20	15
10	10

Table 5.23: Maximum water solubilization along the different dilution lines according to figure 5.23 which is illustrated below.

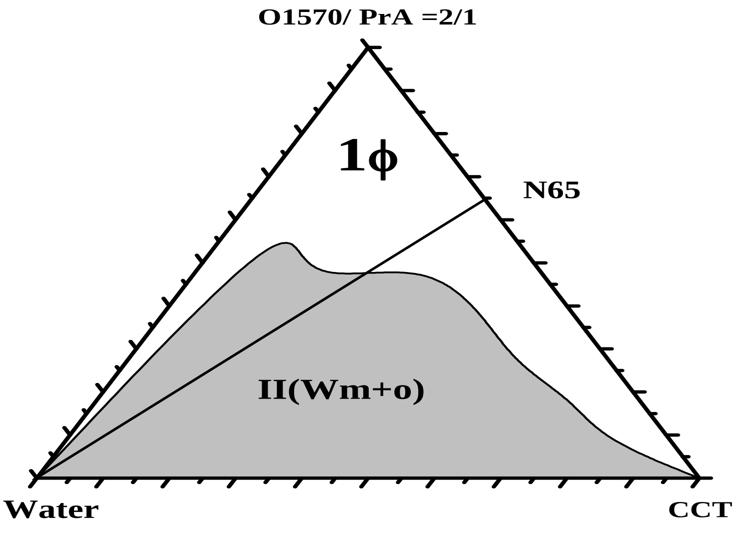


Figure 5.23: Phase diagram of the system: water/ sucrose oleate (O1570) /propionic acid (PrA)/ Caprylic-capric triglyceride (CCT) at 25°C. The mixing ratio of O1570/PrA equals 2/1. N65 is the dilution line where the ratio of (O1570 + PrA)/CCT = 65/35.

Table 5.24: The total monophasic area A_T % for the system W/O1570/PrA/oils for different oil types at different temperatures at a ratio (2/1) between O1570/PrA.

	A_T (Total monophasic area)		
Oil	**25°C**	**37°C**	**45°C**
LIM	36	36	33
IPM	38	39	41
CCT	38	39	39

Figure 5.24 shows the variations in the total monophasic area A_T % between three types of oils: LIM, IPM and CCT at three different temperatures (25, 37 and 45°C) for the system W/ O1570/PrA/ oils at ratio 2/1 (w/w) between O1570/PrA.

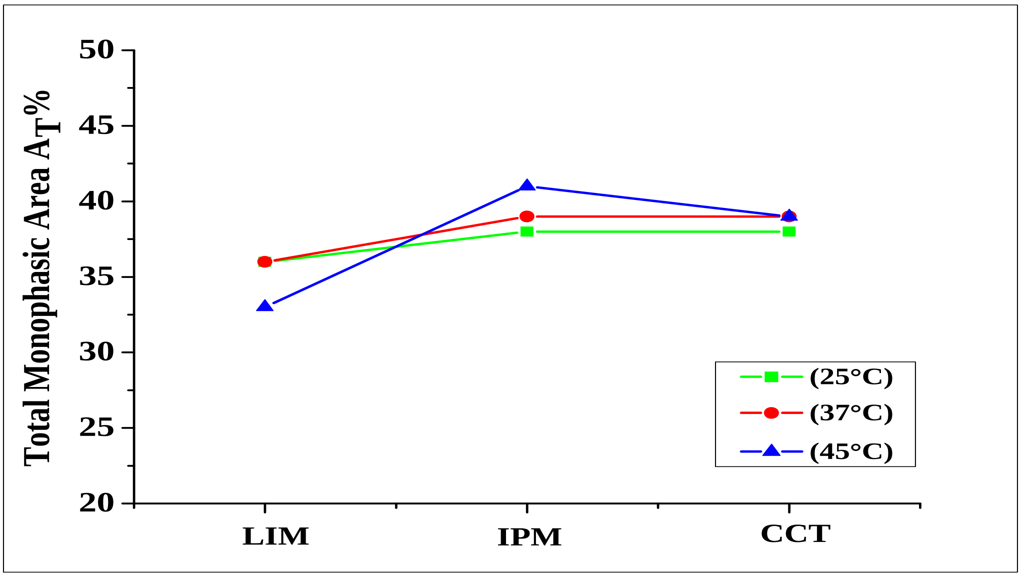


Figure 5.24: Variations in the total monophasic area A_T % of the system W/O1570/PrA/oils at three different temperatures (25, 37 and 45°C) at ratio 2/1 (w/w) between O1570/PrA.

Table 5.24 shows the results of different types of oils (linear, cyclic, triglyceride oil) that being studied in microemulsion systems, IPM linear oil gave higher total monophasic area A_T % comparing with other oils. It seems that the effective carbon number (ECN) of the oil plays the major role in determining the degree of order of the microemulsions formed. The effective carbon numbers of the oils are 7 and 14 for LIM and IPM, respectively. It is the better chain length compatibility between the IPM oil and the surfactant tail that improves the order in the microemulsions based on this oil.

5.1.1.c water/ sucrose oleate (O1570)/glycerol (GLY) / oils systems

- Ratio of O1570/GLY of equals unity

Figure 5.25 presents the phase diagram of the system water/sucrose oleate (O1570)/glycerol (GLY)/R (+)-limonene (LIM) at 25°C. The one phase region is designated by 1ϕ and the multiphase region is designated by heterogeneous region. The mixing ratio of O1570/GLY equals 1/1. N65 is the dilution line where the ratio of (O1570 + GLY)/LIM=65/35.

O1570 + GLY (wt%)	Maximum water solubilization (wt%)
90	100
80	25
40	15
20	10
10	5

Table 5.25: Maximum water solubilization along the different dilution lines according to figure 5.25 which is illustrated below.

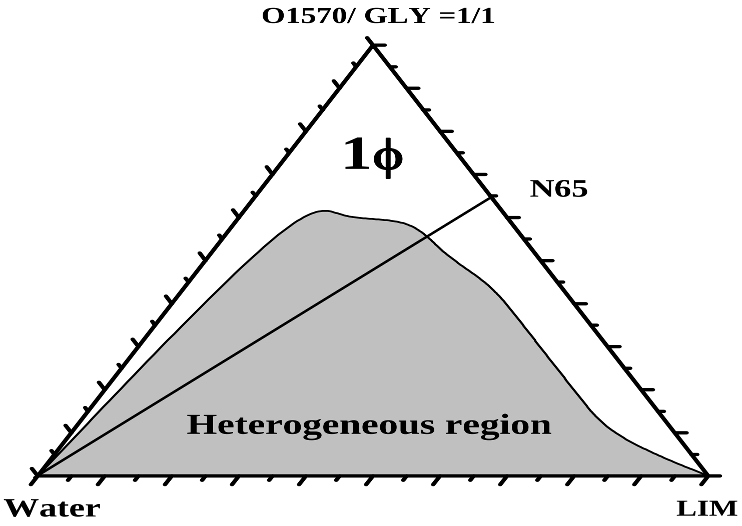


Figure 5.25: Phase diagram of the system: water/ sucrose oleate (O1570) /glycerol (GLY)/

R (+)-limonene oil (LIM) at 25°C. The mixing ratio of O1570/GLY equals 1/1. N65 is the dilution line where the ratio of (O1570 + GLY)/LIM = 65/35.

Figure 5.26 presents the phase diagram of the system water/sucrose oleate (O1570)/glycerol (GLY)/isopropyl myristate (IPM) at 25°C. The mixing ratio of O1570/GLY equals 1/1. N65 is the dilution line where the ratio of (O1570 + GLY)/IPM=65/35.

O1570 + GLY (wt%)	**Maximum water solubilization (wt%)**
90	100
80	35
40	27
20	15
10	10

Table 5.26: Maximum water solubilization along the different dilution lines according to figure 5.26 which is illustrated below

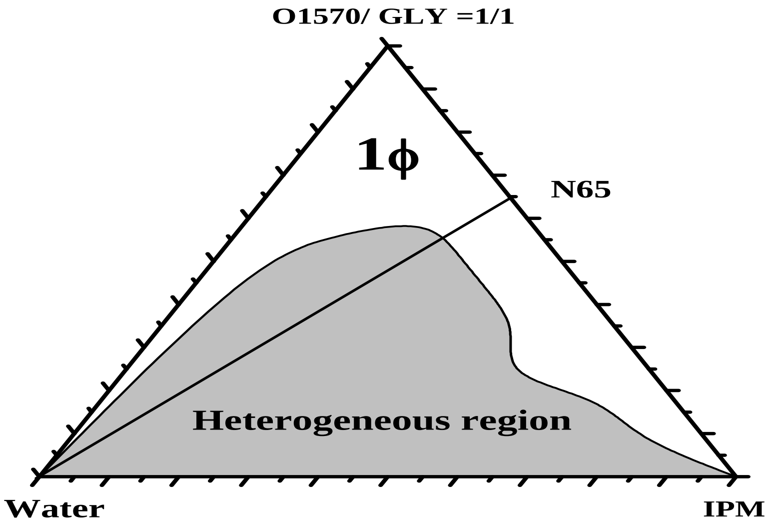


Figure 5.26: Phase diagram of the system: water/ sucrose oleate (O1570) /glycerol (GLY)/ isopropyl myristate (IPM) at 25°C. The mixing ratio of O1570/GLY equals 1/1. N65 is the dilution line where the ratio of (O1570 + GLY)/LIM = 65/35.

Figure 5.27 presents the phase diagram of the system water/sucrose oleate (O1570)/glycerol (GLY)/caprylic-capric triglyceride (CCT) at 25°C. The mixing ratio of O1570/GLY equals 1/1. N65 is the dilution line where the ratio of (O1570 + GLY)/CCT=65/35.

O1570 + GLY (wt%)	Maximum water solubilization (wt%)
90	100
80	30
40	25
20	15
10	10

Table 5.27: Maximum water solubilization along the different dilution lines according to figure 5.27 which is illustrated below.

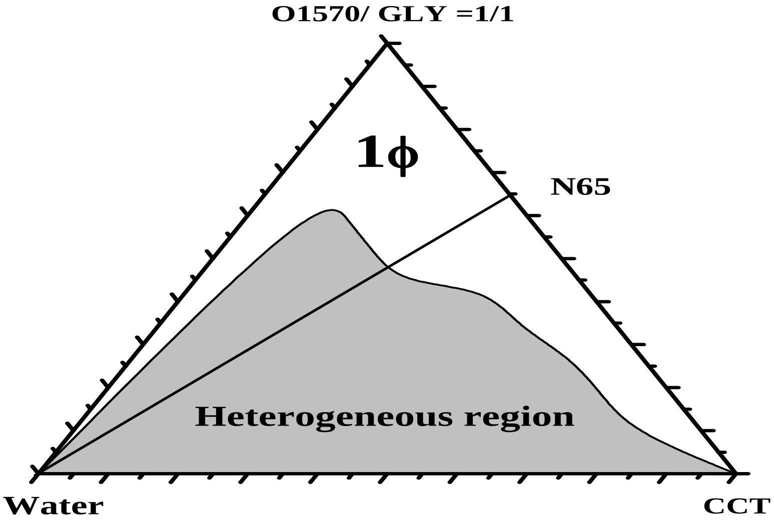


Figure 5.27: Phase diagram of the system: water/ sucrose oleate (O1570) /glycerol (GLY)/ Caprylic-capric triglyceride (CCT) at 25°C. The mixing ratio of O1570/GLY equals 1/1. N65 is the dilution line where the ratio of (O1570 + GLY)/CCT = 65/35.

Table 5.28: The total monophasic area A_T % for the system W/O1570/GLY/oils for different oil types at different temperatures at a ratio (1/1) between Sur and Cos.

	A_T % (Total monophasic area)		
Oil	**25ºC**	**37ºC**	**45ºC**
LIM	33	33	32
IPM	38	36	40
CCT	38	37	37

Figure 5.28 shows the variations in the total monophasic area A_T % between three types of oils LIM, IPM and CCT at three different temperatures (25, 37, and 45ºC) for the system W/ O1570/GLY/ oils at ratio 1/1 (w/w) between O1570/GLY.

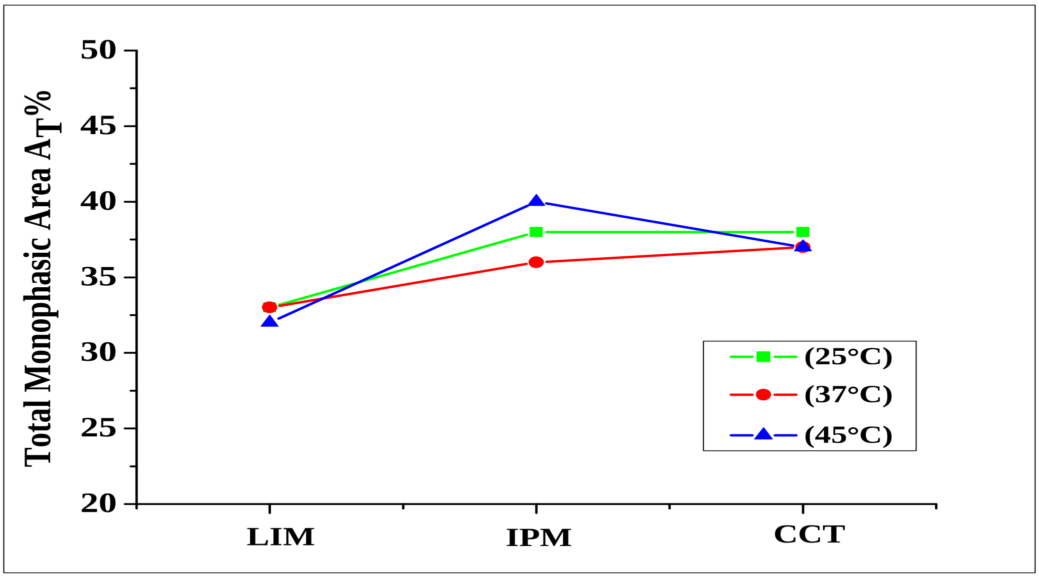


Figure 5.28: Variations in the total monophasic area A_T % of the system W/O1570/GLY/oils at three different temperatures (25, 37 and 45ºC) at ratio 1/1 (w/w) between O1570/GLY.

From the table 5.28 which is presented above, there is a comparable result between IPM, CCT oils with little preference to IPM oil; this explained in term of chain length compatibility and penetration tendency of the oil to entrap in the surfactant palisade layer. Effective carbon number of these oils are equal 14, 11 for IPM and CCT respectively; so the better chain length compatibility between IPM oil and the surfactant tail that improves order in the microemulsions based on this oil, on the other hand CCT oil have bulky shape (fork-like shape) which decrease the penetration tendency in the surfactant palisade layer, on the contrary to IPM oil which have linear shape and more easily to penetrate in the surfactant palisade layer to form ordered microemulsion system.

- Ratio of O1570/GLY equals two fold

Figure 5.29 presents the phase diagram of the system water/sucrose oleate (O1570)/glycerol (GLY)/R (+)-limonene (LIM) at 25°C. The mixing ratio of O1570/GLY equals 2/1. N65 is the dilution line where the ratio of (O1570 + GLY)/LIM=65/35.

O1570 + GLY (wt%)	Maximum water solubilization (wt%)
90	100
80	27
40	20
20	15
10	10

Table 5.29: Maximum water solubilization along the different dilution lines according to figure 5.29 which is illustrated below.

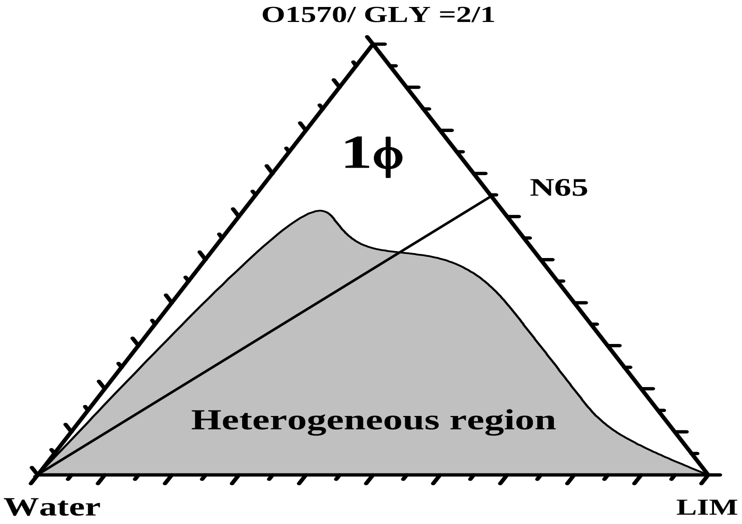


Figure 5.29: Phase diagram of the system: water/ sucrose oleate (O1570) /glycerol (GLY)/ R (+)-limonene oil (LIM) at 25°C. The mixing ratio of O1570/GLY equals 2/1. N65 is the dilution line where the ratio of (O1570 + GLY)/LIM = 65/35.

Figure 5.30 presents the phase diagram of the system water/sucrose oleate (O1570)/glycerol (GLY)/isopropyl myristate (IPM) at 25°C. The mixing ratio of O1570/GLY equals 2/1. N65 is the dilution line where the ratio of (O1570 + GLY)/IPM=65/35.

O1570 + GLY (wt%)	Maximum water solubilization (wt%)
90	100
80	35
40	25
20	15
10	10

Table 5.30: Maximum water solubilization along the different dilution lines according to figure 5.30 which is illustrated below.

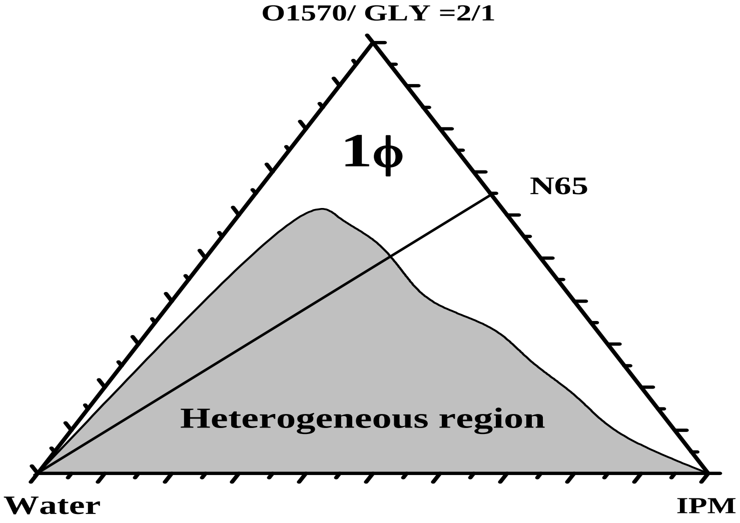


Figure 5.30: Phase diagram of the system: water/ sucrose oleate (O1570) /glycerol (GLY)/ isopropyl myristate (IPM) at 25°C.The mixing ratio of O1570/GLY equals 2/1. N65 is the dilution line where the ratio of (O1570 + GLY)/IPM = 65/35.

Figure 5.31 presented the phase diagram of the system water/sucrose oleate (O1570)/glycerol (GLY)/caprylic-capric triglyceride (CCT) at 25°C. The mixing ratio of O1570/GLY equals 2/1. N65 is the dilution line where the ratio of (O1570 + GLY)/CCT=65/35.

O1570 + GLY (wt%)	Maximum water solubilization (wt%)
90	100
80	30
40	25
20	15
10	10

Table 5.31: Maximum water solubilization along the different dilution lines according to figure 5.31 which is illustrated below.

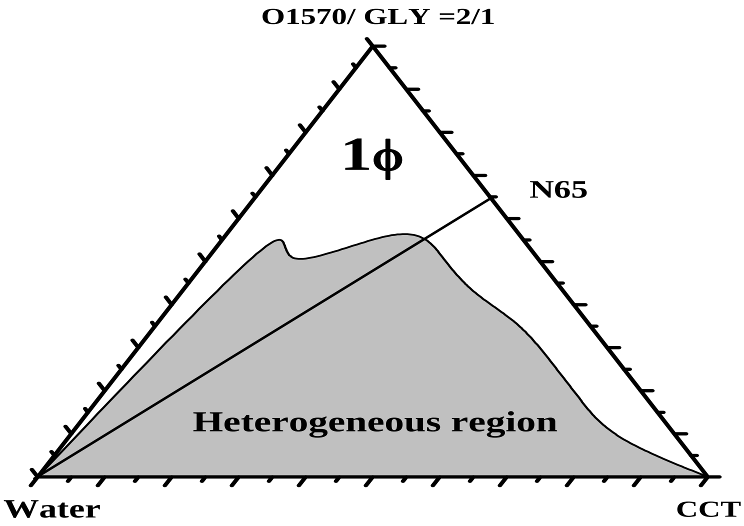


Figure 5.31: Phase diagram of the system: water/ sucrose oleate (O1570) /glycerol (GLY)/ Caprylic-capric triglyceride (CCT) at 25°C. The mixing ratio of O1570/GLY equals 2/1. N65 is the dilution line where the ratio of (O1570 + GLY)/CCT = 65/35.

Table 5.32: The total monophasic area A_T % for the system W/O1570/GLY/oils for different oil types at different temperatures at a ratio (2/1) between O1570/GLY.

	A_T % (Total monophasic area)		
Oil	**25ºC**	**37ºC**	**45ºC**
LIM	34	34	34
IPM	39	37	38
CCT	36	35	32

Figure 5.32 shows the variations in the total monophasic area A_T % between three types of oils: LIM, IPM and CCT at three different temperatures (25, 37, and 45ºC) for the system W/ O1570/GLY/ oils at ratio 2/1 (w/w) between O1570/GLY.

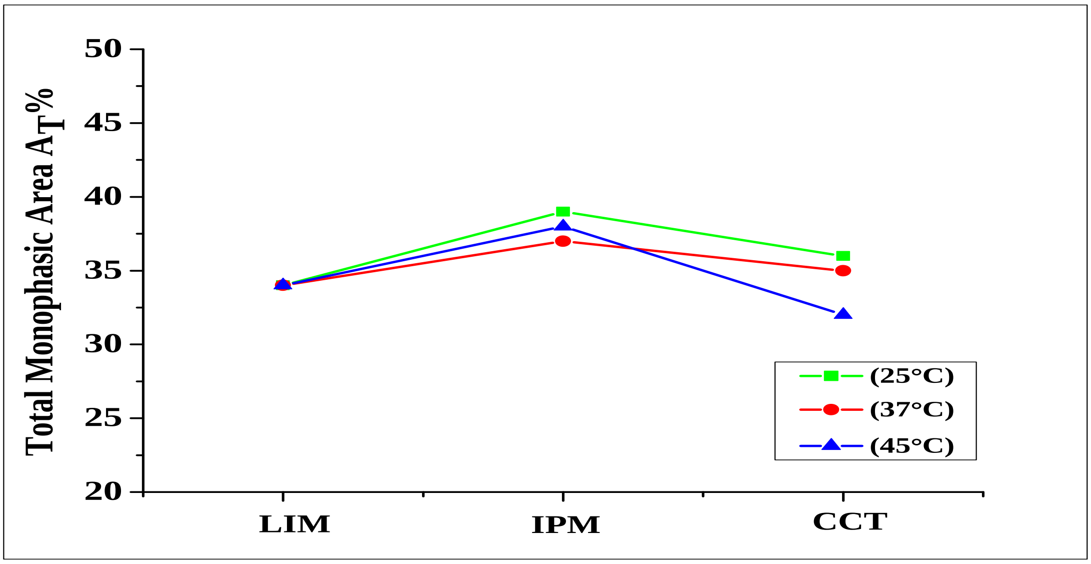


Figure 5.32: Variations in the total monophasic area A_T % of the system W/O1570/GLY/oils at three different temperatures (25, 37 and 45ºC) at ratio 2/1 (w/w) between O1570/GLY.

Table 5.32 which is presented above shows that IPM oil has higher total monophasic area compared to other oils studied, this due to chain length compatibility between oil (IPM) and surfactant (O1570) that changes the surfactant layer curvature, hence gives an ordered microemulsion system.

In this section (5.1.1) we study single surfactant microemulsion system (sucrose oleate O1570) with different three types of oils (cyclic LIM, linear IPM and triglyceride oil CCT), beside four types of co-surfactants which is (EtOH, PG, PrA and GLY) at two different weight ratios (1/1, 2/1 w/w) between surfactant and co-surfactants.

Despite the large molecular volume of IPM and CCT oilscompared with LIM, it gives higher total monophasic area (A_T %) of all systems studied in this section; this means molecular volume is not the key role to determine the strength of microemulsions formed, table blow shows the molecular volume of these oils.

Oil	Molecular volume
LIM	181
IPM	317
CCT	530

Table 5.33 The molecular volume of three different types of oils (the unit of molecular volume is cm^3/mole).

The formulation of microemulsion system is not only affected by this factor but also there are other factors affect the formulation; among these factors effective carbon number (ECN) of oils gives an order of microemulsion formed, therefore an increase of ECN will be increase in ordered of microemulsions formed, table below present the ECN of three types of oils studied.

Oil	Effective carbon number (ECN)
LIM	7
IPM	14
CCT	11

Table 5.34 Effective carbon number (ECN) of three different types of oils.

[Bansal. V, Shah. D and O'Connell. J, 1980] proposed the empirical equation (BSO) as an empirical condition for maximum water solubilization capacity in microemulsion systems in relation to the surfactant, co-surfactant, alcohol and oil chain length, i.e. $N_S = N_O + N_A$, where N_S, N_O, N_A are the chain length of surfactant, oil, and alcohol respectively. This study demonstrates that a maximum water solubilization is obtained when the $N_S = (N_O \pm 3) + N_A$ for N_S is greater than 14, when N_S is less than 14, this equation cannot predict the maximum water solubilization.

They was conducted that the chain length compatibility of microemulsion systems containing anionic surfactant, oils and alcohols was reached to a maximum water solubilization capacity when the carbon number of surfactant is equal the sum of carbon number of co-surfactant and oil, this due to the maximum cohesive interactions between hydrocarbon chains (or due to the minimum disruptive effect in the interfacial region).

[Garti. N, et al, 1995] re-examine the applicability of BSO equation in the presence of nonionic surfactants and alcohols instead of ionic surfactant, they show for the first time that BSO equation and the chain length compatibility can applicable in nonionic microemulsion systems with some limitations; the limitation is, i.e. the co-surfactant (alcohol) neither insoluble in oil nor in water, [Ezrahi. S, et al, 2005] extended to that work, they elucidate some limitation on applicability of BSO equation in nonionic surfactant systems, among this limitation the surfactant that are too hydrophobic are insufficient in promoting water solubilization, and of too hydrophilic one fare no better.

The surfactant chain lengths, oil and alcohol (co-surfactant) respectively, the BSO equation (NS = NO + NA) for the systems used in this section present in tables 5.35, 5.36, 5.37 and 5.38.

Table 5.35 shows surfactant chain lengths, oil and alcohol (co-surfactant) respectively, the BSO equation ($N_S = N_O + N_A$) for the system W/O1570/EtOH/ oil system for three different types of oils (LIM, IPM and CCT).

System	N_S	N_O	N_A	$N_S - N_A$	BSO($N_O + N_A$)
W/O1570/EtOH/LIM	15	7	3	12	10
W/O1570/EtOH/IPM	15	14	3	12	17
W/O1570/EtOH/CCT	15	11	3	12	14

Table 5.35 Surfactant chain lengths, oil and alcohol (co-surfactant) respectively, the BSO equation ($N_S = N_O + N_A$) for the system W/O1570/EtOH/ oil system for three different types of oils (LIM, IPM and CCT).

Table 5.36 shows surfactant chain lengths, oil and alcohol (co-surfactant) respectively, the BSO equation ($N_S = N_O + N_A$) for the system W/O1570/PG/ oil system for three different types of oils (LIM, IPM and CCT).

System	N_S	N_O	N_A	N_S - N_A	BSO($N_O + N_A$)
W/O1570/PG/LIM	15	7	4	11	11
W/O1570/PG/IPM	15	14	4	11	18
W/O1570/PG/CCT	15	11	4	11	15

Table 5.36 Surfactant chain lengths, oil and alcohol (co-surfactant) respectively, the BSO equation ($N_S = N_O + N_A$) for the system W/O1570/PG/ oil system for three different types of oils (LIM, IPM and CCT).

Table 5.37 shows surfactant chain lengths, oil and alcohol (co-surfactant) respectively, the BSO equation ($N_S = N_O + N_A$) for the system W/O1570/PrA/ oil system for three different types of oils (LIM, IPM and CCT).

System	N_S	N_O	N_A	N_S - N_A	BSO($N_O + N_A$)
W/O1570/PrA/LIM	15	7	4	11	11
W/O1570/PrA/IPM	15	14	4	11	18
W/O1570/PrA/CCT	15	11	4	11	15

Table 5.37 Surfactant chain lengths, oil and alcohol (co-surfactant) respectively, the BSO equation ($N_S = N_O + N_A$) for the system W/O1570/PrA/ oil system for three different types of oils (LIM, IPM and CCT).

Table 5.38 shows surfactant chain lengths, oil and alcohol (co-surfactant) respectively, the BSO equation ($N_S = N_O + N_A$) for the system W/O1570/GLY/ oil system for three different types of oils (LIM, IPM and CCT).

System	N_S	N_O	N_A	$N_S - N_A$	BSO($N_O + N_A$)
W/O1570/GLY/LIM	15	7	5	10	12
W/O1570/GLY/IPM	15	14	5	10	19
W/O1570/GLY/CCT	15	11	5	10	16

Table 5.38 Surfactant chain lengths, oil and alcohol (co-surfactant) respectively, the BSO equation ($N_S = N_O + N_A$) for the system W/O1570/GLY/ oil system for three different types of oils (LIM, IPM and CCT).

5.1.2 Mixed surfactants systems phase behavior

In this section, study the phase behavior of mixed surfactants, sucrose oleate (O1570) and sorbitan monoolete (T-MAZ 80) with different three types of oils (LIM, IPM and CCT) in which systems are divided as follows:

- Single oil systems, which are LIM, IPM and CCT at ratio 1/1, 2/1 and 1/2 (w/w) between mixed surfactants (sur:sur)
- Mixed oil systems divided into two parts; firstly the three types of oils (LIM, IPM and CCT) are in combination with EtOH and PG at ratio 1/1 between mixed surfactants and oils, the second part is LIM oil system in combination with IPM and CCT oils.

These systems were studied in order to determine the total monophasic area A_T % (±2%) at three different temperatures (25, 37 and 45ºC).

5.1.2.1 Mixed surfactants with single oil systems

- Ratio of O1570/T-MAZ 80 equal unity

Figure 5.33 presents the phase diagram of the system water/sucrose oleate (O1570)/T-MAZ 80/R (+)-limonene (LIM) at 25ºC. The mixing ratio of O1570/T-MAZ 80 equals 1/1. N65 is the dilution line where the ratio of (O1570 + T-MAZ 80)/LIM=65/35.

O1570 + T-MAZ 80 (wt%)	Maximum water solubilization (wt%)
90	100
80	90
40	70
20	50
10	20

Table 5.39: Maximum water solubilization along the different dilution lines according to figure 5.33 which is illustrated below.

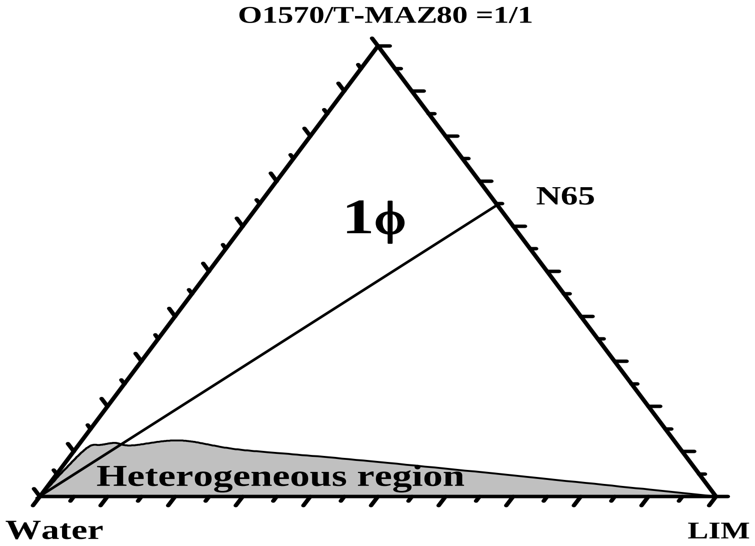


Figure 5.33: Phase diagram of the system: water/ sucrose oleate (O1570) /T-MAZ 80/ R (+)-limonene (LIM) at 25°C. The mixing ratio of O1570/T-MAZ 80 equal unity. The one phase microemulsion region is designated as 1ϕ and the multiple phase region is designated as Heterogeneous region.

Figure 5.34 presents the phase diagram of the system water/sucrose oleate (O1570)/T-MAZ 80/isopropyl myristate (IPM) at 25ºC. The mixing ratio of O1570/T-MAZ 80 equals 1/1. N65 is the dilution line where the ratio of (O1570 + T-MAZ 80)/IPM=65/35.

O1570 + T-MAZ 80 (wt%)	Maximum water solubilization (wt%)
90	100
80	80
40	40
20	20
10	10

Table 5.40: Maximum water solubilization along the different dilution lines according to figure 5.34 which is illustrated below.

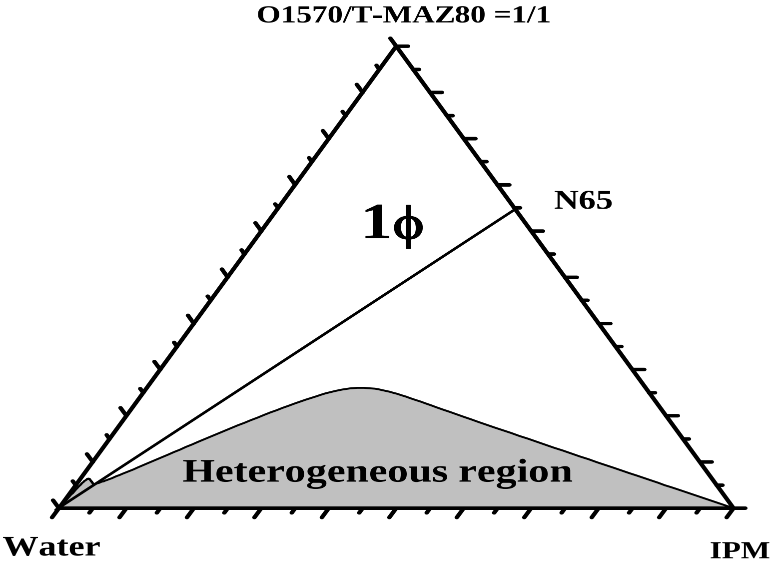


Figure 5.34: Phase diagram of the system: water/ sucrose oleate (O1570) /T-MAZ80/ isopropyl myristate (IPM) at 25°C.The mixing ratio of O1570/T-MAZ 80 equal unity. The one phase microemulsion region is designated as 1ϕ and the multiple phase region is designated as Heterogeneous region.

Figure 5.35 presents the phase diagram of the system water/sucrose oleate (O1570)/T-MAZ 80/Caprylic-capric triglyceride (CCT) at 25^{o}C. The mixing ratio of O1570/T-MAZ 80 equals 1/1. N65 is the dilution line where the ratio of (O1570 + T-MAZ 80)/CCT=65/35.

O1570 + T-MAZ 80 (wt%)	Maximum water solubilization (wt%)
90	100
80	70
40	45
20	20
10	10

Table 5.41: Maximum water solubilization along the different dilution lines according to figure 5.35 which illustrated below.

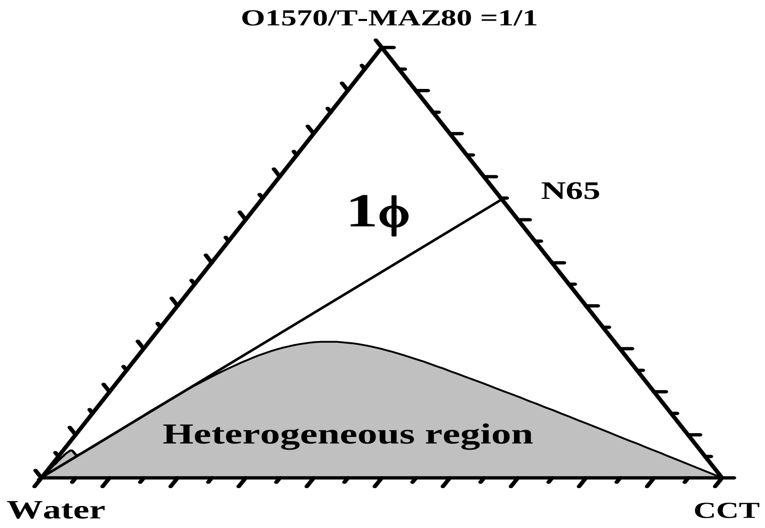


Figure 5.35: Phase diagram of the system: water/ sucrose oleate (O1570) /T-MAZ80/ Caprylic-capric triglyceride at 25°C.The mixing ratio of O1570/T-MAZ 80 equal unity. The one phase microemulsion region is designated as 1ϕ and the multiple phase region is designated as Heterogeneous region.

Table 5.42: The total monophasic area A_T % for the system W/O1570/T-MAZ 80/oils for different oil types at different temperatures 25, 37 and 45ºC, at ratio (1/1) between mixed surfactants

	A_T % (Total monophasic area)		
Oil	**25ºC**	**37ºC**	**45ºC**
LIM	86	87	87
IPM	71	71	71
CCT	64	64	64

Figure 5.36 shows the variations in the total monophasic area A_T % between three types of oils: LIM, IPM and CCT at three different temperatures (25, 37, and 45ºC) for the system W/ O1570/T-MAZ 80/ oils at ratio 1/1 (w/w) between mixed surfactants.

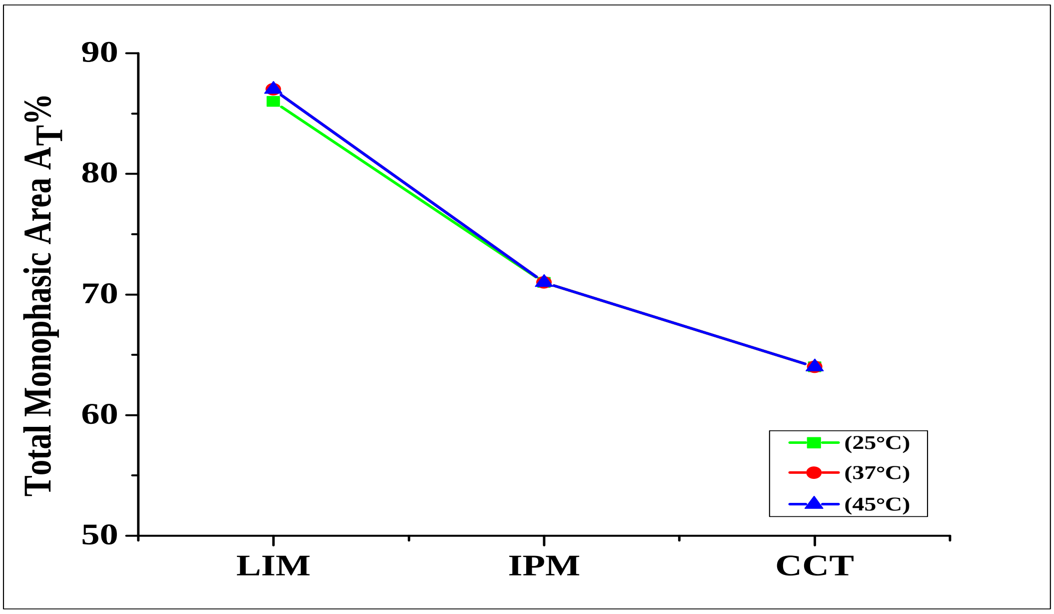


Figure 5.36: Variations in the total monophasic area A_T% of the system W/O1570/T-MAZ 80/oils at three different temperatures (25, 37 and 45ºC) at ratio 1/1 (w/w) between mixed surfactants.

From table 5.42 and figure 5.36 which illustrated above, we observe that for microemulsion based on mixed surfactants (O1570 & T-MAZ 80), R (+)-limonene oil (LIM) has a higher total monophasic area (A_T%) compared to other oils studied. LIM oil is a cyclic monoterpene that has lower molecular volume compared to other oil studied, moreover LIM oil has sphere like shape in three dimensional points of view; on the contrary to other oils which have rod, plate-like shape for IPM and CCT respectively, hence LIM oil can penetrate more easily into the surfactant palisade layer and widen the effective cross-sectional area per surfactant molecule.

Linear and triglyceride oils (IPM & CCT) has a low total monophasic area (A_T %), because of its high molecular volume, and so the ability to penetrate the interfacial film is very low and does not assist in obtaining optimum curvature of the surfactants. As we show from table 5.42 when the temperature changed from 25ºC to 45ºC, the total monophasic area (A_T %) was not affected because of the surfactant nonionic and microemulsion thermodynamic stable. Increasing temperature from 25ºC to 45ºC induces small changes in the monophasic area indicating temperature insensitive microemulsion formation, so when surfactants are sucrose ester (SE) temperature insensitive microemulsions were observed.

- Ratio of O1570/T-MAZ 80 equal one half

Figure 5.37 presents the phase diagram of the system water/sucrose oleate (O1570)/T-MAZ 80/R (+)-limonene (LIM) at 25ºC. The mixing ratio of O1570/T-MAZ 80 equals 1/2. N65 is the dilution line where the ratio of (O1570 + T-MAZ 80)/LIM=65/35.

O1570 + T-MAZ 80 (wt%)	Maximum water solubilization (wt%)
90	100
80	90
40	65
20	40
10	25

Table 5.43: Maximum water solubilization along the different dilution lines according to figure 5.37 which is illustrated below.

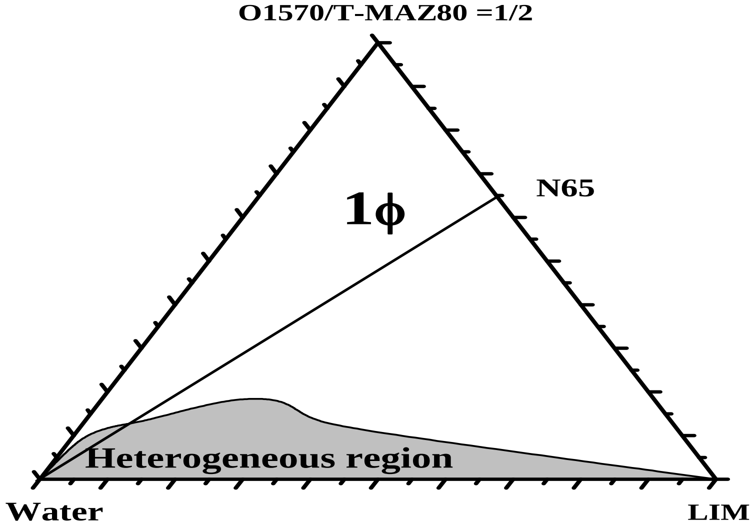


Figure 5.37: Phase diagram of the system: water/ sucrose oleate (O1570) /T-MAZ80/ R (+)-limonene (LIM) at 25°C.The mixing ratio of O1570/T-MAZ 80 equal one half. The one phase microemulsion region is designated as 1ϕ and the multiple phase region is designated as Heterogeneous region.

Figure 5.38 presents the phase diagram of the system water/sucrose oleate (O1570)/T-MAZ 80/ isopropyl myristate (IPM) at 25°C. The mixing ratio of O1570/T-MAZ 80 equals 1/2. N65 is the dilution line where the ratio of (O1570 + T-MAZ 80)/IPM=65/35.

O1570 + T-MAZ 80 (wt%)	**Maximum water solubilization (wt%)**
90	100
80	70
40	35
20	15
10	10

Table 5.44: Maximum water solubilization along the different dilution lines according to figure 5.38 which is illustrated below.

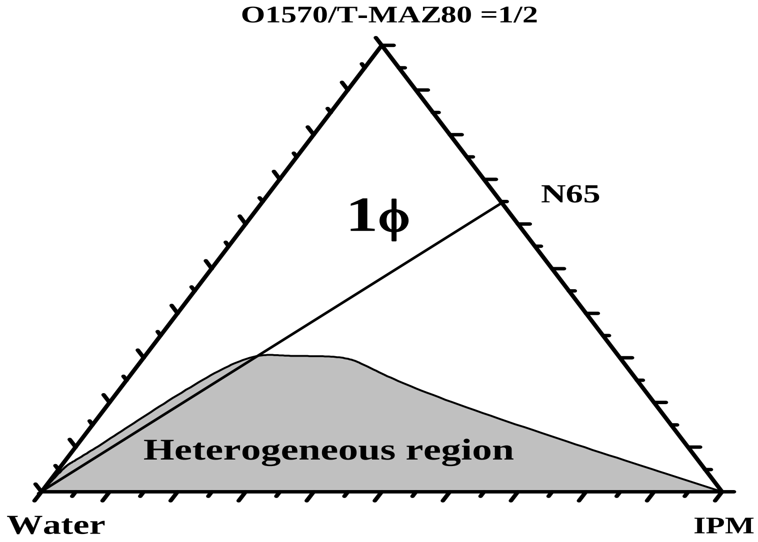


Figure 5.38: Phase diagram of the system: water/ sucrose oleate (O1570) /T-MAZ80/ isopropyl myristate (IPM) at 25°C. The mixing ratio of O1570/T-MAZ 80 equal one half. The one phase microemulsion region is designated as 1ϕ and the multiple phase region is designated as Heterogeneous region.

Figure 5.39 presents the phase diagram of the system water/sucrose oleate (O1570)/T-MAZ 80/Caprylic-capric triglyceride (CCT) at 25^{o}C. The mixing ratio of O1570/T-MAZ 80 equals 1/2. N65 is the dilution line where the ratio of (O1570 + T-MAZ 80)/CCT=65/35.

O1570 + T-MAZ 80 (wt%)	Maximum water solubilization (wt%)
90	100
80	75
40	40
20	20
10	10

Table 5.45: Maximum water solubilization along the different dilution lines according to figure 5.39 which is illustrated below.

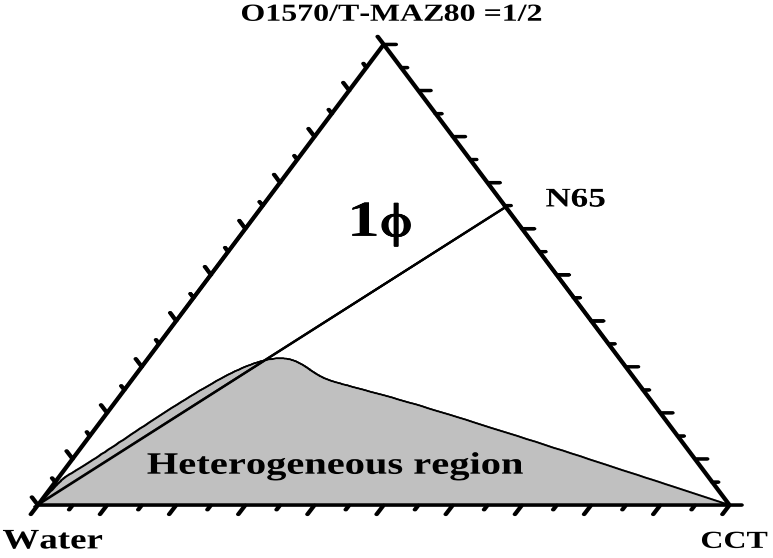


Figure 5.39: Phase diagram of the system: water/ sucrose oleate (O1570) /T-MAZ80/ Caprylic-capric triglyceride (CCT) at 25°C.The mixing ratio of O1570/T-MAZ 80 equal one half. The one phase microemulsion region is designated as 1ϕ and the multiple phase region is designated as Heterogeneous region.

Table 5.46: The total monophasic area A_T % for the system W/O1570/T-MAZ 80/oils for different oil types at different temperatures 25, 37 and 45ºC, at ratio (1/2) between mixed surfactants

	A_T % (Total monophasic area)		
Oil	**25ºC**	**37ºC**	**45ºC**
LIM	81	81	81
IPM	66	66	68
CCT	67	67	67

Figure 5.40 shows the variations in the total monophasic area A_T% between three types of oils LIM, IPM and CCT at three different temperatures (25, 37, and 45ºC) for the system W/ O1570/T-MAZ 80/ oils at ratio 1/2 (w/w) between mixed surfactants.

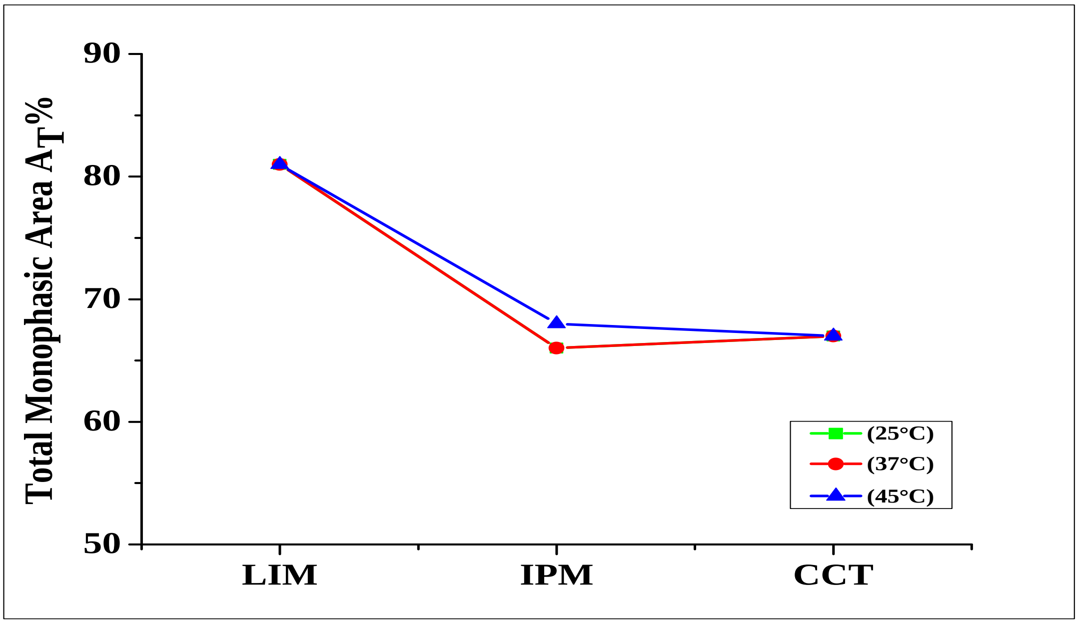


Figure 5.40: Variations in the total monophasic area A_T% of the system W/O1570/T-MAZ 80/oils at three different temperatures (25, 37 and 45ºC) at ratio 1/2 (w/w) between mixed surfactants.

From the table 5.46 mentioned above, we study three types of oils: cyclic, linear and triglyceride oils (LIM, IPM and CCT) respectively, we observe that LIM oil has higher total monophasic area (A_T %), this due to it has ring structure and lower molecular volume compared to other oils studied tends to penetrate in the surfactant palisade layer, and hence change the surfactant layer curvature to less positive or negative.

- Ratio of O1570/T-MAZ 80 equal two fold

Figure 5.41 presents the phase diagram of the system water/sucrose oleate (O1570)/T-MAZ 80/R (+)-limonene (LIM) at 25°C. The mixing ratio of O1570/T-MAZ 80 equals 2/1. N65 is the dilution line where the ratio of (O1570 + T-MAZ 80)/LIM=65/35.

O1570 + T-MAZ 80 (wt%)	Maximum water solubilization (wt%)
90	100
80	80
40	70

20	40
10	20

Table 5.47: Maximum water solubilization along the different dilution lines according to figure 5.41 which is illustrated below.

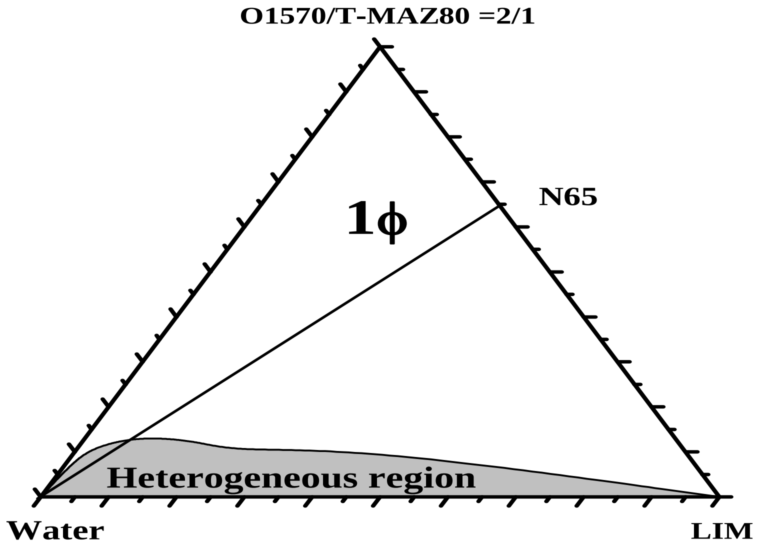


Figure 5.41: Phase diagram of the system: water/ sucrose oleate (O1570) /T-MAZ 80/ R (+)-limonene (LIM) at 25°C.The mixing ratio of O1570/T-MAZ 80 equal 2/1. The one phase microemulsion region is designated as 1ϕ and the multiple phase region is designated as Heterogeneous region.

Figure 5.42 presents the phase diagram of the system water/sucrose oleate (O1570)/T-MAZ 80/ isopropyl myristate (IPM) at 25°C. The mixing ratio of O1570/T-MAZ 80 equals 2/1. N65 is the dilution line where the ratio of (O1570 + T-MAZ 80)/IPM=65/35.

O1570 + T-MAZ 80 (wt%)	**Maximum water solubilization (wt%)**
90	100
80	60
40	45
20	30
10	10

Table 5.48: Maximum water solubilization along the different dilution lines according to figure 5.42 which is illustrated below.

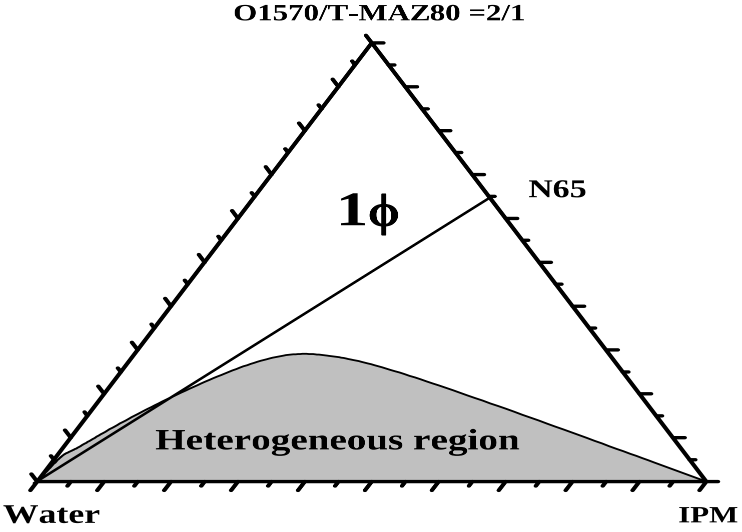


Figure 5.42: Phase diagram of the system: water/ sucrose oleate (O1570) /T-MAZ 80/ isopropyl myristate (IPM) at 25°C.The mixing ratio of O1570/T-MAZ 80 equal 2/1. The one phase microemulsion region is designated as 1ϕ and the multiple phase region is designated as Heterogeneous region.

Figure 5.43 presents the phase diagram of the system water/sucrose oleate (O1570)/T-MAZ 80/Caprylic-capric triglyceride (CCT) at 25°C. The mixing ratio of O1570/T-MAZ 80 equals 2/1. N65 is the dilution line where the ratio of (O1570 + T-MAZ 80)/CCT=65/35.

O1570 + T-MAZ 80 (wt%)	Maximum water solubilization (wt%)
90	100
80	75
40	50
20	25
10	10

Table 5.49: Maximum water solubilization along the different dilution lines according to figure 5.43 which is illustrated below.

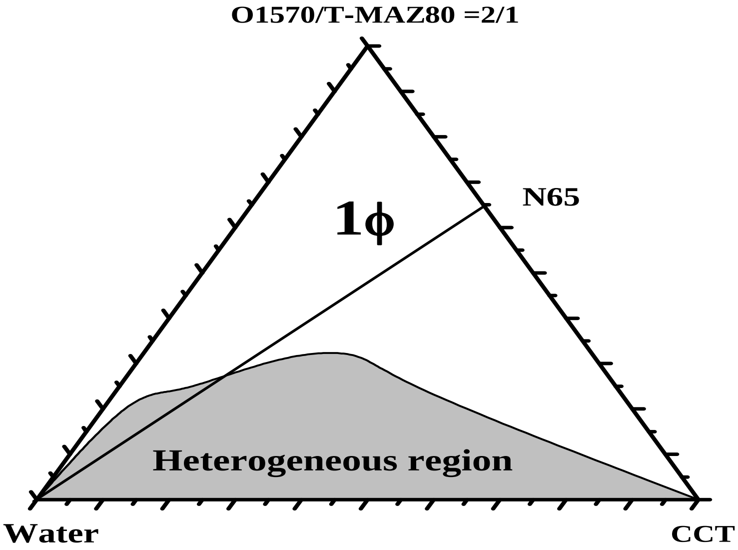


Figure 5.43: Phase diagram of the system: water/ sucrose oleate (O1570) /T-MAZ 80/ Caprylic-capric triglyceride (CCT) at 25°C. The mixing ratio of O1570/T-MAZ 80 equal 2/1. The one phase microemulsion region is designated as 1ϕ and the multiple phase region is designated as Heterogeneous region.

Table 5.50: The total monophasic area A_T % for the system W/O1570/T-MAZ 80/oils for different oil types at different temperatures 25, 37 and 45ºC, at ratio (2/1) between mixed surfactants.

	A_T % (Total monophasic area)		
Oil	**25ºC**	**37ºC**	**45ºC**
LIM	85	85	86
IPM	66	66	67
CCT	62	62	64

Figure 5.44 shows the variations in the total monophasic area A_T % between three types of oils: LIM, IPM and CCT at three different temperatures (25, 37, and 45ºC) for the system W/ O1570/T-MAZ 80/ oils at ratio 2/1 (w/w) between mixed surfactants.

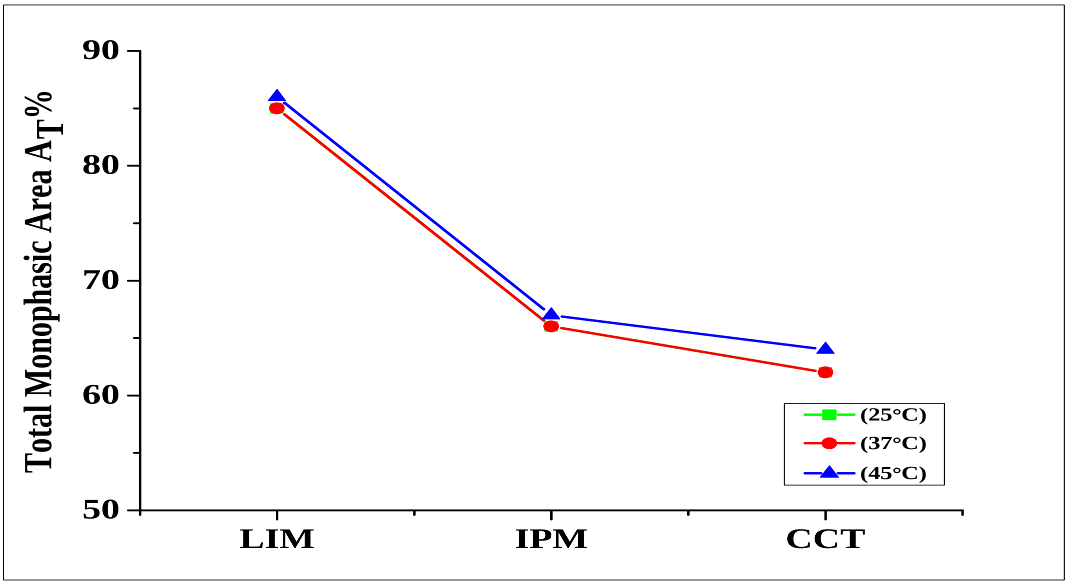


Figure 5.44: Variations in the total monophasic area A_T % of the system W/O1570/T-MAZ 80/oils at three different temperatures (25, 37 and 45ºC) at ratio 2/1 (w/w) between mixed surfactants.

Table 5.50 presents above show total monophasic area (A_T %) of different three types of oils (LIM, IPM and CCT) Arranged increasingly in terms of molecular volume, we observed that LIM oil has a higher total monophasic area (A_T %); because of its lower molecular volume contrariwise of the IPM and CCT oils that has large molecular volume which tends to minimize the ability of penetration in water-oil interface and hence decrease the total monophasic area (A_T %). From these reasons, we conclude an increasing of molecular volume of oils will decreasing in oil penetration of that oil and decreasing in the total monophasic area (A_T %) too.

5.1.2.2 Mixed surfactants with mixed oils and/ or co-surfactant microemulsion systems

- W/O1570/T-MAZ 80/ LIM +EtOH system

Figure 5.45 presents the phase diagram of the system water/sucrose oleate (O1570)/T-MAZ 80/ R (+)-limonene (LIM) + ethanol (EtOH) at 25°C. The mixing ratio of O1570/T-MAZ 80 equals 1/1. N65 is the dilution line where the ratio of (O1570 + T-MAZ 80)/LIM + EtOH =65/35.

O1570 + T-MAZ 80 (wt%)	Maximum water solubilization (wt%)
90	100
80	80
40	50
20	35
10	20

Table 5.51: Maximum water solubilization along the different dilution lines according to figure 5.45 which is illustrated below.

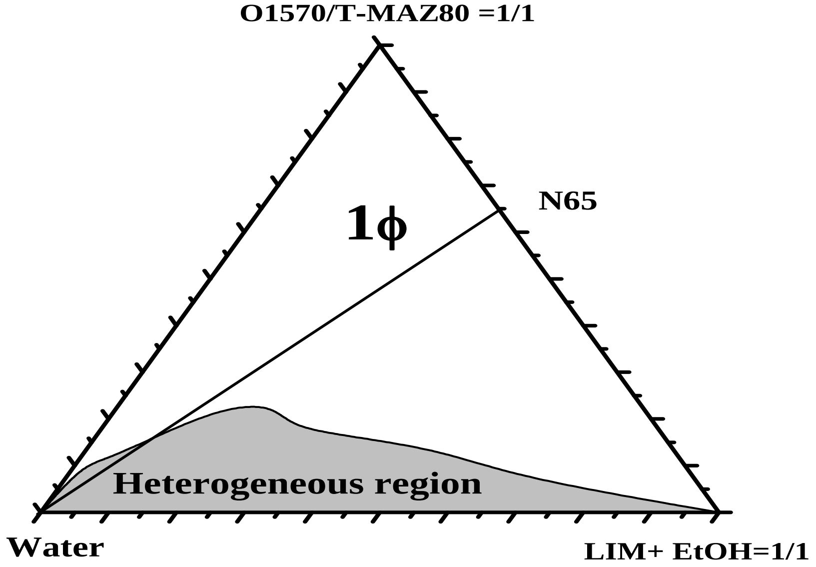


Figure 5.45: Phase diagram of the system: water/ sucrose oleate (O1570) /T-MAZ 80/ R (+)-limonene (LIM) + ethanol (EtOH) at 25°C.The mixing ratio of O1570/T-MAZ 80 and LIM/EtOH equal 1/1. The one phase microemulsion region is designated as 1ϕ and the multiple phase region is designated as Heterogeneous region.

- W/O1570/T-MAZ 80/ IPM +EtOH system

Figure 5.46 presents the phase diagram of the system water/sucrose oleate (O1570)/T-MAZ 80/isopropyl myristate (IPM) + ethanol (EtOH) at 25°C. The mixing ratio of O1570/T-MAZ 80 equals 1/1. N65 is the dilution line where the ratio of (O1570 + T-MAZ 80)/IPM + EtOH =65/35.

O1570 + T-MAZ 80 (wt%)	Maximum water solubilization (wt%)
90	100
80	60
40	40
20	25
10	10

Table 5.52: Maximum water solubilization along the different dilution lines according to figure 5.46 which is illustrated below.

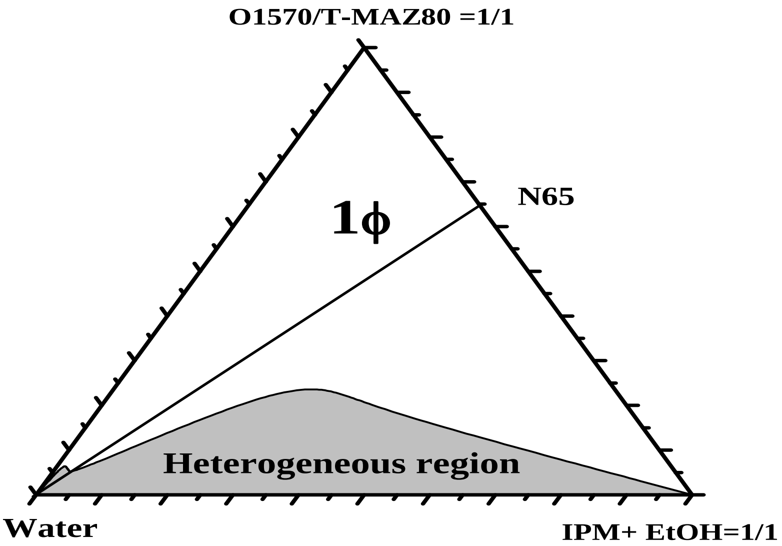


Figure 5.46: Phase diagram of the system: water/ sucrose oleate (O1570) /T-MAZ 80/isopropyl myristate (IPM) + ethanol (EtOH) at 25°C. The mixing ratio of O1570/T-MAZ 80 and IPM/EtOH equal 1/1. The one phase microemulsion region is designated as 1ϕ and the multiple phase region is designated as Heterogeneous region.

- W/O1570/T-MAZ 80/ CCT +EtOH system

Figure 5.47 presents the phase diagram of the system water/sucrose oleate (O1570)/T-MAZ 80/ caprylic-capric triglyceride (CCT) + ethanol (EtOH) at 25°C. The mixing ratio of O1570/T-MAZ 80 equals 1/1. N65 is the dilution line where the ratio of (O1570 + T-MAZ 80)/CCT + EtOH =65/35.

O1570 + T-MAZ 80 (wt%)	Maximum water solubilization (wt%)
90	100
80	55
40	45
20	20
10	10

Table 5.53: Maximum water solubilization along the different dilution lines according to figure 5.47 which is illustrated below.

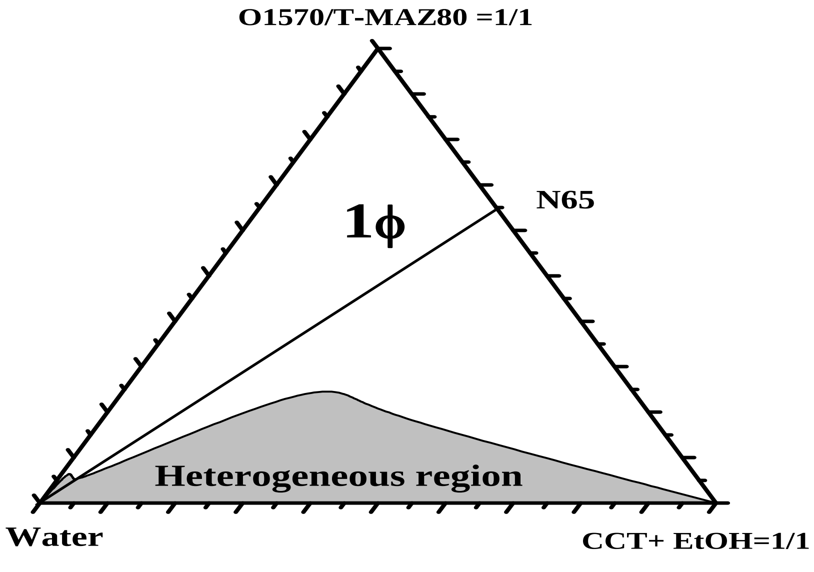


Figure 5.47: Phase diagram of the system: water/ sucrose oleate (O1570) /T-MAZ 80/ Caprylic-capric triglyceride (CCT) + ethanol (EtOH) at 25°C.The mixing ratio of O1570/T-MAZ 80 and CCT/EtOH equal 1/1. The one phase microemulsion region is designated as 1ϕ and the multiple phase region is designated as Heterogeneous region.

Table 5.54: The total monophasic area A_T % for the system W/O1570/T-MAZ 80/oils + EtOH for different oil types at different temperatures 25, 37 and 45ºC, at ratio (1/1) between mixed surfactants.

	A_T % (Total monophasic area)		
Oil	**25ºC**	**37ºC**	**45ºC**
LIM	77	79	80
IPM	75	75	75
CCT	74	74	74

Figure 5.48 shows the variations in the total monophasic area A_T % between three types of oils: LIM, IPM and CCT at three different temperatures (25, 37, and 45ºC) for the system W/ O1570/T-MAZ 80/ oils + EtOH at ratio 1/1 (w/w) between mixed surfactants.

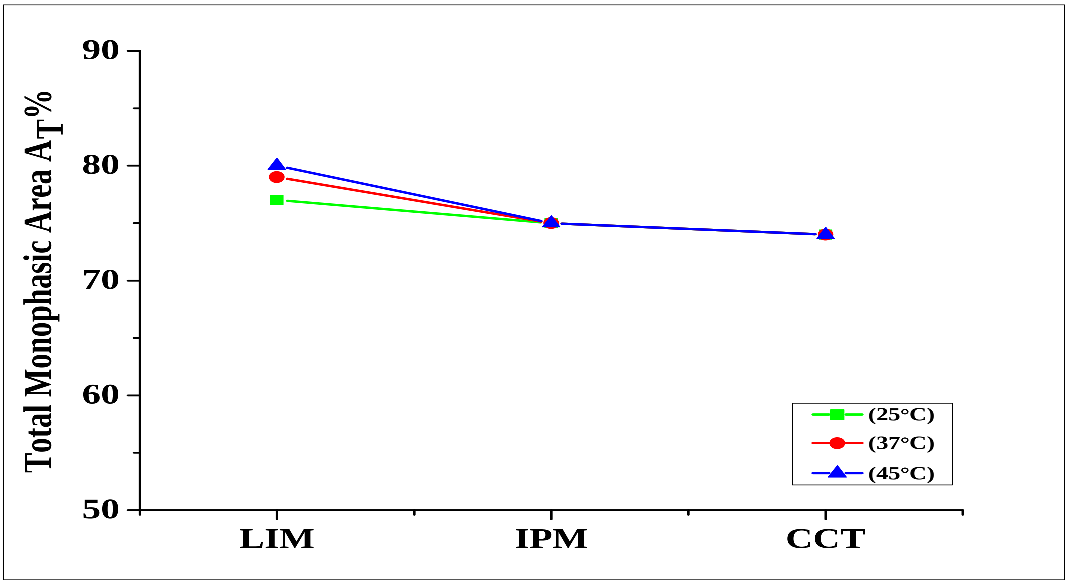


Figure 5.48: Variations in the total monophasic area A_T % of the system W/O1570/T-MAZ 80/oils + EtOH at three different temperatures (25, 37 and 45ºC) at ratio 1/1 (w/w) between mixed surfactants.

From table 5.54 mentioned above shows the total monophasic area (A_T %) of three types of oils studied, LIM oil gave a higher total monophasic area (A_T %) compared to other oils, this because LIM oil has ring structure tends to penetrate more easily into the interfacial film making an ordered one phase microemulsions, on the other hand the presence of ethanol molecules in the system increase the fluidity of interfacial films, and decrease the rigidity of the interface, hence increase the radius of surfactant curvature resultant in increasing of the total monophasic area.

The ethanol co-surfactant contain one hydroxyl group (OH), cause hydration of both the head groups and hydroxyl group co-surfactant associated with droplets, this gives an increase in the total amount of alcohols associated with droplet, so gives an increase in the total monophasic area (A_T %), in addition alcohols considered not just to be a co-surfactant that act on the properties of the amphiphilic monolayer at water/oil interface, but also it considered as co-solvent that distribute between the aqueous and oil-rich bulk phase, thereby decrease the hydrophobicity of the amphiphile as well as hydrophobicity of the oil cause lowering the interfacial tension (IFT) between the water-rich and oil-rich phases.

- W/O1570/T-MAZ 80/ LIM + PG system

Figure 5.49 presents the phase diagram of the system water/sucrose oleate (O1570)/T-MAZ 80/ R (+)-limonene (LIM) + propylene glycol (PG) at 25°C. The mixing ratio of O1570/T-MAZ 80 equals 1/1. N65 is the dilution line where the ratio of (O1570 + T-MAZ 80)/LIM + PG =65/35.

O1570 + T-MAZ 80 (wt%)	Maximum water solubilization (wt%)
90	100
80	90
40	75
20	50
10	25

Table 5.55: Maximum water solubilization along the different dilution lines according to figure 5.49 which is illustrated below.

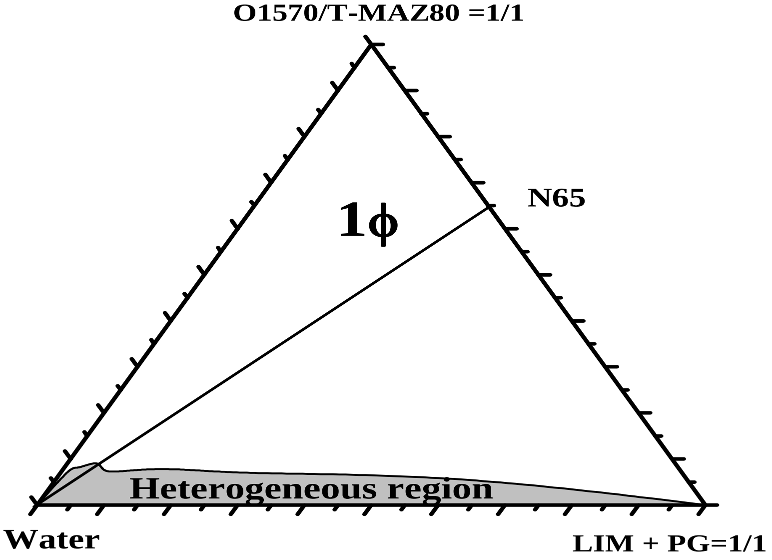


Figure 5.49: Phase diagram of the system: water/ sucrose oleate (O1570) /T-MAZ 80/ R (+)-limonene (LIM) + propylene glycol (PG) at 25°C. The mixing ratio of O1570/T-MAZ 80 and LIM/PG equal 1/1. The one phase microemulsion region is designated as 1ϕ and the multiple phase region is designated as Heterogeneous region.

- W/O1570/T-MAZ 80/ IPM + PG system

Figure 5.50 presents the phase diagram of the system water/sucrose oleate (O1570)/T-MAZ 80/isopropyl myristate (IPM) + propylene glycol (PG) at 25°C. The mixing ratio of O1570/T-MAZ 80 equals 1/1. N65 is the dilution line where the ratio of (O1570 + T-MAZ 80)/IPM + PG =65/35.

O1570 + T-MAZ 80 (wt%)	Maximum water solubilization (wt%)
90	100
80	75
40	55
20	40
10	20

Table 5.56: Maximum water solubilization along the different dilution lines according to figure 5.50 which is illustrated below.

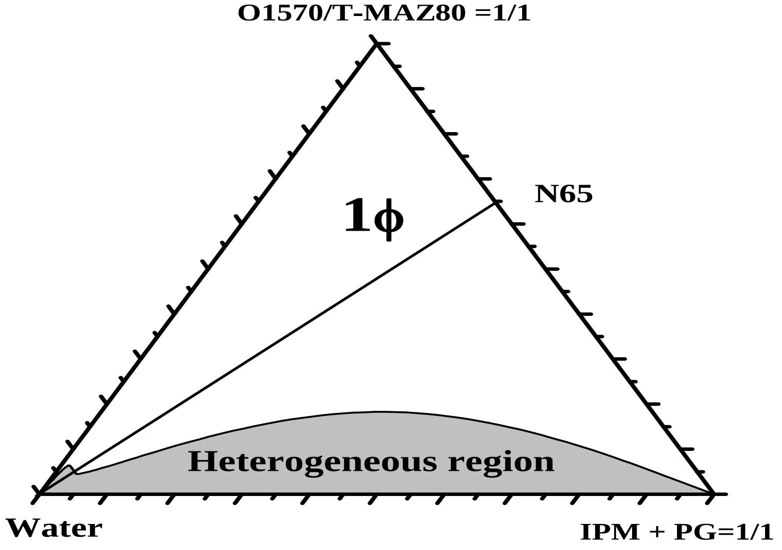


Figure 5.50: Phase diagram of the system: water/ sucrose oleate (O1570) /T-MAZ 80/ isopropyl myristate (IPM) + propylene glycol (PG) at 25°C. The mixing ratio of O1570/T-MAZ 80 and IPM/PG equal 1/1. The one phase microemulsion region is designated as 1ϕ and the multiple phase region is designated as Heterogeneous region.

- W/O1570/T-MAZ 80/ CCT + PG system

Figure 5.51 presents the phase diagram of the system water/sucrose oleate (O1570)/T-MAZ 80/ Caprylic-capric triglyceride (CCT) + propylene glycol (PG) at 25°C. The mixing ratio of O1570/T-MAZ 80 equals 1/1. N65 is the dilution line where the ratio of (O1570 + T-MAZ 80)/CCT + PG =65/35.

O1570 + T-MAZ 80 (wt%)	Maximum water solubilization (wt%)
90	100
80	65
40	45
20	30
10	15

Table 5.57: Maximum water solubilization along the different dilution lines according to figure 5.51 which is illustrated below.

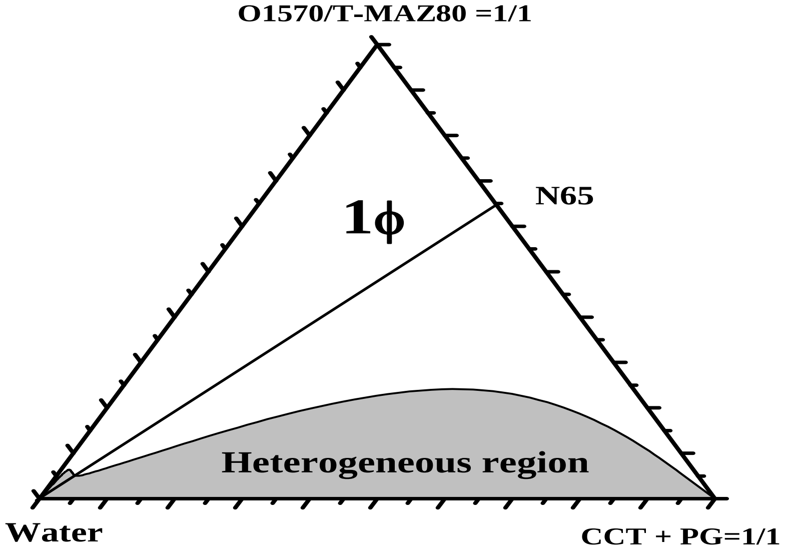


Figure 5.51: Phase diagram of the system: water/ sucrose oleate (O1570) /T-MAZ 80/ Caprylic-capric triglyceride (CCT) + propylene glycol (PG) at 25°C.The mixing ratio of O1570/T-MAZ 80 and CCT/PG equal 1/1. The one phase microemulsion region is designated as 1ϕ and the multiple phase region is designated as Heterogeneous region.

Table 5.58: The total monophasic area A_T % for the system W/O1570/T-MAZ 80/oils + PG for different oil types at different temperatures 25, 37 and 45ºC, at ratio (1/1) between mixed surfactants.

	A_T % (Total monophasic area)		
Oil	**25ºC**	**37ºC**	**45ºC**
LIM	89	89	90
IPM	76	76	76
CCT	69	69	70

Figure 5.52 shows the variations in the total monophasic area A_T % between three types of oils: LIM, IPM and CCT at three different temperatures (25, 37, and 45ºC) for the system W/ O1570/T-MAZ 80/ oils + PG at ratio 1/1 (w/w) between mixed surfactants.

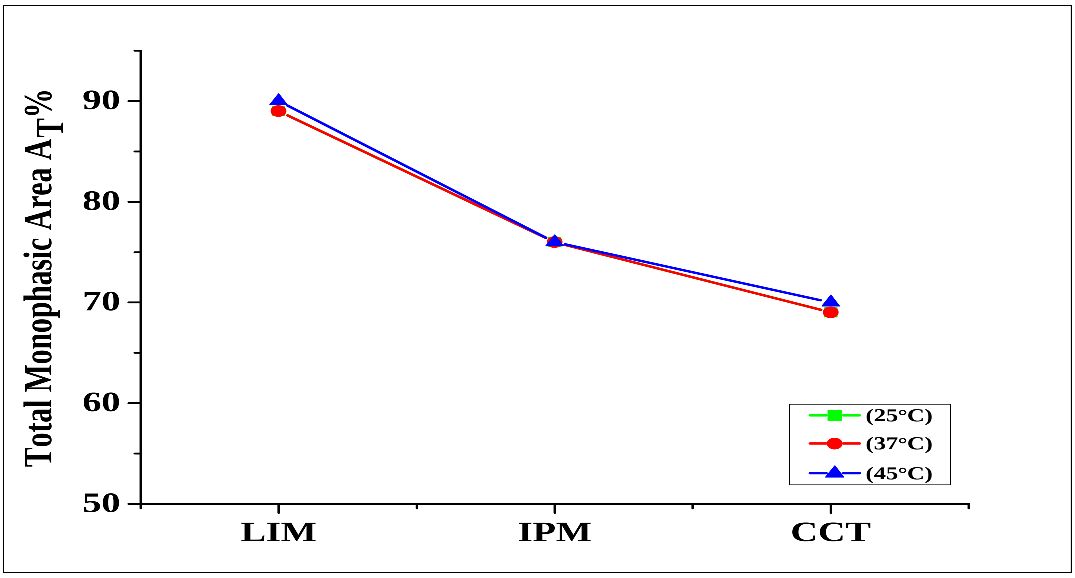


Figure 5.52: Variations in the total monophasic area A_T % of the system W/O1570/T-MAZ 80/oils + PG at three different temperatures (25, 37 and 45ºC) at ratio 1/1 (w/w) between mixed surfactants.

Table 5.58 show a three different types of oils ranking from lower to higher molecular volume of that oil, as the molecular volume of oils increase the total monophasic area (A_T %) decrease, therefore LIM oil which has lower molecular volume compared to other oils studied it gave a higher total monophasic area (A_T %).

Surfactant molecules are self-assemble in polar organic solvent like propylene glycol (PG) and glycerol (GLY), these solvents like water form a hydrogen bonds, have relatively dielectric constants and are immiscible with hydrocarbon solvents, also critical micelle concentrations (CMC) are higher in polar non-aqueous solvents than in water, when these solvents are added to microemulsion systems, their resulting penetration into the surfactant interface leads to smaller or no liquid crystal phase regions.

Polyols like propylene glycol (PG) and glycerol (GLY) are used in microemulsion systems as tuning parameters to change the surfactant layer curvature and to increase the flexibility of the surfactant film, hence increase penetrating into the interface, and destabilizing the liquid crystalline phase by connecting the aqueous and oil phase together.

- W/O1570/T-MAZ 80/ LIM + IPM system

Figure 5.53 presents the phase diagram of the system water/sucrose oleate (O1570)/T-MAZ 80/ R (+)-limonene (LIM) + isopropyl myristate (IPM) at 25°C. The mixing ratio of O1570/T-MAZ 80 equals 1/1. N65 is the dilution line where the ratio of (O1570 + T-MAZ 80)/LIM + IPM =65/35.

O1570 + T-MAZ 80 (wt%)	Maximum water solubilization (wt%)
90	100
80	70
40	50
20	30
10	20

Table 5.59: Maximum water solubilization along the different dilution lines according to figure 5.53 which is illustrated below.

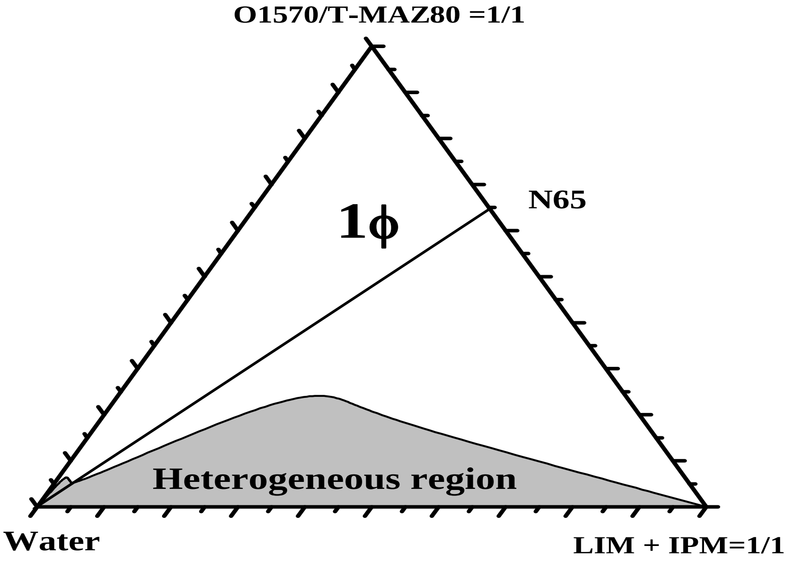


Figure 5.53: Phase diagram of the system: water/sucrose oleate (O1570)/T-MAZ 80/ R (+)-limonene (LIM) + isopropyl myristate (IPM) at 25°C. The mixing ratio of O1570/T-MAZ 80 and LIM/IPM equal 1/1. The one phase microemulsion region is designated as 1ϕ and the multiple phase region is designated as Heterogeneous region.

- W/O1570/T-MAZ 80/ LIM + CCT system

Figure 5.54 presents the phase diagram of the system water/sucrose oleate (O1570)/T-MAZ 80/ R (+)-limonene (LIM) + Caprylic-capric triglyceride (CCT) at 25°C. The mixing ratio of O1570/T-MAZ 80 equals 1/1. N65 is the dilution line where the ratio of (O1570 + T-MAZ 80)/LIM + CCT =65/35.

O1570 + T-MAZ 80 (wt%)	Maximum water solubilization (wt%)
90	100
80	60
40	40
20	25
10	10

Table 5.60: Maximum water solubilization along the different dilution lines according to figure 5.54 which is illustrated below.

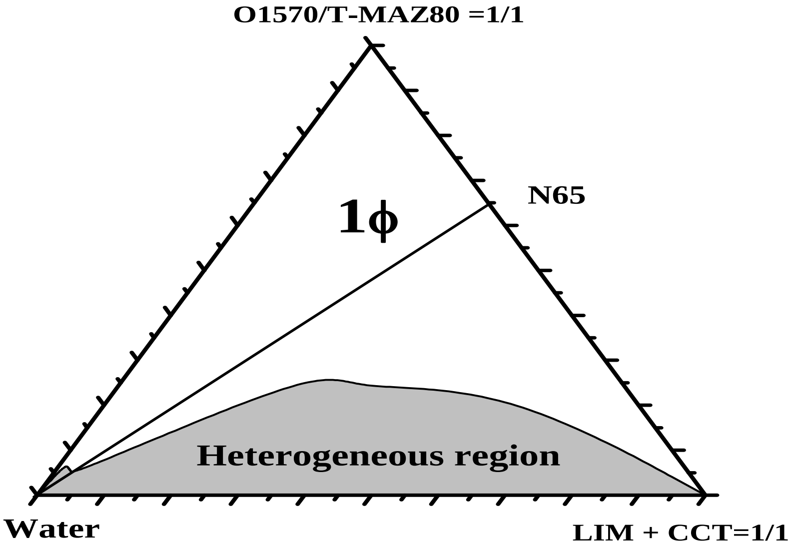


Figure 5.54: Phase diagram of the system: water/sucrose oleate (O1570)/T-MAZ 80/ R (+)-limonene (LIM) + Caprylic-capric triglyceride (CCT) at 25°C.The mixing ratio of O1570/T-MAZ 80 and LIM/CCT equal 1/1. The one phase microemulsion region is designated as 1ϕ and the multiple phase region is designated as Heterogeneous region.

Table 5.61: The total monophasic area A_T % for the system W/O1570/T-MAZ 80/ mixed oils as a function of LIM oil at different temperatures 25, 37 and 45ºC at ratio (1/1) between mixed surfactants and mixed oils.

	A_T % (Total Monophasic area)		
oil type	**25ºC**	**37ºC**	**45ºC**
IPM	68	68	68
CCT	74	75	76

IPM and CCT oils are polar oils that have large tendency to penetrate in the surfactant palisade layer, the polarity of these oils made a variation in the electron density between the polar head and tail of that oils and hence increase the partitioning these oils in the water-oil interface. The chain length compatibility of microemulsion systems plays a key role in determining the interfacial properties and stability of microemulsions formed, therefore LIM + CCT oils have more compatibility to form stable and ordered microemulsion system than LIM + IPM system in mixed nonionic microemulsions.

In this section (5.1.2) we study the mixed nonionic surfactant systems composed of sucrose ester (sucrose oleate O1570) and poly sorbate (T-MAZ 80) with single or mixed oils (LIM, IPM and CCT) at different three mixing ratios (w/w) between mixed surfactants 1/1, 2/1 and 1/2, also we study in this section a mixed surfactants with three types of oils plus ethanol (EtOH) or propylene glycol (PG) co-surfactants at ratio 1/1 (w/w) between mixed surfactants.

We observe from this section that the main factor affecting in determination of total monophasic area (A_T %) is the molecular volume of oils, thus LIM oil gave higher A_T % values in all system studied, because LIM oil has the smallest molecular volume compared to other oils studied, therefore we conclude that as the molecular volume of oils increased the total monophasic area (A_T %) will be decreased and tables 5.42, 46, 50, 54 and 5.58 which outlined above in this section approve this statement, the only exception is the systems of mixed surfactants with mixed oils (W/O1570/T-MAZ 80/ LIM + CCT, W/O1570/T-MAZ 80/ LIM + IPM) which mentioned in table 5.20, the result showed that

LIM + CCT gave a higher A_T %, This interpreted in terms of chain length compatibility between mixed surfactants and mixed oils.

- About phase behavior

Finally, from the study of the phase behavior of different microemulsion systems, we conclude the observations as follows:

- The huge difference in the total monophasic area (A_T %) between single nonionic surfactant systems (5.1.1) and mixed nonionic surfactant systems (5.1.2), the better and large A_T % in mixed surfactant systems observed, this is due to mixture of surfactants have often been found to be more advantageous over the use of single surfactants, since they can extract properties superior to the individual ones. The blending of two nonionic surfactants can provide better solubilization capacity and affect the phase behavior relative to the individual ones, also blending of surfactants can tune the hydrophilic–lipophilic balance (HLB) of the constituting surfactants in order to optimize the solubilization capacity. Synergistic effect of mixed surfactant are different according to the type of surfactants in the formulation, the mixed ionic one have larger synergistic effect due to electrostatic interactions between charged head group, the main driving force in contribution of synergism are critical micelle concentration (CMC) of surfactant molecules and the entropic energy of the head group, thus synergistic effect calculated as interaction parameter (β) [Bergstrom. R, Eriksson. J, 2000].

- We study different types of microemulsion systems with three types of oils (LIM, IPM and CCT), the oil penetration in the surfactant palisade layer depends upon the tendency of that oil to penetrate, thus change the surfactant layer curvature to less positive or negative, also the three-dimensional arrangement of oils effect on the stability and extension of microemulsions formed, i.e. LIM oil has a sphere-like shape which tends to penetrate more easily into the water- oil interface. On the contrary to IPM and CCT oils which haverod, plate-like shape respectively that more difficult in penetration as we showed in section 5.1.2, moreover there are other factors that have effect on the phase behavior of microemulsions such as chain length compatibility and effective carbon number (ECN) as shown in section 5.1.1.

- Solubilization and phase equilibria of water in oil microemulsions depends on two phenomenological parameters, namely the spontaneous curvature and elasticity of the interfacial films, the elasticity is related to the energy required to bend the interface (attractive interactions between droplets in the system). The presence of co-surfactants (ethanol, propylene glycol, propionic acid and glycerol) in the microemulsion systems will be modified and extend the A_T %, thereby increasing the fluidity of the interfacial film Consequently minimizing interfacial bending stress and the attractive interdroplet interaction of fluid interface. These competing effects lead to maximum solubilization, as observed experimentally.

5.2 Electrical conductivity

For understanding the properties and phase transitions in microemulsion systems, it must study the effect of electric field conductance in these systems, thus much of work has been done in the last few decades in this particular area [Glatter. O, et al, 2001] [Bumajdad. A,Eastoe.J, 2004] [De campo.L, et al, 2004]. Microemulsions are capable of encapsulating large amounts of water. Due to their unique properties microemulsions have been used in a variety of technological applications, including environmental protection, nanoparticle formation, product formulations, delivery systems, polymerization and chemical media [Brusseau. M, Gierke. J, Sabatini. D, 1999] [Sabatini. D, Knox. R, 1992] [Texter.J, 2001].

Microemulsion domain structures are often as water– continuous in water- in– oil (w/o) microemulsions, oil- continuous in oil- in- water (o/w) microemulsions or bicontinuous. These structures in electrical conductivity measurements are influenced by different factors such as water volume fraction and temperature, that conductivity remains low up to a certain volume fraction of water (ϕ) at constant temperature, when increase in water volume fraction conductivity will be increased and percolation threshold were observed, as well as temperature increased the electrical conductivity increase too. Structural features of microemulsion systems also depend on the nature of radius (R) of droplets and the aggregation number of surfactants and co-surfactants molecules per droplets in the interface [Bisal. S, et al, 1990].

In this section, we will study the properties and phase transitions of microemulsion systems by electrical conductivity. We examined the effect of changing mixing ratio (w/w) between mixed nonionic surfactants, effect of different temperatures (25, 37 and 45ºC), effect of types of oils (LIM, IPM and CCT) and co-surfactants (EtOH, PG) on electrical conductivity and the effect of water volume fraction (ϕ) by gradually adding fixed amount of water to microemulsion systems.

We choose systems that give a highest total monophasic area (A_T %) to study electrical conductivity along the dilution line N65, these systems are: W/O1570/T-MAZ 80/ LIM, W/O1570/T-MAZ 80/ IPM, W/O1570/T-MAZ 80/ CCT, W/O1570/T-MAZ 80/ LIM +

EtOH, W/O1570/T-MAZ 80/ LIM + PG, W/O1570/T-MAZ 80/ LIM + IPM, W/O1570/T-MAZ 80/ LIM + CCT at ratio 1/1 (w/w) between mixed surfactants, W/O1570/T-MAZ 80/ LIM at ratio 2/1, W/O1570/T-MAZ 80/ LIM at ratio 1/2 (w/w) between mixed surfactants, also to predict the type of microemulsions formed (i.e. water- in-oil (w/o), bicontinuous and oil- in-water (o/w) by electrical conductivity measurements.

5.2.1 Mixed surfactants with single oil systems

5.2.1.a W/ O1570/ T-MAZ 80/ LIM at ratio 1/1 (w/w)

The electrical conductivity was measured for the system W/ O1570/ T-MAZ 80/ LIM were the mixing ratio of mixed surfactants is equal 1/1 (w/w) along the dilution line N65. Figure 5.55 and table 5.62display the influence of water content and temperature on the electrical conductivity (σ).

Table 5.62: The electrical conductivity (σ) for the system W/ O1570/ T-MAZ 80/ LIM at different water contents and different temperatures (25, 37 and 45ºC).

Water content (Wt. %)	**σ (µS/cm)**		
	25ºC	**37ºC**	**45ºC**
0	0.4	0.4	0.8
10	1.1	2.1	5.8
20	6.2	9.3	21.7
30	44.4	48.5	85.4
40	59.5	62.7	100.4
50	139.8	142.1	209
60	231	242	421

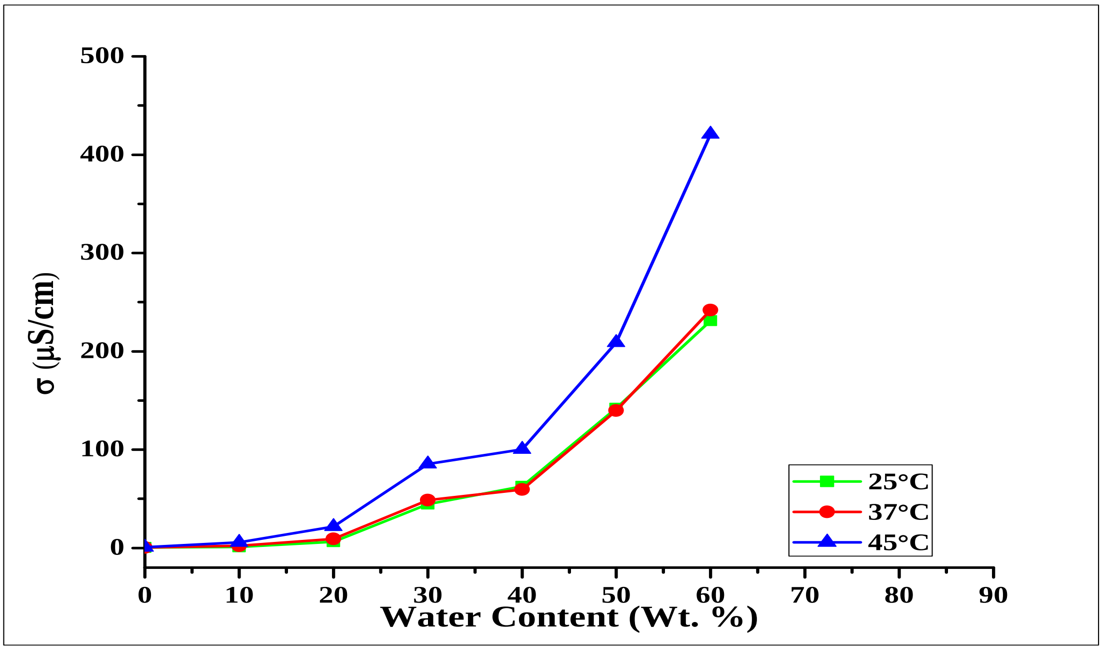


Figure 5.55 Variation of the electrical conductivity (σ) of the system W/ O1570/ T-MAZ 80/ LIM as a function of water content along the dilution line N65 at different temperatures (25, 37 and 45ºC). The mixing ratio between (O1570/T-MAZ 80) is equal unity.

At water content below 20%, electrical conductivity has low values as shown in figure 5.55, this indicates restricted water mobility in this region, then above 20% water content electrical conductivity continuously increase with the increase in water content. The sudden change in electrical conductivity value in the water content 50% suggest that the system undergoes a structural inversion from water-in-oil (w/o) to the bicontinuous microemulsion. In this water content, the percolation threshold occurred, conductivity increased as temperature increases in steadily fashioning at water content higher than 50%.

5.2.1.b W/O1570/T-MAZ 80/ LIM at ratio 1/2 (w/w)

The electrical conductivity was measured for the system W/ O1570/ T-MAZ 80/ LIM were the mixing ratio of mixed surfactants is equal 1/2 (w/w) along the dilution line N65. Figure 5.56 and table 5.63display the influence of water content and temperature on the electrical conductivity (σ).

Table 5.63: The electrical conductivity (σ) for the system W/ O1570/ T-MAZ 80/ LIM at different water contents and different temperatures (25, 37 and 45ºC).

Water content (Wt. %)	σ (µS/cm)		
	25ºC	37ºC	45ºC
0	0.2	0.2	0.4
10	1.1	2	5.3
20	4.5	5.4	12.8
30	7.6	10.8	20.1
40	40.5	34.7	59.1
50	119.5	116.5	149.4
60	134.6	121.2	171.2

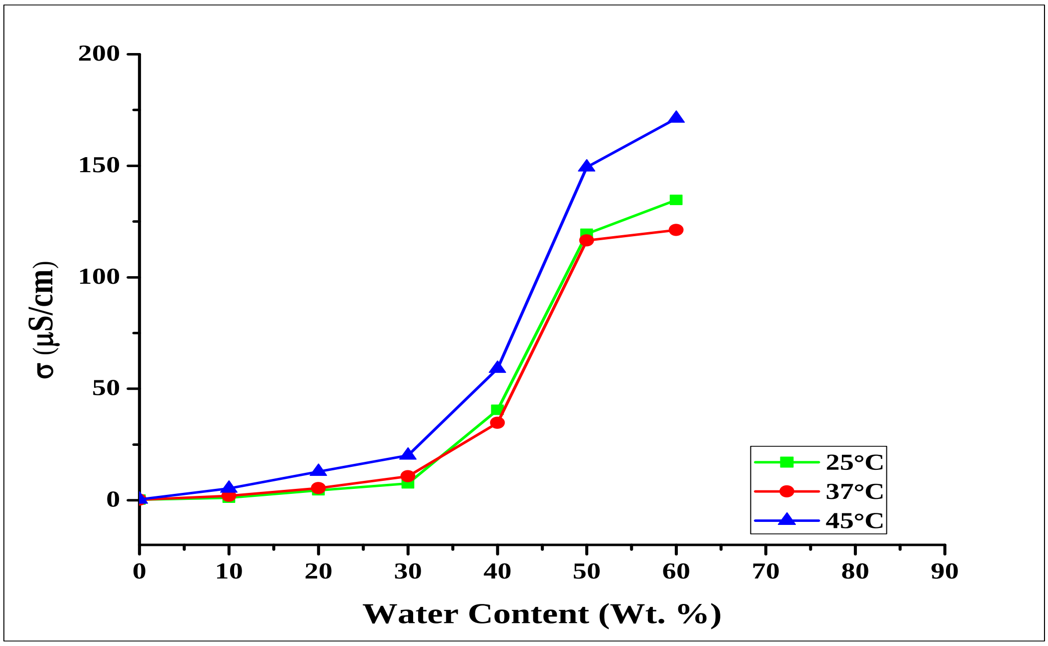


Figure 5.56 Variation of the electrical conductivity (σ) of the system W/ O1570/ T-MAZ 80/ LIM as a function of water content along the dilution line N65 at different temperatures (25, 37 and 45ºC). The mixing ratio between (O1570/T-MAZ 80) is equal 1/2 (w/w).

At 0% water content the electrical conductivity values is very low as shown in table 5.63 due to the microemulsion system in this region is suggested to be micelles and have a high viscosity. This high viscosity makes a microemulsion system more network, thus restricted water mobility and ion exchange will happen. Electrical conductivity values still to have low values until the water content reaches 40% sudden changes in σ values in this region explained that a percolation threshold occurred and the beginning of structural inversion to the bicontinuous microemulsion. In the case of LIM oil based microemulsion, a high viscosity of microemulsion and the gel-like structure was formed extended low values of electrical conductivity up to 30% water content.

5.2.1.c W/O1570/T-MAZ 80/ LIM at ratio 2/1 (w/w)

The electrical conductivity was measured for the system W/ O1570/ T-MAZ 80/ LIM were the mixing ratio of mixed surfactants is equal 2/1 (w/w) along the dilution line N65. Figure 5.57 and table 5.64display the influence of water content and temperature on the electrical conductivity (σ).

Table 5.64: The electrical conductivity (σ) for the system W/ O1570/ T-MAZ 80/ LIM at different water contents and different temperatures (25, 37 and 45ºC).

Water content (Wt. %)	σ (µS/cm)		
	25ºC	37ºC	45ºC
0	0.3	0.2	0.5
10	1.4	2.8	7.8
20	10.3	16	36.4
30	11.2	18.1	42.5
40	48.5	54.3	102.1
50	112.4	115	146.2
60	131.4	134	189.3
70	212	217	418

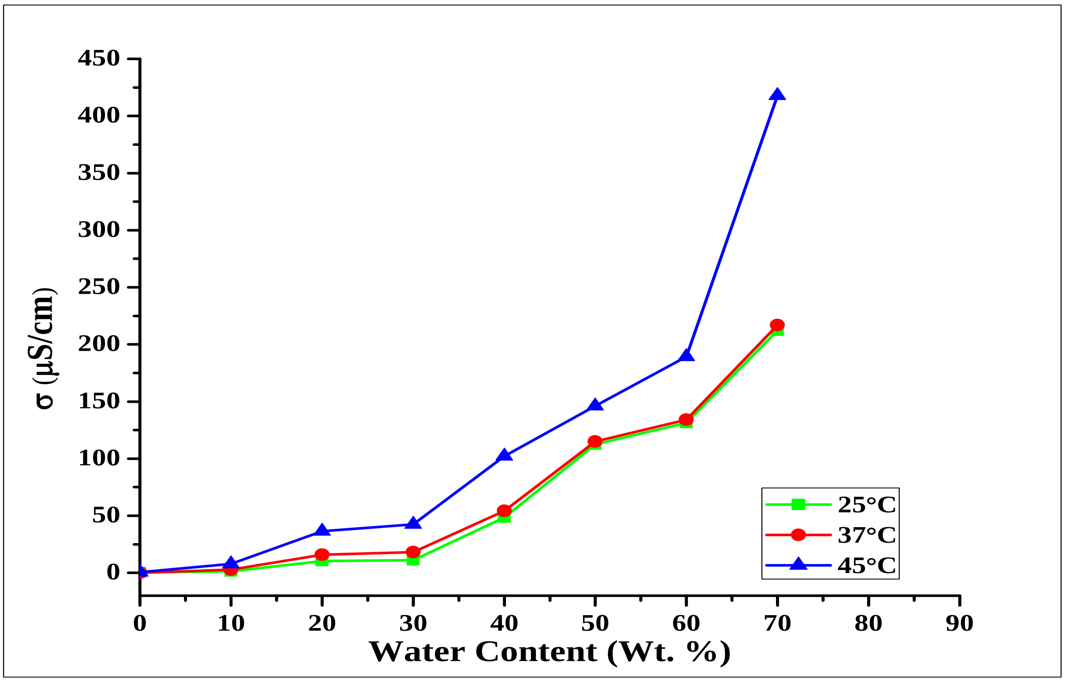


Figure 5.57 Variation of the electrical conductivity (σ) of the system W/ O1570/ T-MAZ 80/ LIM as a function of water content along the dilution line N65 at different temperatures (25, 37 and 45ºC). The mixing ratio between (O1570/T-MAZ 80) is equal 2/1 (w/w).

This system W/O1570/T-MAZ 80/LIM at ratio 2/1 (w/w) contribute the same observation of the previous system. We also noted the effect of temperature on the electrical conductivity values, the electrical conductivity values at temperature 45ºC have the highest values followed by 37ºC and then 25ºC, it is explained in term of kinetic energy and interdroplet interactions between formulated droplet. An increase in temperature will increase the kinetic energy between droplets and increase of thermal motion, this allows to more ion exchanges and therefore high electrical conductivity will be produced.

Table 5.65 and figure 5.58 shows the variation in the electrical conductivity values (σ) of microemulsion system: W/O1570/LIM with mixing ratio 1/1, 1/2 and 2/1 (w/w) at three different temperatures (25, 37 and 45ºC) along the dilution line N65.

Water content (Wt. %)	**σ (µS/cm)**		
	LIM 1/1	**LIM 1/2**	**LIM 2/1**

0	0.4	0.2	0.3
10	1.1	1.1	1.4
20	6.2	4.5	10.3
30	44.4	7.6	11.2
40	62.7	40.5	48.5
50	142.1	119.5	112.4
60	231	134.6	131.4
70			212

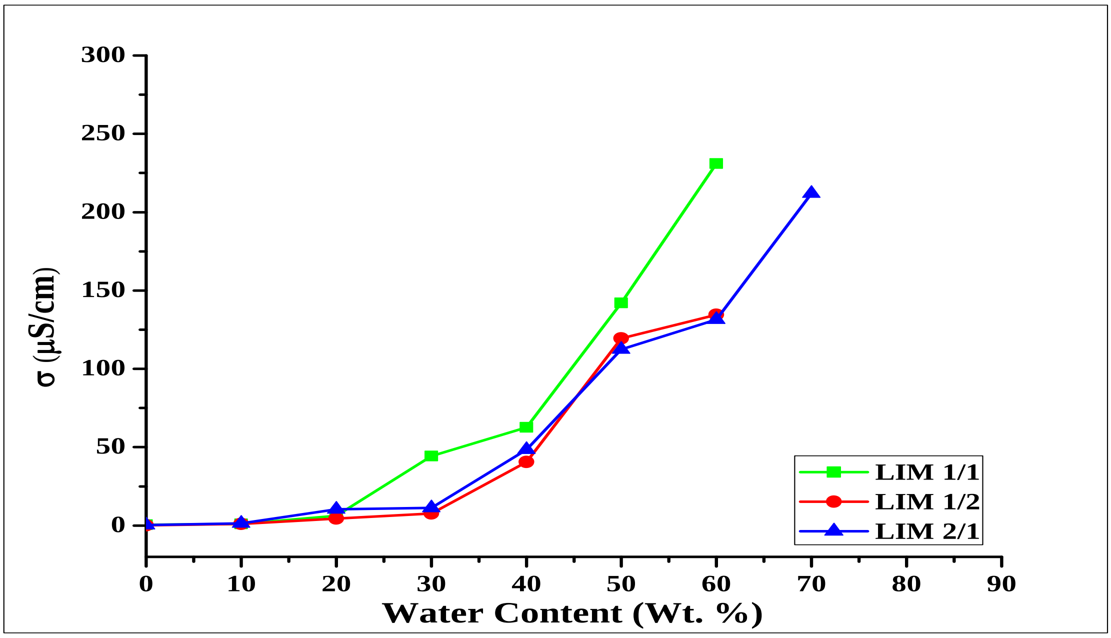


Figure 5.58 Variation in the electrical conductivity values (σ) of microemulsion system: W/O1570/LIM with mixing ratio 1/1, 1/2 and 2/1 (w/w) at three different temperatures (25, 37 and 45°C) along the dilution line N65.

We study here the effect of surfactant mixing ratio on the electrical conductivity of mixed microemulsion system with LIM oil. As shown in figure 5.58 we observe that system containing LIM at ratio 1/1 gives a high electrical conductivity values compared to other mixing ratios, it can be interpreted in term of the synergistic effects of nonionic surfactants that the microemulsion contains equal amounts of surfactant make a synergetic effects more pronounced, because of equilibrium interactions between these molecules.

5.2.1.d W/ O1570/ T-MAZ 80/ IPM at ratio 1/1 (w/w)

The electrical conductivity was measured for the system W/ O1570/ T-MAZ 80/IPM were the mixing ratio of mixed surfactants of equal unity along the dilution line N65. Figure 5.59 and table 5.66display the influence of water content and temperature on the electrical conductivity (σ).

Table 5.66: The electrical conductivity (σ) for the system W/ O1570/ T-MAZ 80/ IPM at different water contents and different temperatures (25, 37 and 45ºC).

Water content (Wt. %)	σ (µS/cm)		
	25ºC	37ºC	45ºC
0	0.4	0.1	0.2
10	1.3	3.5	8.9
20	20.5	27.3	60.8
30	145	154	293
40	248	257	485
50	321	319	579
60	329	338	612
70	219	204	314
80	179	184	245
90	100	105	165

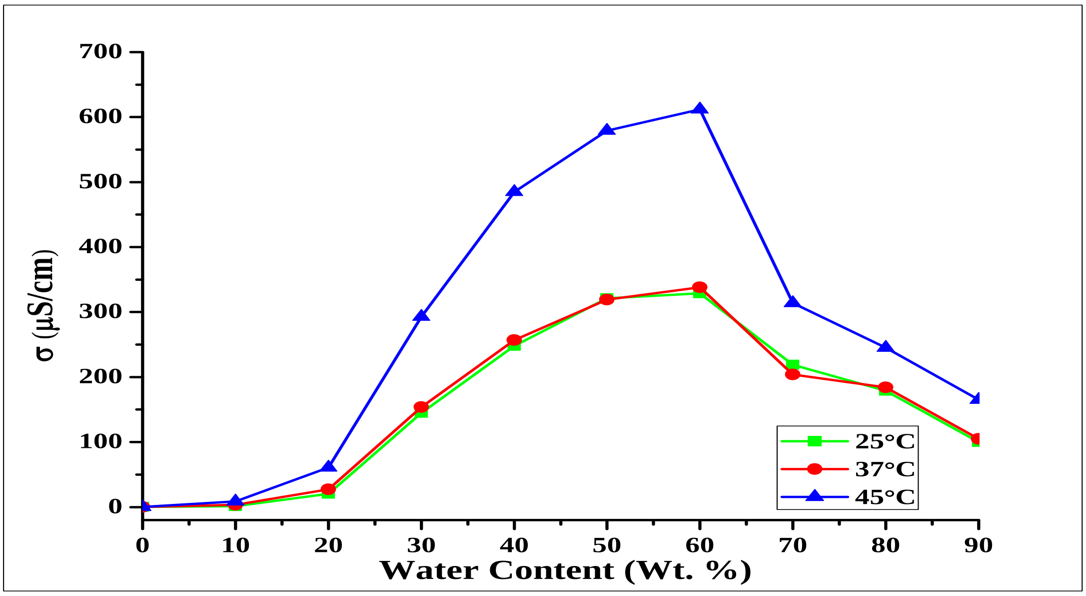


Figure 5.59 Variation of the electrical conductivity (σ) of the system W/ O1570/ T-MAZ 80/ IPM as a function of water content along the dilution line N65 at different temperatures (25, 37 and 45ºC). The mixing ratio between (O1570/T-MAZ 80) is equal unity.

As shown in table 5.66 and figure 5.59 the electrical conductivity (σ) at water content equal 0 wt. % is very low and then slightly increased until reach 20% water content; this due the formation of water- in- oil (w/o) microemulsion. At water content 30% the electrical conductivity exponentially increased three to four times, this increase in conductivity (σ) explain the structural inversion in microemulsion system, hence it is suggested that system converted from w/o to bicontinuous. From 30% to 60% water content the system continue to increase in conductivity (σ). At water content equal 70% the conductivity (σ) become to decrease suggested that a system undergoes structural inversion to oil – in- water (o/w).

Also it was observed from the figure 5.59 which mentioned above, it is obvious that the electrical conductivity (σ) has highest values at temperature 45ºC followed by 37ºC and then 25ºC, so that as the temperature increased, the electrical conductivity (σ) was increased.

5.2.1.e W/ O1570/ T-MAZ 80/ CCT at ratio 1/1 (w/w)

The electrical conductivity was measured for the system W/ O1570/ T-MAZ 80/CCT were the mixing ratio of mixed surfactants of equal unity along the dilution line N65. Figure 5.60 and table 5.67display the influence of water content and temperature on the electrical conductivity (σ).

Table 5.67: The electrical conductivity (σ) for the system W/ O1570/ T-MAZ 80/ CCT at different water contents and different temperatures (25, 37 and 45ºC).

Water content (Wt. %)	**σ (µS/cm)**		
	25ºC	**37ºC**	**45ºC**
0	0.3	0.2	0.3
10	0.8	1.3	3.6
20	21.5	26.2	56.4
30	87.5	96.7	214
40	157	186	357
50	229	249	448
60	338	352	618
70	248	243	365
80	200	207	237
90	144	156	188

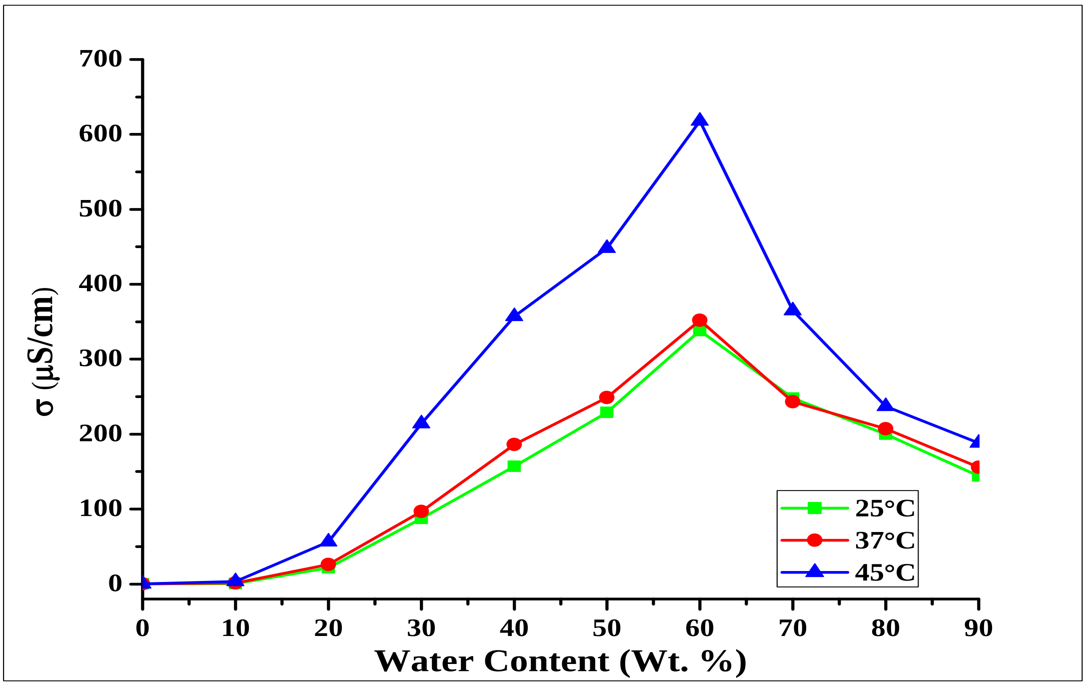


Figure 5.60 Variation of the electrical conductivity (σ) of the system W/ O1570/ T-MAZ 80/ CCT as a function of water content along the dilution line N65 at different temperatures (25, 37 and 45ºC). The mixing ratio between (O1570/T-MAZ 80) is equal unity.

At water content below 20%, the samples along the dilution line N65 were tested. The system: W/ O1570/ T-MAZ 80/ CCT as shown in figure 5.60, has low values of electrical conductivity, the low values in this region indicates restricted water mobility. Electrical conductivity continuous increase with the increase in water content until reach 60% water content. The sudden change in electrical conductivity at water content 30% predict that the percolation threshold occurred, thus it is suggested that a structural inversion to bicontinuous microemulsion happened in this region. Bicontinuous structure region continuous as the electrical conductivity increase attendant water content increase up to 60%, after a water content 60% the electrical conductivity become to decrease indicates to another structural inversion happened, thus it is proposed that microemulsion converted into oil- in- water (o/w).

As shown from results present in table 5.67 and figure 5.60, we consider that the microemulsion system: W/ O1570/ T-MAZ 80/ CCT can be divided into three different regions according to the water content, from 0 to 20% water content micelles and w/o microemulsion region, from 30 to 60% water content bicontinuous microemulsion region and the third one is from 70 to 90% water content o/w microemulsion region.

Table 5.68 and figure 5.61 shows the variation in the electrical conductivity values (σ) of mixed microemulsion systems with different three types of oils (LIM, IPM and CCT) at 25ºC along the dilution line N65. The weight ratio between mixed surfactants (O1570/ T-MAZ 80) is 1/1 (w/w).

Water content (Wt. %)	**σ (µS/cm)**		
	LIM	**IPM**	**CCT**
0	0.4	0.4	0.3
10	1.1	1.3	0.8
20	6.2	20.5	21.5
30	44.4	145	87.5
40	62.7	248	157
50	142.1	321	229
60	231	329	338
70		219	248
80		179	200
90		100	144

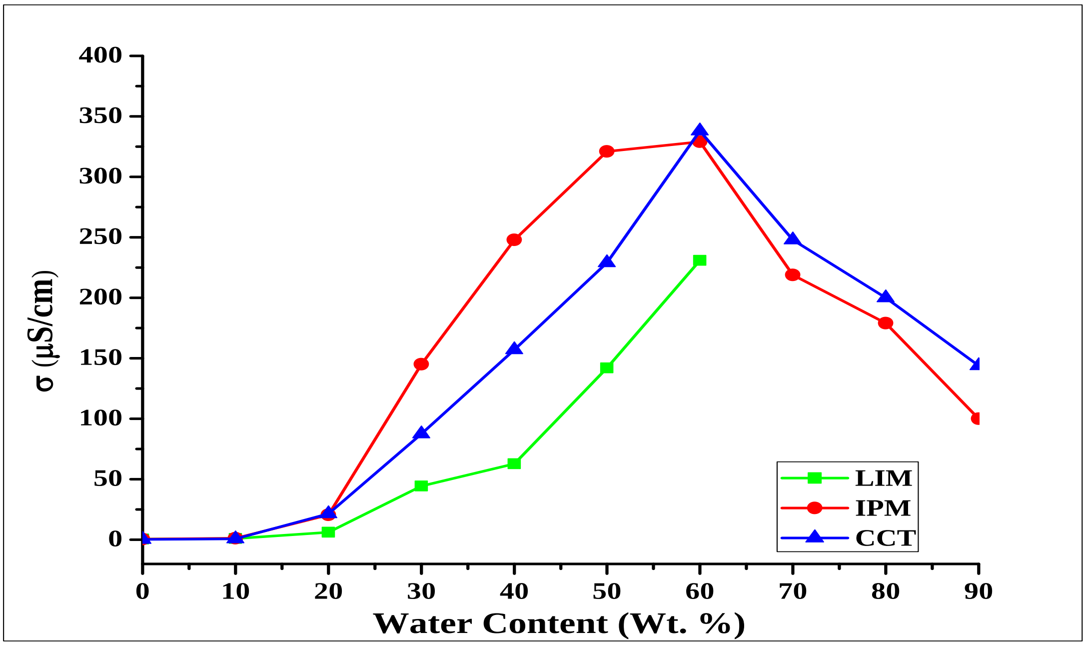


Figure 5.61 Variation in the electrical conductivity values (σ) of mixed microemulsion systems with different three types of oils (LIM, IPM and CCT) at 25ºC along the dilution line N65.

Table 5.69 and figure 5.62 shows the variation in the electrical conductivity values (σ) of mixed microemulsion systems with different three types of oils (LIM, IPM and CCT) at 37ºC along the dilution line N65. The weight ratio between mixed surfactants (O1570/ T-MAZ 80) is 1/1 (w/w).

Water content (Wt. %)	**σ (µS/cm)**		
	LIM	**IPM**	**CCT**
0	0.4	0.1	0.2
10	2.1	3.5	1.3
20	9.3	27.3	26.2
30	48.5	154	96.7
40	59.5	257	186
50	139.8	319	249
60	242	338	352

70		204	243
80		184	207
90		105	156

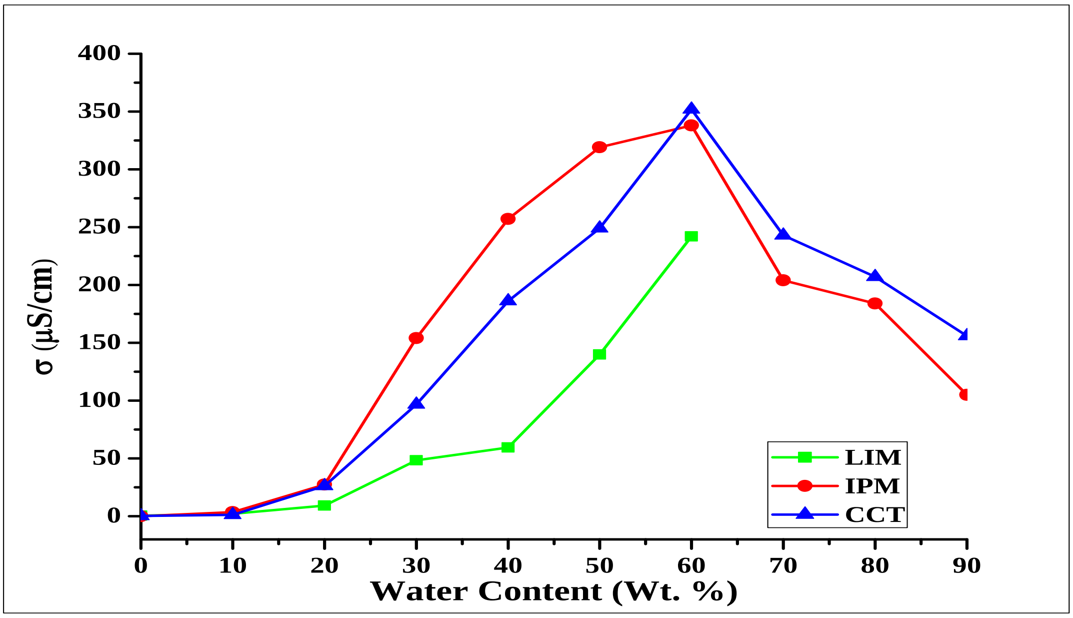


Figure 5.62 Variation in the electrical conductivity values (σ) of mixed microemulsion systems with different three types of oils (LIM, IPM and CCT) at 37ºC along the dilution line N65.

Table 5.70 and figure 5.63 shows the variation in the electrical conductivity values (σ) of mixed microemulsion systems with different three types of oils (LIM, IPM and CCT) at 45ºC along the dilution line N65. The weight ratio between mixed surfactants (O1570/ T-MAZ 80) is 1/1 (w/w).

Water content (Wt. %)	**σ (µS/cm)**		
	LIM	**IPM**	**CCT**
0	0.8	0.2	0.3
10	5.8	8.9	3.6
20	21.7	60.8	56.4
30	85.4	293	214

40	100.4	485	357
50	209	579	448
60	421	612	618
70		314	365
80		245	237
90		165	188

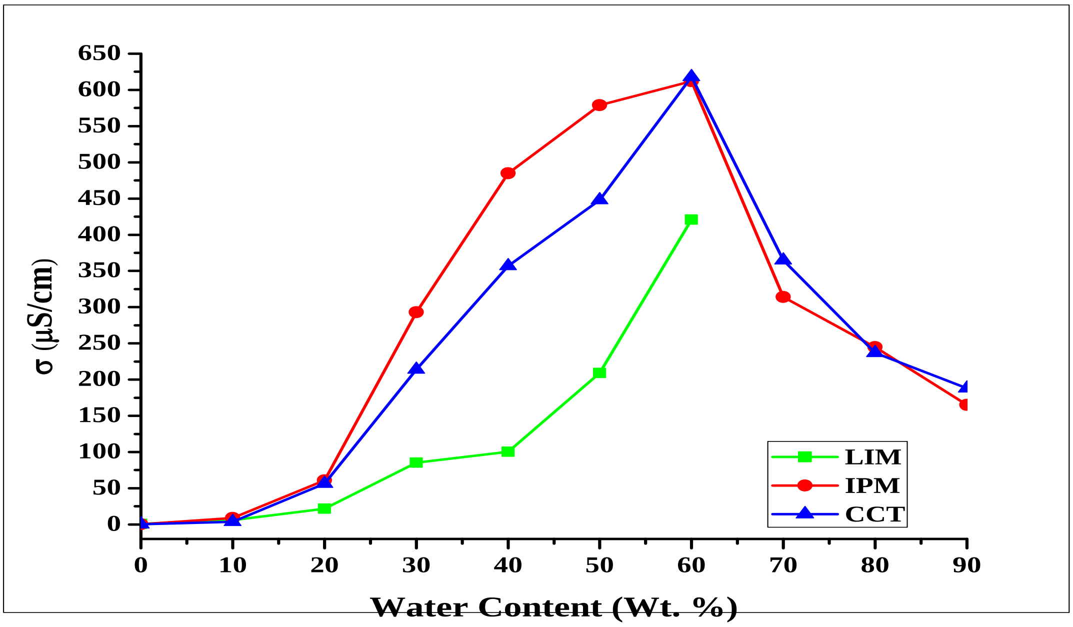


Figure 5.63 Variation in the electrical conductivity values (σ) of mixed microemulsion systems with different three types of oils (LIM, IPM and CCT) at 45ºC along the dilution line N65.

As shown in the result illustrated in figures 5.61, 5.62 and 5.63, it is distinctly that the electrical conductivity increases continuously as the temperature increases from 25ºC to 45ºC. Figure 5.61 has low values of electrical conductivity, the low electrical conductivity at temperature 25ºC because of restricted water mobility and the kinetic energy between droplets is low thus the ion exchanges are so low. But the increase in temperature will be increase in the electrical conductivity as shown experimentally, due to increase in kinetic energy, collision between droplets and hence increase in thermal motion causes increases in ion exchanges.

In low water contents (0-10 wt. %) in different types of oils in microemulsion systems as shown in figure 5.63, the water- in- oil (w/o) microemulsion that are formed in this region slowly swell and distort upon addition of water, and at a certain point (30% water content for LIM, IPM and CCT) the water migrates out of the inner phase the curvature adjust so that the conductivity increases and sponge like domains are formed termed the bicontinuous phase. This bicontinuous region is quite large until reaching the maximum value on plateau. After 60% water content the systems become decreasing in electrical conductivity suggested of another structural inversion to oil- in- water (o/w) was occurred. It is predicted that the decreasing in electrical conductivity due to the oil molecules captured within the water becomes continuous phase decrease in water mobility and ion exchanges hence decrease in electrical conductivity (σ).

For more details in determining the oil that gives a highest electrical conductivity values in a comparing of different three types of oils (LIM, IPM and CCT), we take four water content regions (0, 20, 40 and 60 wt. %) separately for these oils at three different temperatures (25, 37 and 45ºC) illustrated in tables and figures below.

Table 5.71 and figure 5.64 which presented below shows the electrical conductivity (σ) for the system: W/ O1570/ T-MAZ 80/ LIM, IPM and CCT at different three temperatures (25, 37 and 45 ºC) and 0% water content, measured along the dilution line N65.

	σ (µS/cm)		
Oil	**25ºC**	**37ºC**	**45ºC**
LIM	0.4	0.4	0.8
IPM	0.4	0.1	0.2
CCT	0.3	0.2	0.3

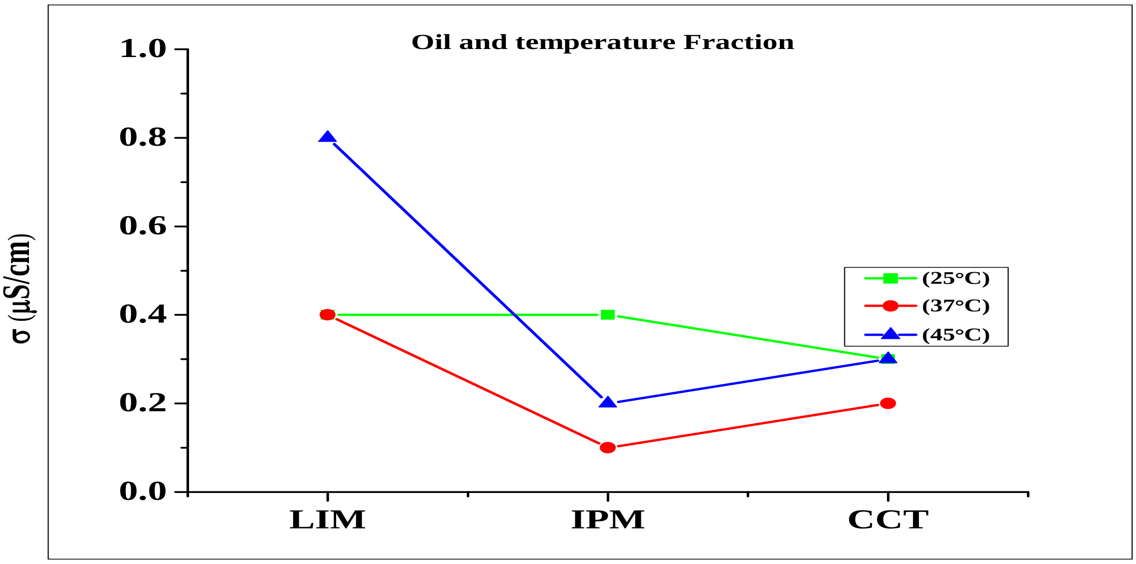


Figure 5.64 Variation in the electrical conductivity values (σ) of mixed microemulsion systems with different three types of oils (LIM, IPM and CCT) at 25, 37 and 45ºC, at water content 0% along the dilution line N65.

Values of electrical conductivity σ (µS/cm) for the system: W/ O1570/ T-MAZ 80/ LIM, IPM and CCT at different three temperatures (25, 37 and 45 ºC) and 20% water content, measured along the dilution line N65 presented in table 5.72 and figure 5.65.

	σ (µS/cm)		
Oil	**25ºC**	**37ºC**	**45ºC**
LIM	6.2	9.3	21.7
IPM	20.5	27.3	60.8
CCT	21.5	26.2	56.4

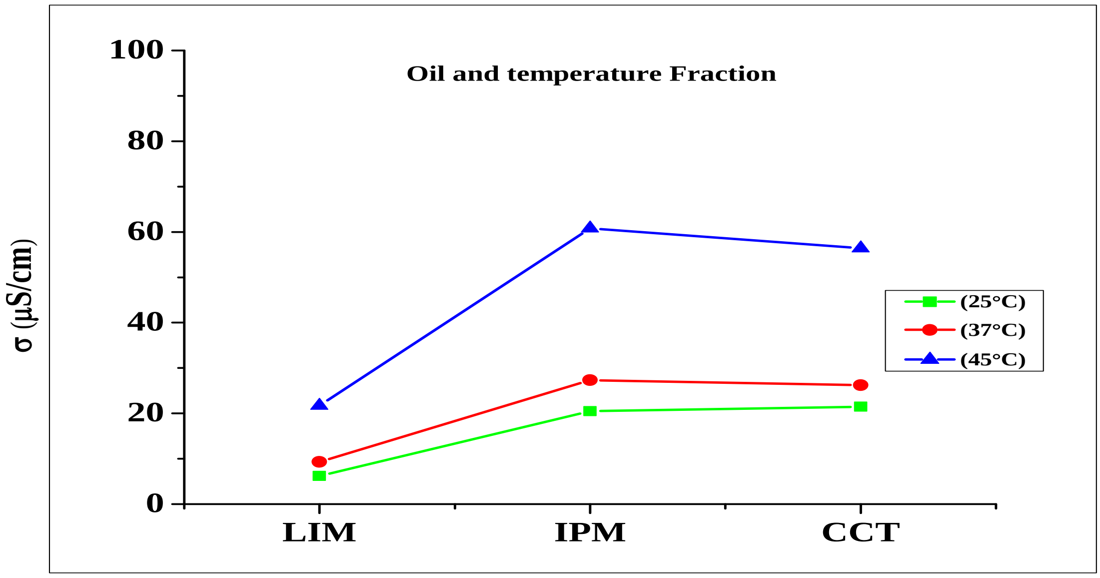


Figure 5.65 Variation in the electrical conductivity values (σ) of mixed microemulsion systems with different three types of oils (LIM, IPM and CCT) at 25, 37 and 45ºC, 20% at water content along the dilution line N65.

Values of electrical conductivity σ (µS/cm) for the system: W/ O1570/ T-MAZ 80/ LIM, IPM and CCT at different three temperatures (25, 37 and 45 ºC) and 40% water content, measured along the dilution line N65 presented in table 5.73 and figure 5.66.

	σ (µS/cm)		
Oil	**25ºC**	**37ºC**	**45ºC**
LIM	62.7	59.5	100.4
IPM	248	257	485
CCT	157	186	357

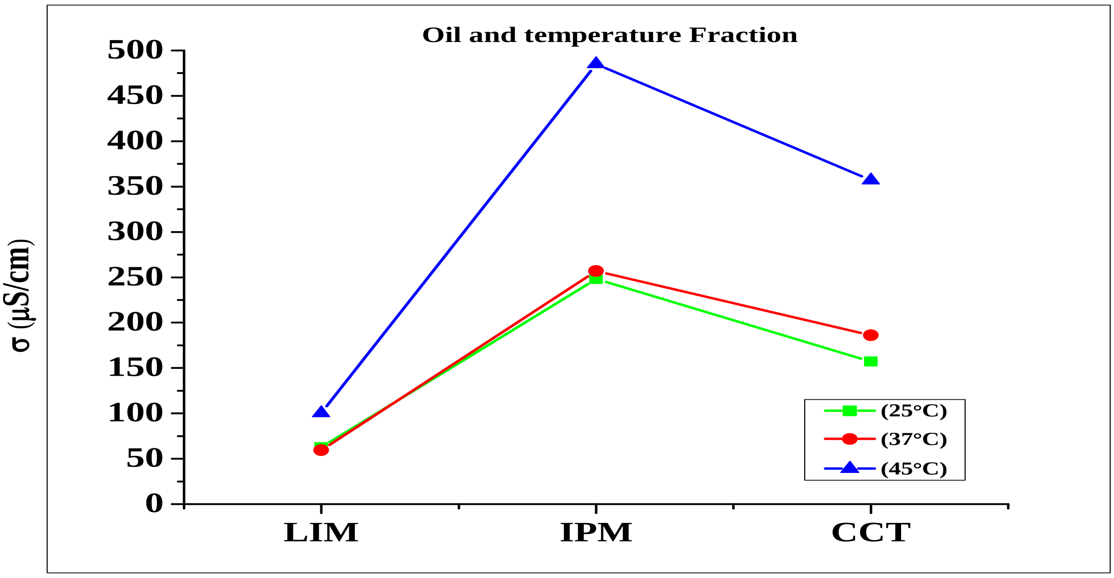


Figure 5.66 Variation in the electrical conductivity values (σ) of mixed microemulsion systems with different three types of oils (LIM, IPM and CCT) at 25, 37 and 45ºC, 40% at water content along the dilution line N65.

Values of electrical conductivity σ (μS/cm) for the system: W/ O1570/ T-MAZ 80/ LIM, IPM and CCT at different three temperatures (25, 37 and 45 ºC) and 60% water content, measured along the dilution line N65 presented in table 5.74 and figure 5.67.

	σ (μS/cm)		
Oil	**25ºC**	**37ºC**	**45ºC**
LIM	231	242	421
IPM	329	338	612
CCT	338	352	618

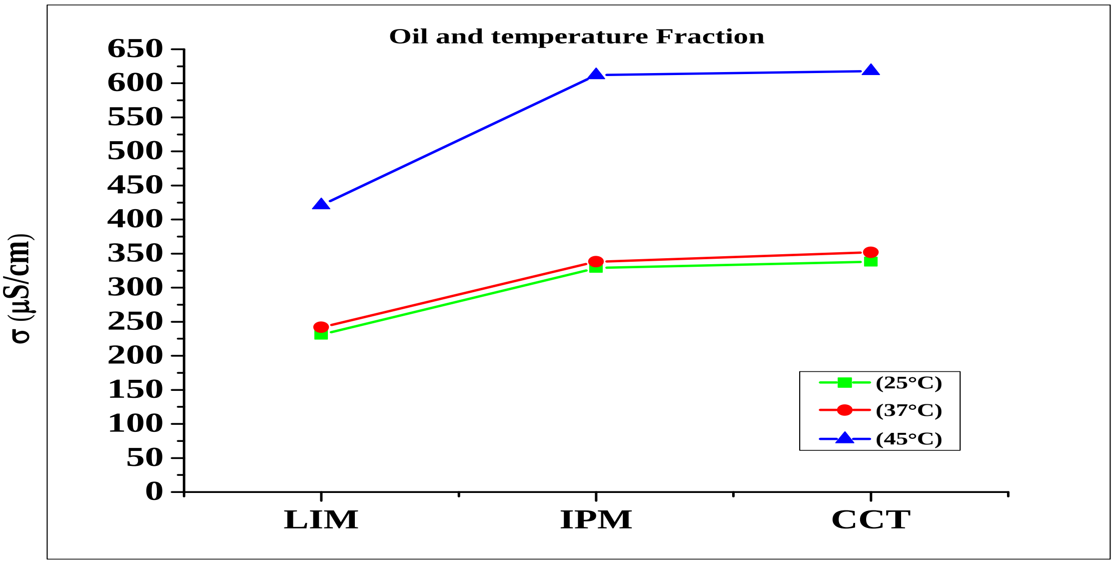


Figure 5.67 Variation in the electrical conductivity values (σ) of mixed microemulsion systems with different three types of oils (LIM, IPM and CCT) at 25, 37 and 45ºC, 60% at water content along the dilution line N65.

From figures 5.64, 5.65, 5.66, 5.67 and related tables of these figures, IPM oil have a highest electrical conductivity compared to other oils, because IPM oil have ketones functional group in its structure that is soluble in water, ketones that contains carbonyl compounds (carbon- oxygen double bond) can make a hydrogen bond with water molecules, also IPM act in microemulsion as penetration enhancer its causes to increase in electrical conductivity values.

For LIM oil, the high viscosity microemulsion is observed for water content lower than 20% and it tends to form gel microemulsion, so the viscus microemulsion have lower electrical conductivity values because the structure more network form between water and surfactant the movement of water between droplets is low.

We also conclude from the figures illustrated above (5.64, 5.65, 5.66 and 5.67) that as increases in water content, it is increases in electrical conductivity and the same behavior result in increase of temperature from 25, 37 and 45ºC.

5.2.2 Mixed surfactants with mixed oils and/ or co-surfactant microemulsion systems

5.2.2.a W/ O1570/ T-MAZ 80/ LIM + EtOH at ratio 1/1 (w/w)

The electrical conductivity was measured for the system W/ O1570/ T-MAZ 80/LIM + EtOH were the mixing ratio of mixed surfactants of equal unity and of oil and co-surfactant along the dilution line N65. Figure 5.68 and table 5.75display the influence of water content and temperature on the electrical conductivity (σ).

Table 5.75: The electrical conductivity (σ) for the system W/ O1570/ T-MAZ 80/ LIM + EtOH at different water contents and different temperatures (25, 37 and 45ºC).

Water content (Wt. %)	σ (µS/cm)		
	25ºC	37ºC	45ºC
0	0.2	0.2	0.6
10	2.3	4	10.4
20	26.3	38.7	81.4
30	76.5	84.1	172.8
40	83.7	95.3	190.3
50	198	211	401
60	248	248	456
70	197	201	324

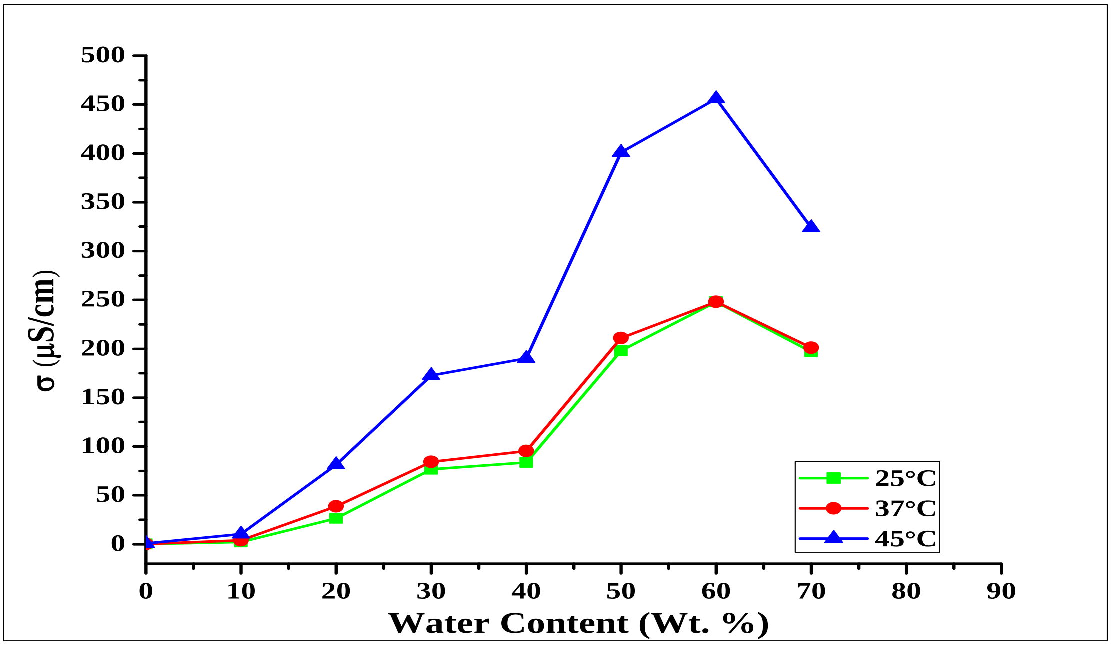


Figure 5.68 Variation of the electrical conductivity (σ) of the system W/ O1570/ T-MAZ 80/ LIM + EtOH as a function of water content along the dilution line N65 at different temperatures (25, 37 and 45ºC). The mixing ratio between (O1570/T-MAZ 80) is equal unity.

It is clear from figure 5.68 that of large difference in electrical conductivity values between temperatures 25, 37 and 45ºC, a temperature of 45ºC gives a highest values of electrical conductivity due to high interdroplet interactions between microemulsions droplets causes an active ion exchanges and therefor high electrical conductivity values, so that we can consider as a temperature increases the electrical conductivity will increases.

As shown in table 5.75 and figure 5.68 the low electrical conductivity values according to LIM oil extended until reach 30 wt.% water content, we was explained the reason of these low values in previous section (5.2.1.b).

5.2.2.b W/ O1570/ T-MAZ 80/ LIM + PG at ratio 1/1 (w/w)

The electrical conductivity was measured for the system W/ O1570/ T-MAZ 80/LIM + PG were the mixing ratio of mixed surfactants of equal unity and of oil and co-surfactant along the dilution line N65. Figure 5.69 and table 5.76display the influence of water content and temperature on the electrical conductivity (σ).

Table 5.76: The electrical conductivity (σ) for the system W/ O1570/ T-MAZ 80/ LIM + PG at different water contents and different temperatures (25, 37 and 45°C).

Water content (Wt. %)	**σ (µS/cm)**		
	25°C	**37°C**	**45°C**
0	0.8	1.2	3.1
10	3.2	4.7	12.8
20	15.5	21.6	49.2
30	61.8	68.9	139.9
40	96.2	131.4	338
50	194	245	461
60	306	329	512

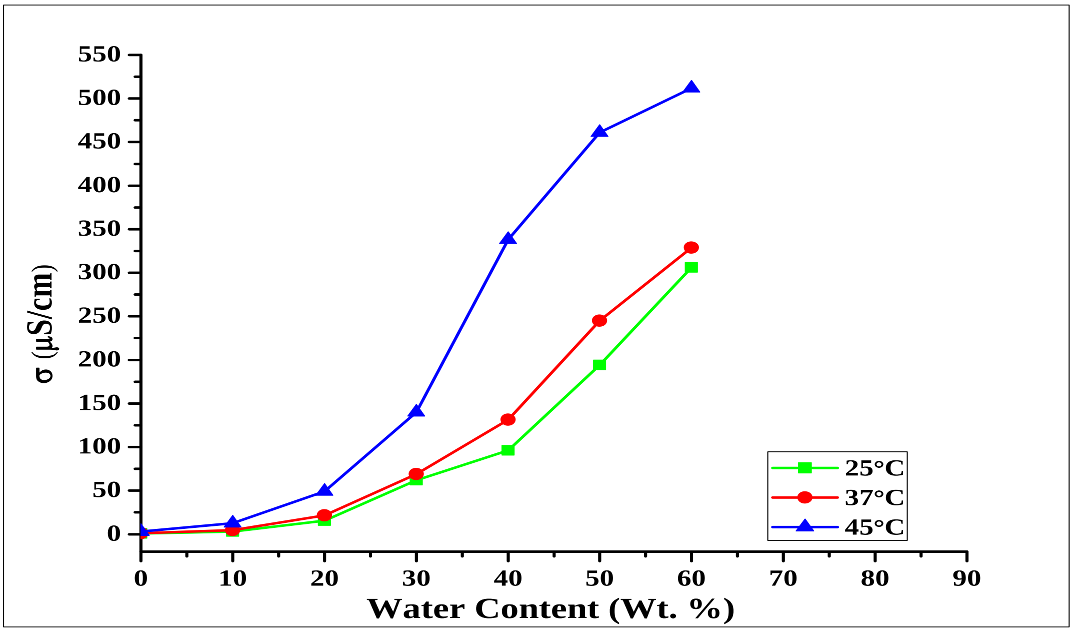


Figure 5.69 Variation of the electrical conductivity (σ) of the system W/ O1570/ T-MAZ

80/ LIM + PG as a function of water content along the dilution line N65 at different temperatures (25, 37 and 45ºC). The mixing ratio between (O1570/T-MAZ 80) is equal unity.

Table 5.77 and figure 5.70 shows the variation in the electrical conductivity values (σ) of microemulsion system: W/O1570/LIM + EtOH, PG at three different temperatures (25, 37 and 45ºC) along the dilution line N65.

Water content (Wt. %)	**σ (µS/cm)**	
	LIM + EtOH	**LIM+PG**
0	0.2	0.8
10	2.3	3.2
20	26.3	15.5
30	76.5	61.8
40	83.7	96.2
50	198	194
60	248	306
70	197	

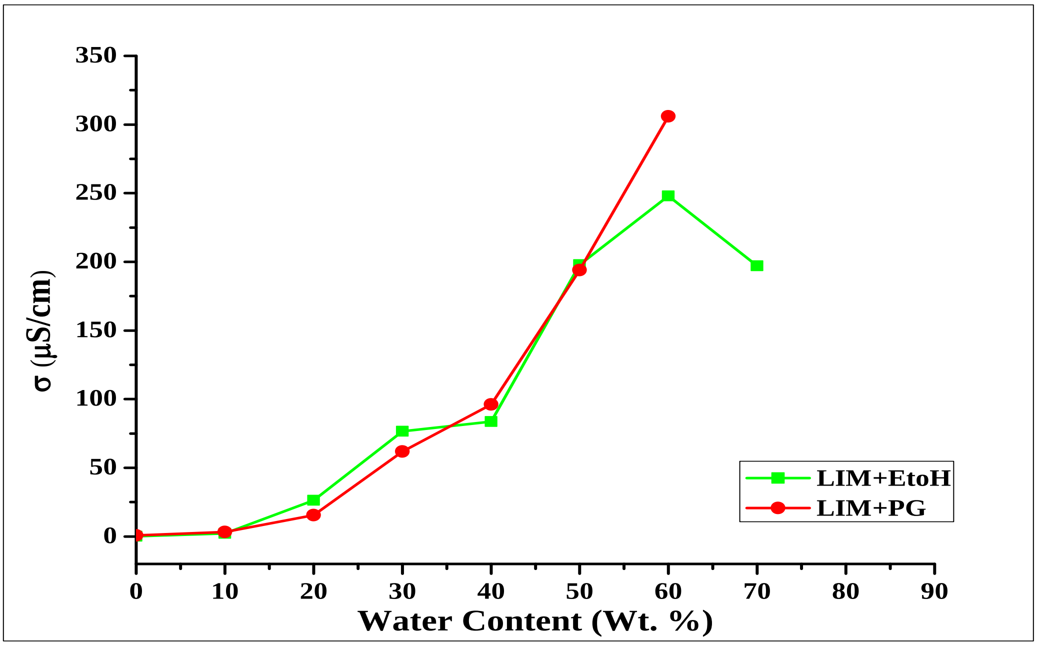


Figure 5.70 Variation of the electrical conductivity (σ) of the system W/ O1570/ T-MAZ 80/ LIM + EtOH, PG as a function of water content along the dilution line N65 at different temperatures (25, 37 and 45ºC). The mixing ratio between (O1570/T-MAZ 80) is equal unity.

EtOH and PG used in microemulsion systems not just as co-surfactants but also used as co-solvents, these compounds are hydrophilic in character, EtOH have one hydroxyl group whereas PG is polyol that have three hydroxyl group (OH) which makes a hydrogen bonds with water molecules and stabilize microemulsion systems, thus make a systems of high viscosity. A more network between water and microemulsion systems was happened due to high viscosity and hence restricted water mobility causes a little ion exchanges produce a low values of electrical conductivity.

As shown in figure 5.70 the LIM with EtOH have higher electrical conductivity values, because EtOH have one hydroxyl group (OH) so the interaction with water is little tends to increase of system fluidity and more ion exchanges contributes a higher electrical conductivity values. On the contrary of PG that have three OH groups which interacts strongly to H_2O molecules results in restricted water mobility and lower of electrical conductivity values.

5.2.2.c W/ O1570/ T-MAZ 80/ LIM + IPM at ratio 1/1 (w/w)

The electrical conductivity was measured for the system W/ O1570/ T-MAZ 80/LIM + IPM were the mixing ratio of mixed surfactants of equal unity and of mixed oils along the dilution line N65. Figure 5.71 and table 5.78display the influence of water content and temperature on the electrical conductivity (σ).

Table 5.78: The electrical conductivity (σ) for the system W/ O1570/ T-MAZ 80/ LIM + IPM at different water contents and different temperatures (25, 37 and 45ºC).

Water content (Wt. %)	**σ (µS/cm)**		
	25ºC	**37ºC**	**45ºC**
0	0.8	0.6	0.9
10	1.2	2.4	6.7
20	3.1	4.4	11.2
30	72.7	50.9	60.3
40	153	137	208
50	227	177	276
60	188	188	211
70	173	176	189
80	107	113	134
90	95	105	117

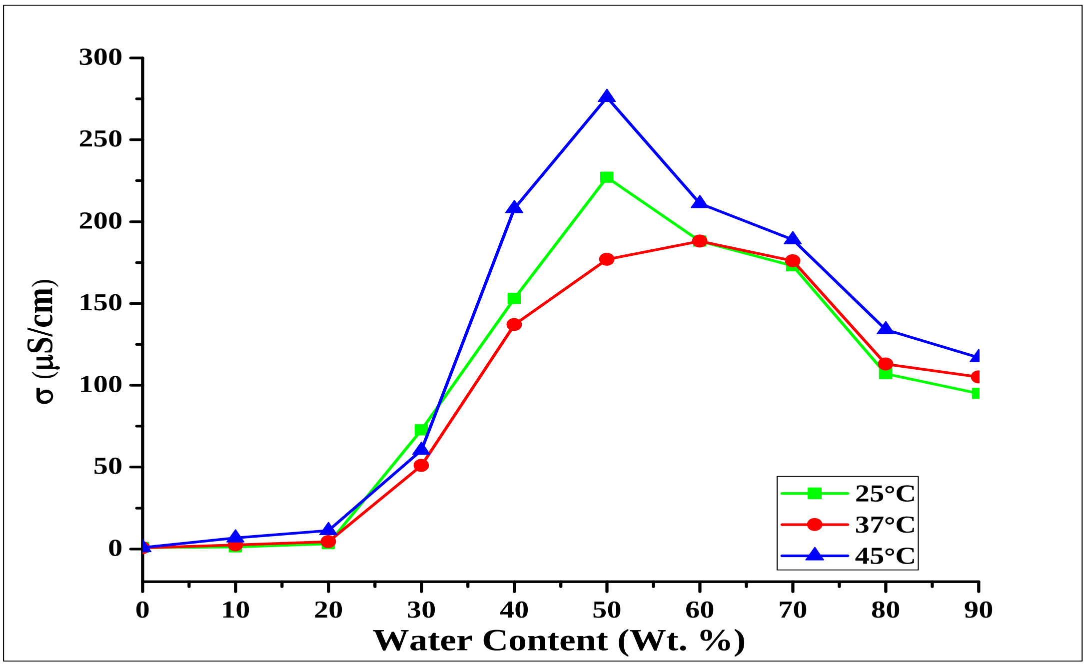


Figure 5.71 Variation of the electrical conductivity (σ) of the system W/ O1570/ T-MAZ 80/ LIM + IPM as a function of water content along the dilution line N65 at different temperatures (25, 37 and 45ºC). The mixing ratio between (O1570/T-MAZ 80) is equal unity.

From 0 to 20% water content the system have low electrical conductivity values as shown in figure presented above, this low values indicates a restricted water mobility and little amount of ion exchanges. At 30% water content a sudden changes in electrical conductivity values was observed suggested to be a percolation threshold was appeared and a structural inversion to bicontinuous microemulsion was proposed. The bicontinuous structure continuous to reach the maximum at 50% water content, while the bicontinuous microemulsion increase, it is increase in the electrical conductivity values. Another decrease in electrical conductivity values was observed at 60% water content suggested that a system converted to o/w microemulsion, thus according to the table 5.78 which presented above the system can be divided into three different regions related to its structures, from (0- 20 wt. %) water content the system are micelles and w/o microemulsions, from (30- 50 wt. %) the system are bicontinuous microemulsions and from (60- 90 wt. %) the system are o/w microemulsions.

5.2.2.d W/ O1570/ T-MAZ 80/ LIM + CCT at ratio 1/1 (w/w)

The electrical conductivity was measured for the system W/ O1570/ T-MAZ 80/LIM + CCT were the mixing ratio of mixed surfactants of equal unity and of mixed oils along the dilution line N65. Figure 5.72 and table 5.79display the influence of water content and temperature on the electrical conductivity (σ).

Table 5.79: The electrical conductivity (σ) for the system W/ O1570/ T-MAZ 80/ LIM + CCT at different water contents and different temperatures (25, 37 and 45°C).

Water content (Wt. %)	**σ (µS/cm)**		
	25°C	**37°C**	**45°C**
0	0.5	0.3	0.6
10	2.8	4.7	11.3
20	8.5	15.3	37.3
30	39.3	42.2	65.6
40	103.4	104.7	140.4
50	109	168	312
60	227	246	431

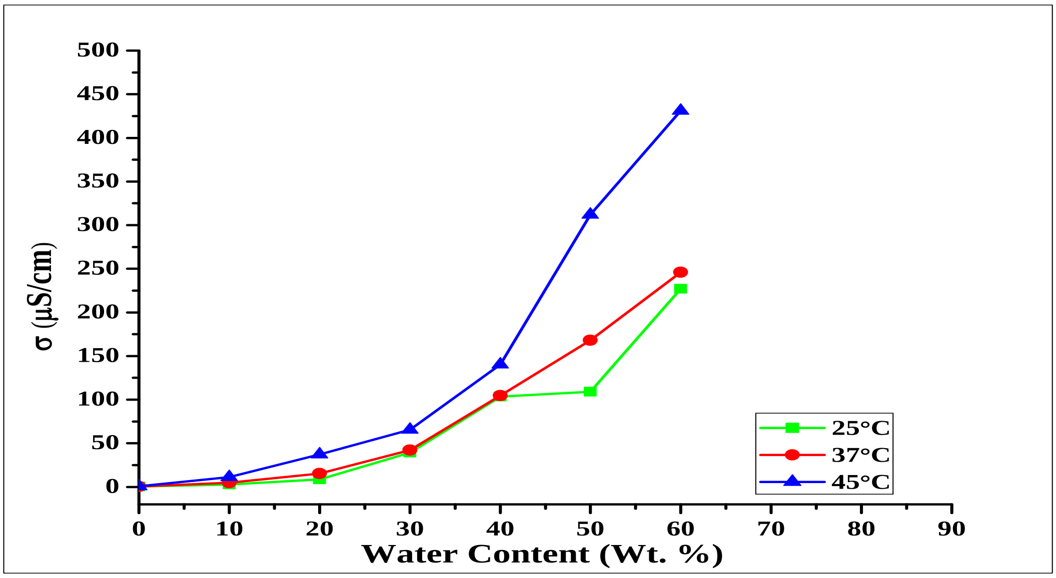


Figure 5.72 Variation of the electrical conductivity (σ) of the system W/ O1570/ T-MAZ

80/ LIM + CCT as a function of water content along the dilution line N65 at different temperatures (25, 37 and 45ºC). The mixing ratio between (O1570/T-MAZ 80) is equal unity.

Table 5.80 and figure 5.73 shows the variation in the electrical conductivity values (σ) of microemulsion system: W/O1570/LIM + IPM, CCT at three different temperatures (25, 37 and 45ºC) along the dilution line N65.

Water content (Wt. %)	**σ (µS/cm)**	
	LIM+CCT	**LIM+IPM**
0	0.5	0.8
10	2.8	1.2
20	8.5	3.1
30	39.3	72.7
40	103.4	153
50	109	227
60	227	188
70		173
80		107
90		95

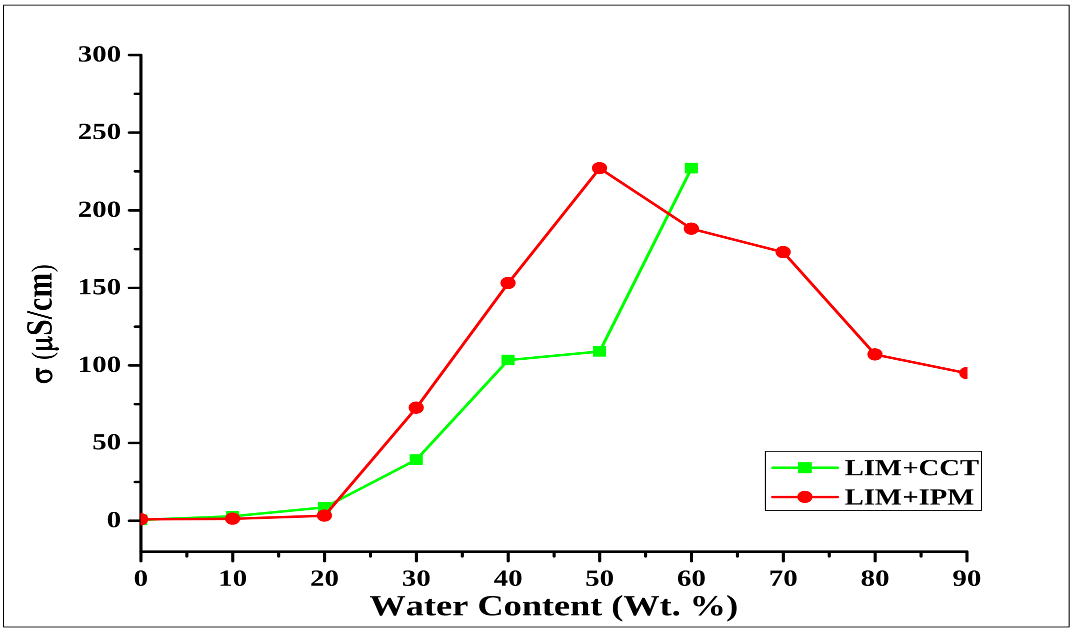


Figure 5.73 Variation of the electrical conductivity (σ) of the system W/ O1570/ T-MAZ 80/ LIM + CCT, IPM as a function of water content along the dilution line N65 at different temperatures (25, 37 and 45ºC). The mixing ratio between (O1570/T-MAZ 80) is equal unity.

From results presented in table 5.80 the mixed oils (LIM + IPM) have a higher electrical conductivity values than (LIM + CCT), because of chain length compatibility between LIM and IPM, also IPM oil has a linear structure with ketone functional groups contains carbonyl compounds which is easily combined with water molecules and modify the stability of microemulsion, in addition LIM oil is cyclic and have small molecular volume which in turn allow to penetrate in water- oil interface and alter the curvature of the interface, thus improve structure and mobility of water to contribute high electrical conductivity values. These reasons also enhance the stability of this microemulsion system (W/O1570/T-MAZ 80/ LIM+ IPM) to extend the phase behavior to reach 90% water content.

On the contrary to CCT oil which have a bulky shape that decrease the ability of penetration in the surfactant palisade layer and have a high molecular volume tends to decrease the association to form stable microemulsion system, hence decrease of interdroplet interaction causes few in ion exchanges and therefore results of low electrical conductivity values.

- About electrical conductivity

From the study of electrical conductivity (section 5.2), we observe the following notes:

- It is clear from all of systems studied that the electrical conductivity values increased as a function of water content increased. This increase in electrical conductivity is due to the interaction between droplets and therefore ion exchanges are resulting by fraction of ionized droplets that are not enclosed in the core of microemulsion systems.

On the other hand, we observed from all of microemulsion systems studied that at low water content, the electrical conductivity have low values indicates micelles microemulsions which in turn converted to water-in-oil microemulsion system by addition of water, so the droplets become in contact to each other forming a clusters of droplet. This clusters generates a network produced by short range attractive interaction leads to important changes of the transport properties, such as droplet size, the rate of exchange of materials between droplets and electrical conductivity. The phenomena has been described in terms of percolation [Feldman. Y, Kozlovich. N, Nir. I, Garti.N, 1995]. According to percolation model, the conductivity suddenly raising to give the high value at certain water volume fraction at constant temperature or at certain temperature with constant water volume fraction, however as the water volume fraction increase to reach the percolation threshold volume fraction the droplets contact to each other forming clusters, these clusters allow to exchange ions among droplet or from droplet to another by opening channels resulting of high electrical conductivity values. Another explanation of percolation is that at the beginning, the microemulsion droplets are slowly swell by adding of water forming larger droplets with opening channels (fuse) caused by the collision and attractive interdroplet interaction, thus the ions and mass transfer through these channels at certain water content. Then the droplets breakdown (fission) into smaller droplets, these steps repeated many times until reach the maximum. This phenomena is called fusion-fission reaction, but it is happened in such systems at least probability. [Moulik. S, Paul. B, 1998].

- The electrical conductivity values increase with the increase in temperature at a given dispersed phase volume fraction, it is shown in all microemulsion systems which presented above that the high electrical conductivities as increase in temperature are explained by the fact that increase in temperature will increase in kinetic energy which increase the collision between droplets and increase movement of ions. By increasing temperature, the collisions between droplets increase and the opening and reforming of droplets will increase the mobility of water and the electrical conductivity will gain rise with temperature. In addition, the possibility of percolation become larger and the formation of water channels will increase the electrical conductivity of the systems.

- The relatively high values of electrical conductivity of microemulsion studied can be explained by the chemical structure of the oil and its ability to penetrate in oil- water interface. So that in this section, we compared between different three types of oils used in this research, and the results can be explained as following: in the single oil surfactant system, we observe that IPM oil gives the best results as shown in tables 5.68, 5.69, 5.70 and related figures. It can interpreted in term of chain length compatibility between oil and surfactant, so the IPM and CCT are more compatible than LIM with preference to IPM oil, hence the compatibility increase of synergism between surfactants and oil resulting in extended of microemulsion stability and so increase the capability the amount of water content added to the microemulsion systems as shown experimentally (see figures 5.61, 5.62 and 5.63).

In the second part of this study, we examine the mixed oils and LIM oil with co-surfactants EtOH, PG and we found that the system LIM + EtOH reaches to 70 wt. % water content while LIM + PG system reaches to 60 wt. %, therefore the addition of short chain alcohols like ethanol as co-surfactant will be reduce the interfacial free energy and tension by its incorporation into the interfacial curvature. This allows the interfacial film to take up the different curvature required to form a balanced microemulsion, so that EtOH promote the fluidity of the interfacial film, thus increase water mobility and ion exchange.

- All of microemulsion systems studied by electrical conductivity shows a sign in electrical conductance in spite of the mixed surfactants are nonionic type. A possible for such behavior is the origin of surfactant which associated with the presence of impurities that contribute the electrical conductance to the systems studied without further addition of electrolytes.

5.3 Drug solubilization

One of the most important issues that faced scientists according to the drug formulations are solubility and bioavailability of low soluble drugs, and it is estimated that 40% of new drug compounds may be regards as low soluble in water [Kumar. P, singh.C, 2013]. These drugs with biopharmaceutical classification systems (BCS) are class II (low solubility, high permeability) or class IV (low solubility, low permeability), the former one is considered to be the challenge to the developer because it has low membrane permeability and poor aqueous solubility, on the contrary of class II drug which is highly permeable and the rate and extent of absorption of class II compounds is highly dependent on the performance of the formulated product [Pouton. C, 2006].

Surfactants or surface active agents has unique properties over other types of molecules due to their amphiphilic character that means it has a dual parts, hydrophilic part (a head group of surfactant) and lipophilic part (hydrocarbon chain). This unique behavior make them suitable for large scale food- based and pharmaceutical applications. However as we uses in our drug solubilization experiments a sucrose ester nonionic surfactants are more favorable, because it is nontoxic, biodegradable and helpful in formulation of microemulsions for pharmaceutical use [Akoh. C, 1992], moreover it was approved by FAO/WHO in Japan, the USA, the EU, as food additives owing to their high safety and excellent properties [Thevenin. M, et al, 1996].

One of the most beneficial interest of using microemulsions in drug delivery systems is that these systems can incorporate a wide range of drug molecules (hydrophobic and hydrophilic) therefore a lot of water poorly soluble drugs will be solved by this technique, furthermore microemulsions characteristic enable them to use as drug carriers for tropical, oral, parenteral and other routes of administration due to the small size of dispersed phase (< 100 nm) thereby micellar systems can form a variety of self assembled structures for instance; micelles, o/w, w/o and bicontinuous structures.

Drug can be entrapped in the interfacial layer of surfactant micelles surrounded by oil phase, thus the drug molecules have been protected against the external environments such as hydrolysis, enzyme degradation and oxidation [Dos Santos. S, et al, 2013]. The hydrophobic drug loading capacity in microemulsion systems is highly influenced by the curvature of the interface, so as the curvature in the interface is positive and towards the dispersed phase, which is determined by the volume of dispersed phase and spontaneous curvature of surfactant molecules. Entrapment of drug in the interface is facilitated, leading to higher drug loading capacity [Narang. A, et al, 2007]. This higher loading capacity at the interface was attributed to the locus of drug solubilization, which has higher solubilization capacity than the core. Higher solubilization capacity at the interface is a function of drug- surfactant associations leading to drug association at the interface, so that the drug loading capacity depends on the type of surfactant, hydrophobicity of the drug and the type of structure being formed.

Over the years, many researchers tried to solve the low water soluble drugs by variety of techniques to enhance the solubility and bioavailability of this hydrophobic drugs such as, pulverization, crystal polymorphism, complex formation agent like liposomes, cyclodextrin, emulsion and microemulsions. The later one is frequently used, because of their high solubilization capacity, thermodynamic stability, transparency and facility of preparation, by means of oral administration it is possible for this formulation to raise lymph directivity and to avoid hepatic first pass metabolism [Mandal. S, Mandal.S, 2011]. Topical drug delivery has much compensation over the oral route of administration, because is easier and more convenient for the patient and there is possibility of immediate removal of the treatment if required.

In this section, we investigate the solubilization capacity of cefuroxime axetil in different microemulsion systems.

5.3.1 Drug solubilization capacity of cefuroxime axetil in mixed surfactants with single oil systems

5.3.1.a Drug solubilization capacity of the system W/O1570/T-MAZ 80/LIM at ratio 1/1 (w/w) between mixed surfactants

The solubilization capacity (SC) of cefuroxime axetil at 25ºC as a function of water content along the dilution line N65 is presented in table 5.81 and figure 5.74.

Table 5.81: SC (mg/g) for the system W/O1570/T-MAZ 80/LIM at different water content. The weight ratio is 1/1 (w/w) between mixed surfactants.

	SC (mg/ g microemulsion)
Water content (wt. %)	**25ºC**
0	8
10	12
20	13
30	13
40	8
50	8
60	8
70	5

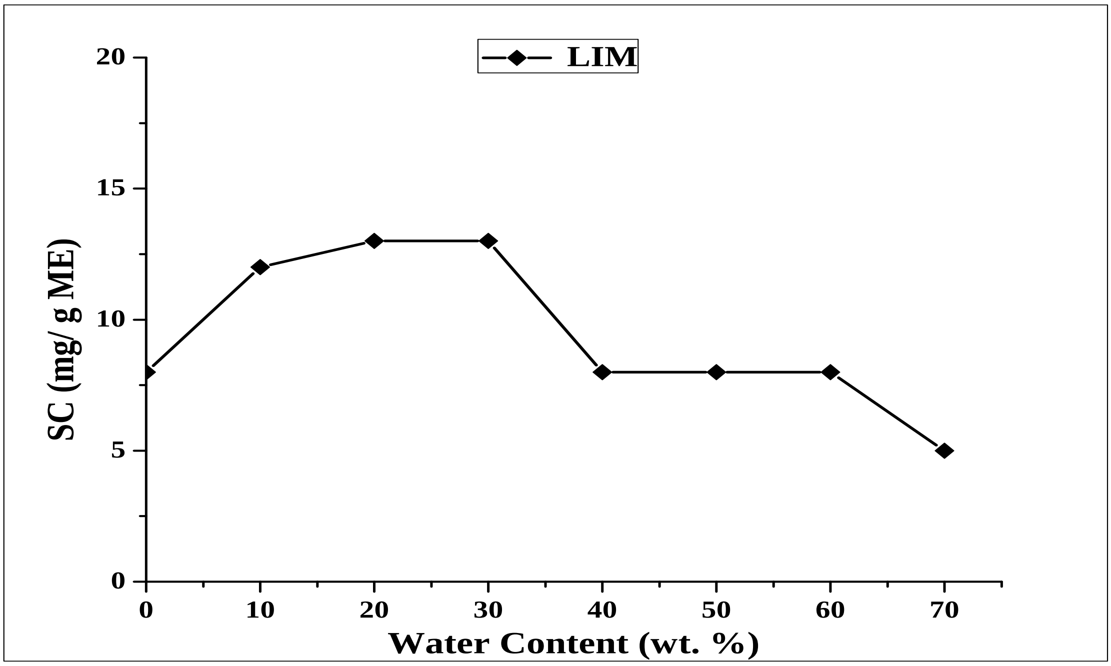


Figure 5.74: The solubilization capacity (SC) of cefuroxime axetil (mg drug/g

microemulsion) as a function of water content in the system: W/ O1570/ T-MAZ 80/ LIM at ratio 1/1 (w/w) between mixed surfactants along the dilution line N65.

The solubilization capacity increase from 8mg/g microemulsion at water content equal 0 wt. % to about 12mg/g microemulsion at water content equal 10 wt. %, then the solubilization capacity increase to 13mg/ g microemulsion at water content 20 to 30 wt. %. The solubilization capacity decrease from 13mg/g to 8mg/g microemulsion at 40 % water content, then it became stable of equal amount of drug about 8mg/g from 40 to 70 wt. % water content.

5.3.1.b Drug solubilization capacity of the system W/O1570/T-MAZ 80/LIM at ratio 1/2 (w/w) between mixed surfactants

The solubilization capacity (SC) of cefuroxime axetil at 25ºC as a function of water content along the dilution line N65 is presented in table 5.82 and figure 5.75.

Table 5.82: SC (mg/g) for the system W/O1570/T-MAZ 80/LIM at different water content. The weight ratio is 1/2 (w/w) between mixed surfactants.

	SC (mg/ g microemulsion)
Water content (wt. %)	**25ºC**
0	10
10	12
20	12
30	12
40	10
50	10
60	7

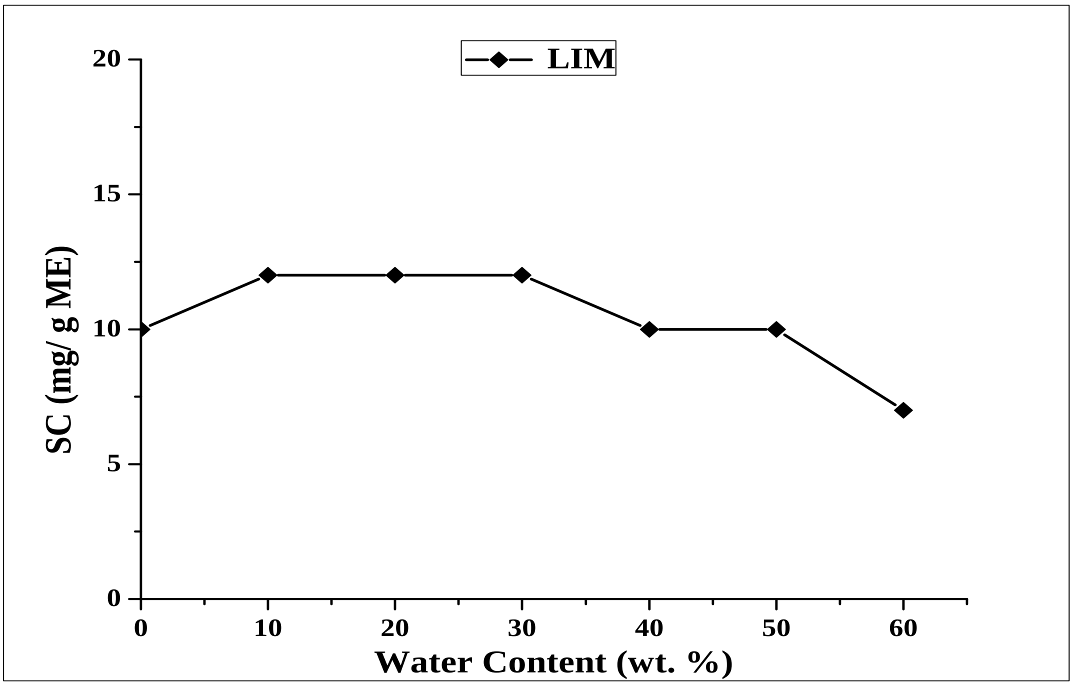


Figure 5.75: The solubilization capacity (SC) of cefuroxime axetil (mg drug/g microemulsion) as a function of water content in the system: W/ O1570/ T-MAZ 80/ LIM at ratio 1/2 (w/w) between mixed surfactants along the dilution line N65.

From the figure 5.75 which presented above, the solubilization capacity of cefuroxime axetil is increased form 10mg/g microemulsion to 12mg/g microemulsion, then the solubilization capacity stability from 12mg/g at water content equal 10 wt. % to water content equal 30 wt. %. The solubilization capacity at water content 40 wt. % decrease to 10mg/g microemulsion and stable until reach 50 wt. % water content and then decreases to 7mg/g at water content 60 wt. %.

5.3.1.c Drug solubilization capacity of the system W/O1570/T-MAZ 80/LIM at ratio 2/1 (w/w) between mixed surfactants

The solubilization capacity (SC) of cefuroxime axetil at 25ºC as a function of water content along the dilution line N65 is presented in table 5.83 and figure 5.76.

Table 5.83: SC (mg/g) for the system W/O1570/T-MAZ 80/LIM at different water content. The weight ratio is 2/1 (w/w) between mixed surfactants.

	SC (mg/ g microemulsion)
Water content (wt. %)	**25ºC**
0	10
10	13
20	13
30	10
40	10
50	10
60	10
70	7

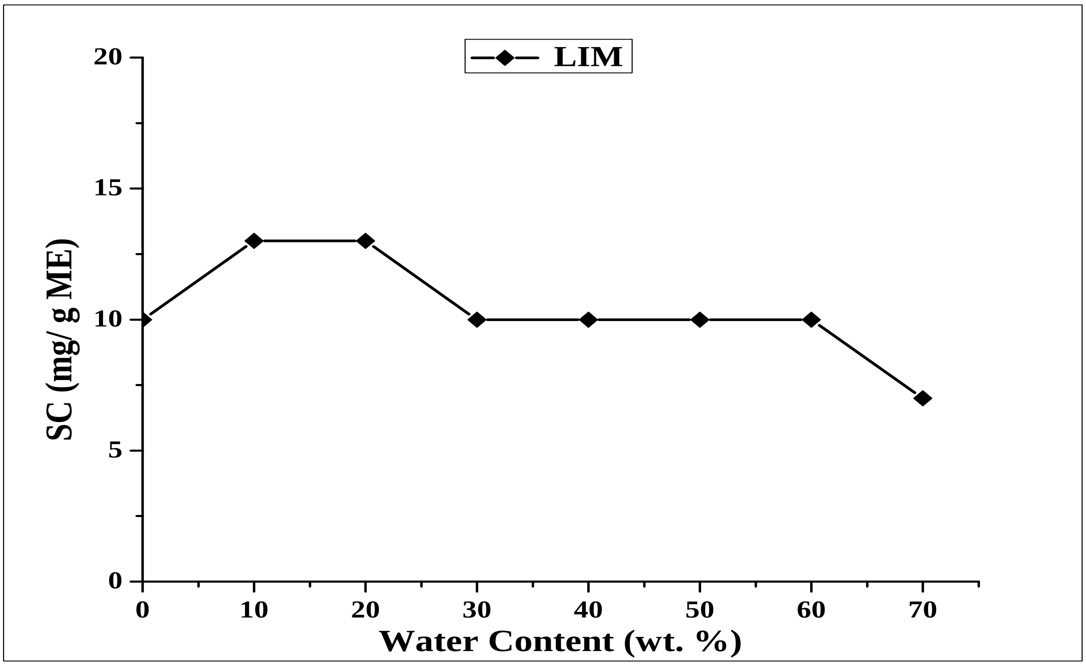


Figure 5.76: The solubilization capacity (SC) of cefuroxime axetil (mg drug/g microemulsion) as a function of water content in the system: W/ O1570/ T-MAZ 80/ LIM at ratio 2/1 (w/w) between mixed surfactants along the dilution line N65.

We can divide the figure presented above into two regions according to solubilization capacity of cefuroxime axetil, the first region the solubilization capacity increase from 10mg/g microemulsion to 13mg/g microemulsion at water content 10% and become stability of this value to reach 20% water content, in the second region the solubilization capacity decrease to 10mg/g at water content form 30% to 60% and then to 7mg/g microemulsion at water content 70%

Table 5.84 and figure 5.77 shows the variation in the solubilization capacity (SC) of microemulsion system: W/O1570/T-MAZ 80/LIM with mixing ratio 1/1, 1/2 and 2/1 (w/w) at temperature 25ºC along the dilution line N65.

Water content (wt. %)	**SC (mg/g)**		
	25°C		
	LIM 1/1	**LIM 1/2**	**LIM 2/1**
0	8	10	10
10	12	12	13
20	13	12	13
30	13	12	10
40	8	10	10
50	8	10	10
60	8	7	10
70	5		7

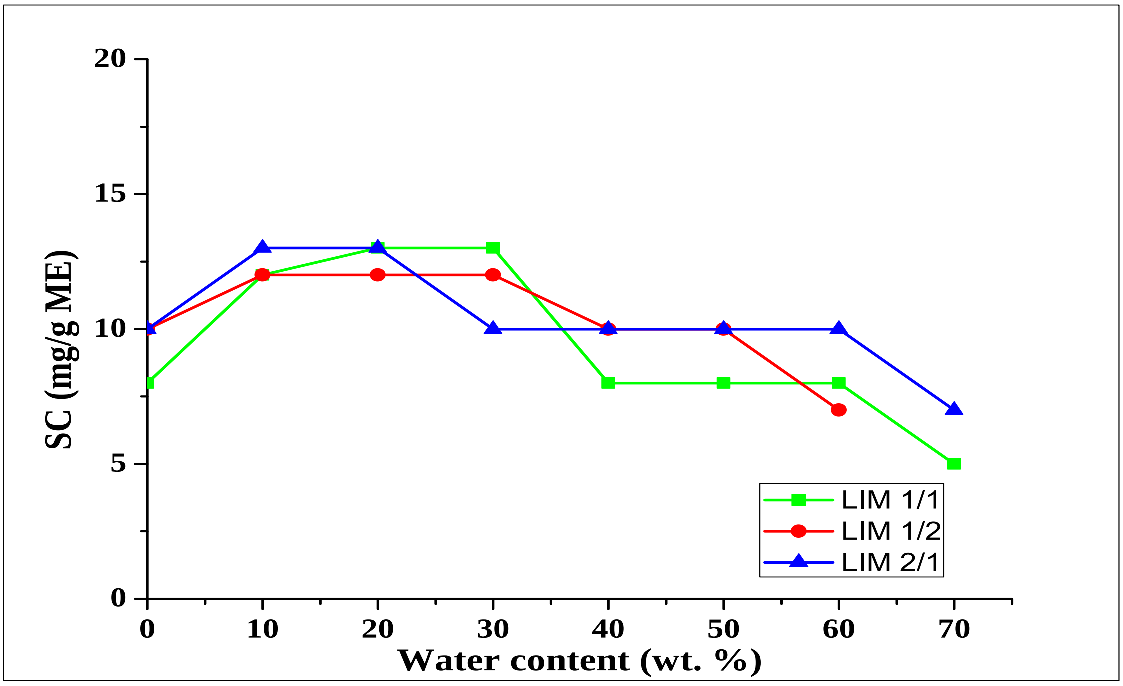


Figure 5.77: The variation in the solubilization capacity (SC) of microemulsion system: W/O1570/T-MAZ 80/LIM with mixing ratio 1/1, 1/2 and 2/1 (w/w) between mixed surfactants at temperature 25ºC along the dilution line N65.

Form figure 5.77 which presented above, it clear that there is no observable effects on the solubilization capacity in the microemulsion systems contain LIM oil with different weight ratios between mixed surfactants (1/1, 1/2 and 2/1), but with little preference to LIM at ratio 1/1, so that tables below 5.85, 5.86 and 5.87 with related figures shows the solubilization capacity at 0%, 30% and 50% water content respectively, in order to verify which of these ratios gives the best results.

		SC (mg/g)
Oil	**Ratio of O1570/T-MAZ80**	**25ºC**
LIM	**1/1**	8
LIM	**1/2**	10
LIM	**2/1**	10

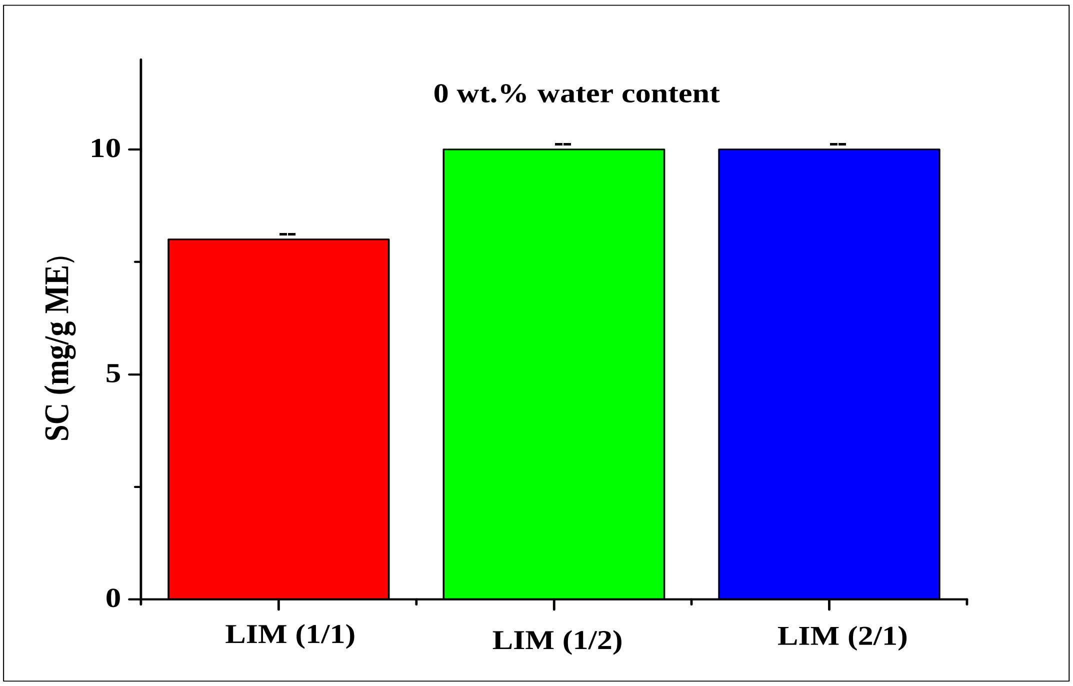


Figure 5.78: The solubilization capacity (SC) of cefuroxime axetil (mg/g microemulsion) system: W/O1570/T-MAZ 80/LIM with different weight ratios (1/1, 1/2 and 2/1) at water content equal 0% and of temperature 25ºC along the dilution line N65.

Table 5.86 and figure 5.79 shows the variation in the solubilization capacity (SC) at 30% water content of microemulsion system: W/O1570/T-MAZ 80/LIM with mixing ratio 1/1, 1/2 and 2/1 (w/w) at temperature 25ºC along the dilution line N65.

		SC (mg/g)
Oil	**Ratio of O1570/T-MAZ80**	**25ºC**
LIM	**1/1**	13
LIM	**1/2**	12
LIM	**2/1**	10

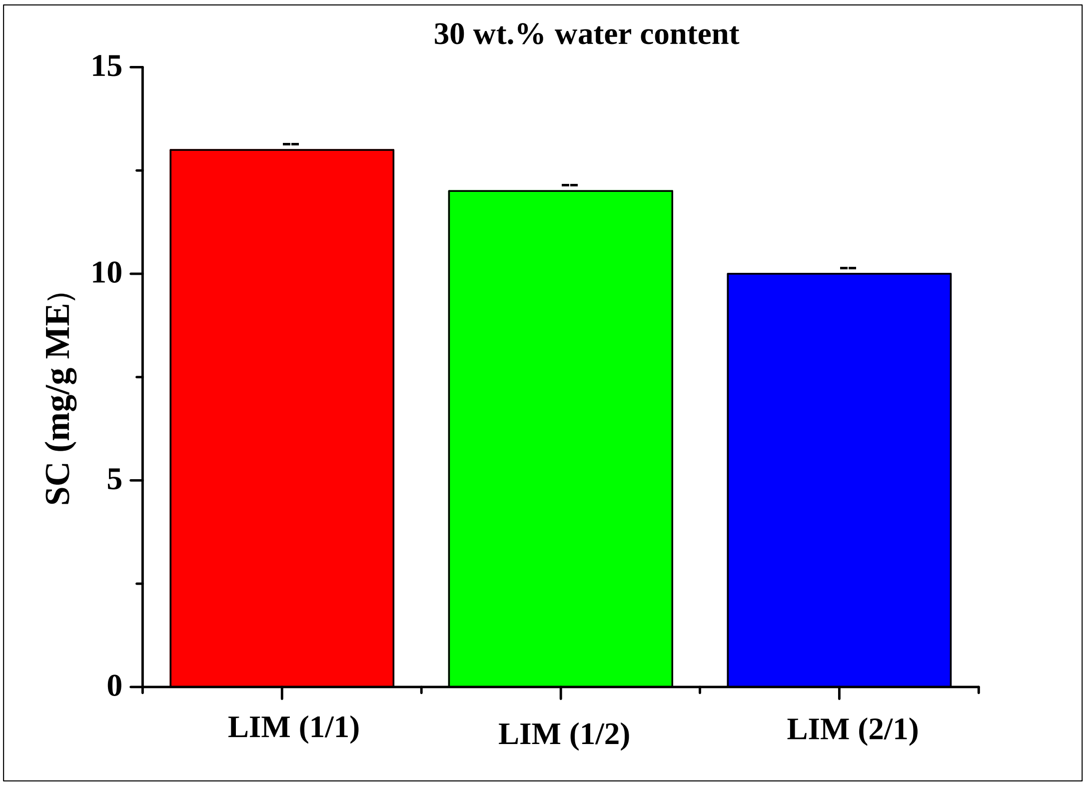


Figure 5.79: The solubilization capacity (SC) of cefuroxime axetil (mg/g microemulsion) system: W/O1570/T-MAZ 80/LIM with different weight ratios (1/1, 1/2 and 2/1) at water content equal 30% and of temperature 25ºC along the dilution line N65.

Table 5.87 and figure 5.80 shows the variation in the solubilization capacity (SC) at 50% water content of microemulsion system: W/O1570/T-MAZ 80/LIM with mixing ratio 1/1, 1/2 and 2/1 (w/w) at temperature 25ºC along the dilution line N65.

		SC (mg/g)
Oil	**Ratio of O1570/T-MAZ80**	**25ºC**
LIM	**1/1**	8
LIM	**1/2**	10
LIM	**2/1**	10

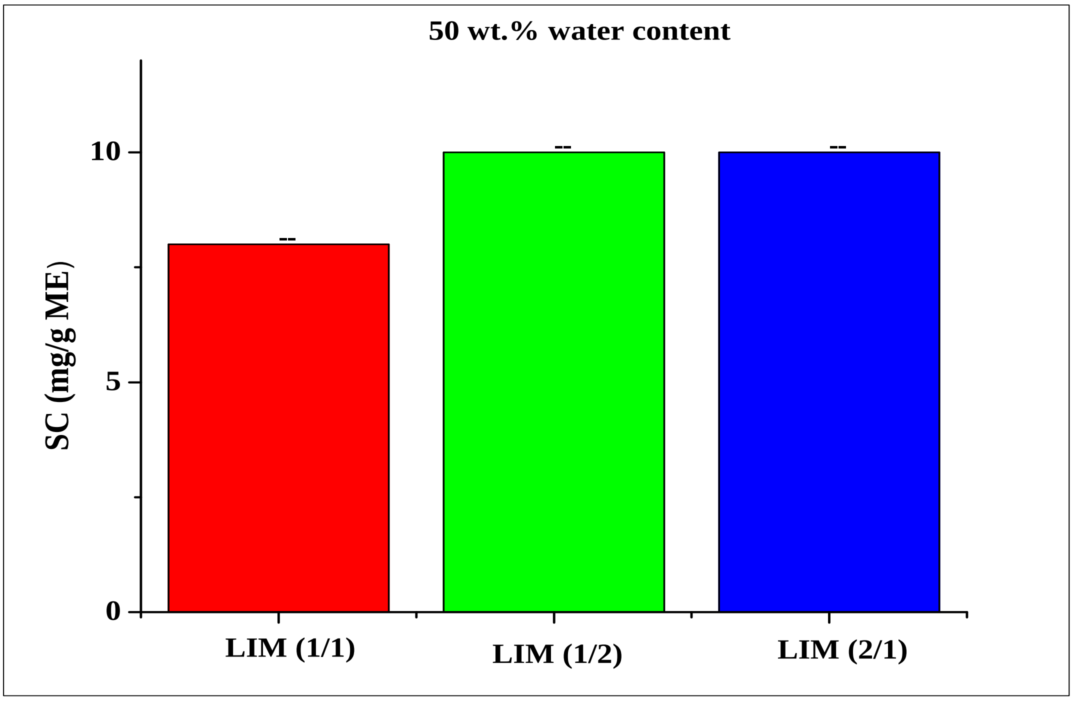


Figure 5.80: The solubilization capacity (SC) of cefuroxime axetil (mg/g microemulsion) system: W/O1570/T-MAZ 80/LIM with different weight ratios (1/1, 1/2 and 2/1) at water content equal 50% and of temperature 25ºC along the dilution line N65.

Therefore from figures 5.78, 5.79 and 5.80, the LIM oil of mixing ratio at equal unity (1/1) gives solubilization capacity more than other mixing ratios (1/2, 2/1) especially at water content equal 30%. This can explained in term of mixed surfactants and oil distribution in microemulsion system, the equal unity of mixed surfactants make a system of more uniform and stable to associate between each other of oils entrapped in the surfactant palisade layer resultant in increase of solubilization capacity of drug in microemulsion systems.

5.3.1.d Drug solubilization capacity of the system W/O1570/T-MAZ 80/IPM at ratio 1/1 (w/w) between mixed surfactants

The solubilization capacity (SC) of cefuroxime axetil at 25ºC as a function of water content along the dilution line N65 is presented in table 5.87 and figure 5.81.

Table 5.88: SC (mg/g) for the system W/O1570/T-MAZ 80/IPM at different water content. The weight ratio is 1/1 (w/w) between mixed surfactants.

	SC (mg/ g microemulsion)
Water content (wt. %)	**25ºC**
0	8
10	12
20	13
30	13
40	8
50	8
60	8
70	5

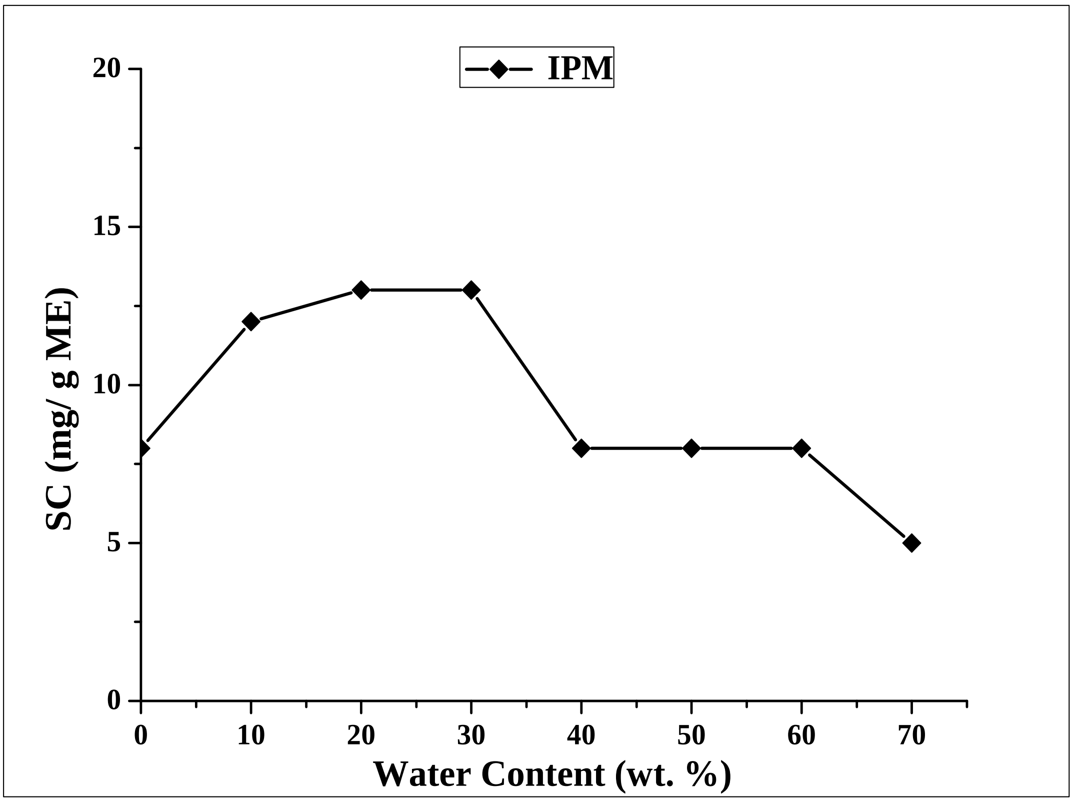


Figure 5.81: The solubilization capacity (SC) of cefuroxime axetil (mg drug/g microemulsion) as a function of water content in the system: W/ O1570/ T-MAZ 80/ IPM at ratio 1/1 (w/w) between mixed surfactants along the dilution line N65.

At 0 wt. % water content, solubilization capacity is 8mg/g microemulsion, then the solubilization capacity increase to 13mg/g microemulsion at water content equal 20 wt. % and become stable until reach 30 wt. %. At 40 wt. % water content, the solubilization capacity decrease to 8mg/g microemulsion extend to reach 60% water content with the same amount of solubilization capacity, and then decrease again to 5mg/g microemulsion at water content 70%.

5.3.1.e Drug solubilization capacity of the system W/O1570/T-MAZ 80/CCT at ratio 1/1 (w/w) between mixed surfactants

The solubilization capacity (SC) of cefuroxime axetil at 25ºC as a function of water content along the dilution line N65 is presented in table 5.88 and figure 5.82.

Table 5.89: SC (mg/g) for the system W/O1570/T-MAZ 80/CCT at different water content. The weight ratio is 1/1 (w/w) between mixed surfactants.

	SC (mg/ g microemulsion)
Water content (wt. %)	**25ºC**
0	10
10	12
20	13
30	13
40	13
50	12
60	10
70	10

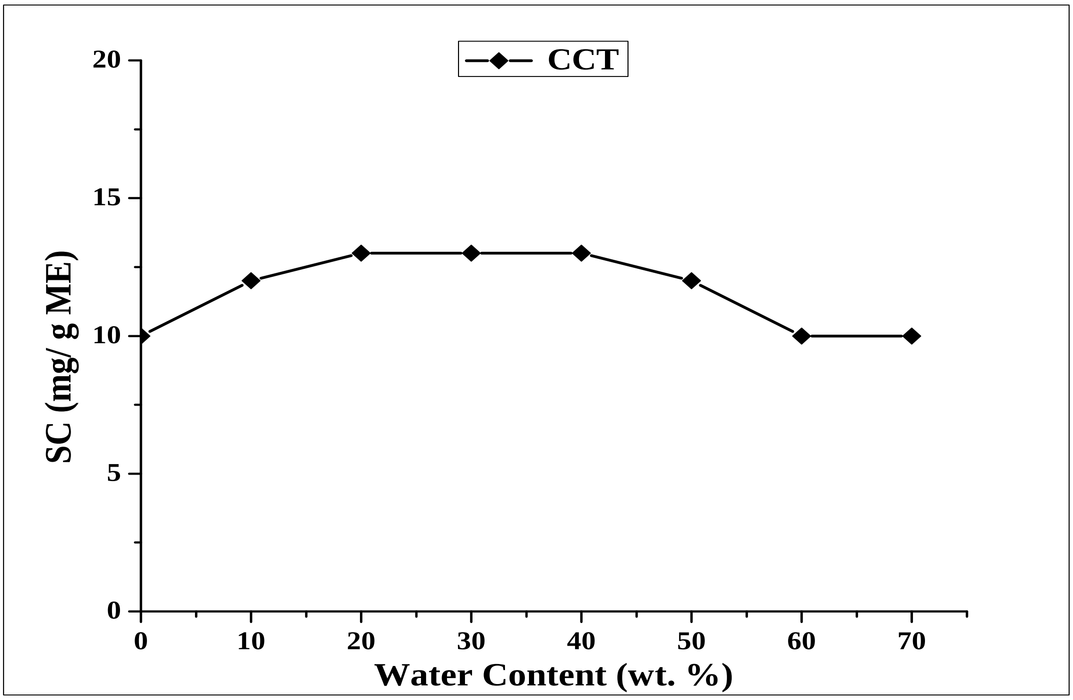


Figure 5.82: The solubilization capacity (SC) of cefuroxime axetil (mg drug/g

microemulsion) as a function of water content in the system: W/ O1570/ T-MAZ 80/ CCT at ratio 1/1 (w/w) between mixed surfactants along the dilution line N65.

It is shown from the figure 5.82 that the solubilization capacity increased from 10mg/g microemulsion to 13mg/g microemulsion at water content equal 20% and the value become stable to reach 40% water content. After this, the solubilization capacity decrease to 12mg/g microemulsion and then to 10mg/g microemulsion at 50% and 60% water content respectively.

Table 5.90 and figure 5.83 shows the variation in the solubilization capacity (SC) between different types of oils (LIM, IPM and CCT) in mixed nonionic surfactants systems at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity.

Water content (Wt. %)	**SC (mg/g)**		
	25°C		
	LIM	**IPM**	**CCT**
0	8	8	10
10	12	12	12
20	13	13	13
30	13	13	13
40	8	8	13
50	8	8	12
60	8	8	10
70	5	5	10

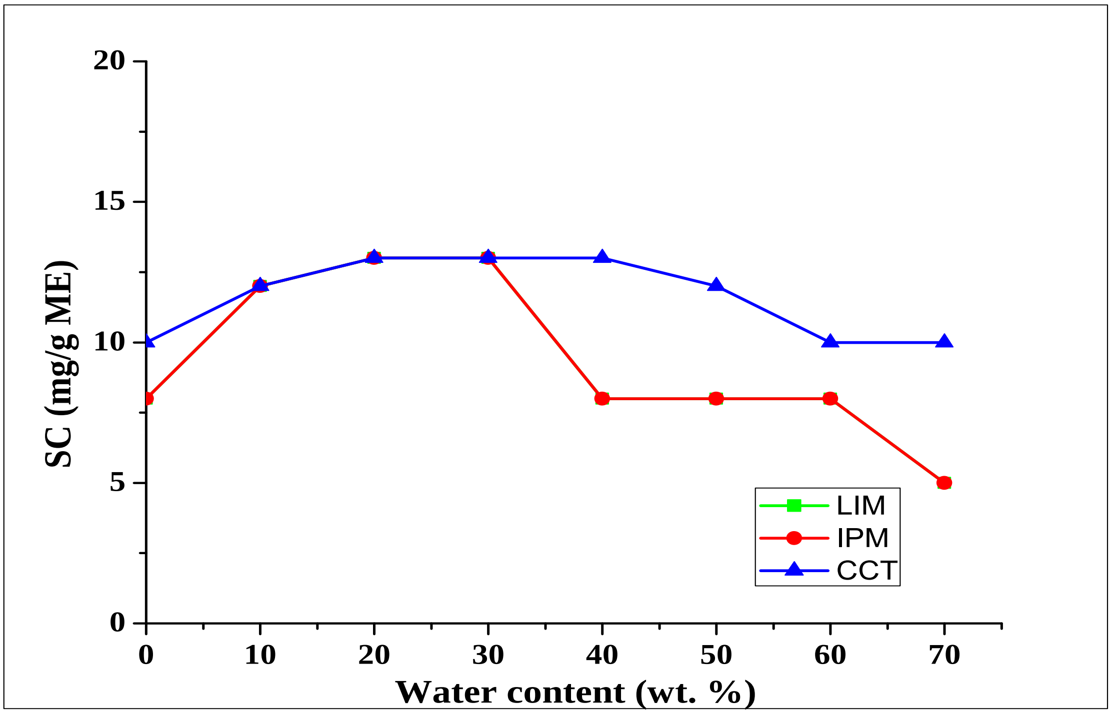


Figure 5.83: The variation in the solubilization capacity (SC) of microemulsion system: W/O1570/T-MAZ 80/LIM with mixing ratio 1/1, 1/2 and 2/1 (w/w) between mixed surfactants at temperature 25ºC along the dilution line N65.

Table 5.91 and figure 5.84 shows the variation in the solubilization capacity (SC) at 0% water content of microemulsion system: W/O1570/oils with different three types of oils (LIM, IPM and CCT) at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity.

	SC (mg/g)
Oil	**25ºC**
LIM	8
IPM	8
CCT	10

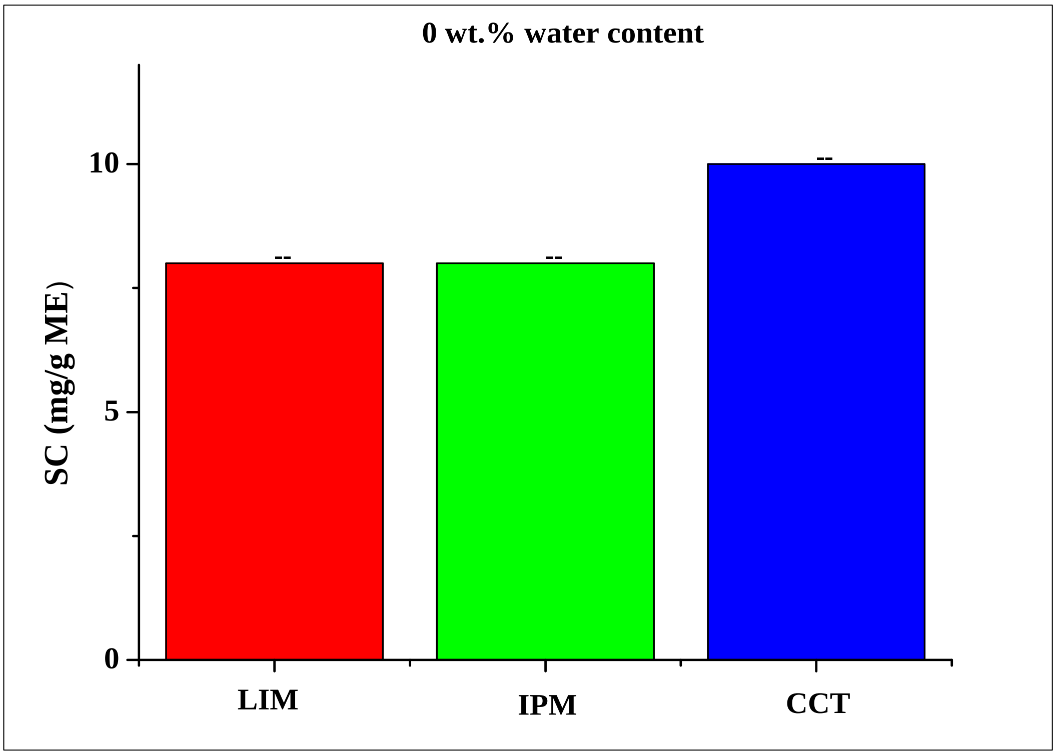


Figure 5.84: The solubilization capacity (SC) of cefuroxime axetil (mg/g microemulsion) system: W/O1570/T-MAZ 80/oils with different three types of oils (LIM, IPM and CCT) at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity.

Table 5.92 and figure 5.85 shows the variation in the solubilization capacity (SC) at 30% water content of microemulsion system: W/O1570/oils with different three types of oils (LIM, IPM and CCT) at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity.

	SC (mg/g)
Oil	**25ºC**
LIM	13
IPM	13
CCT	13

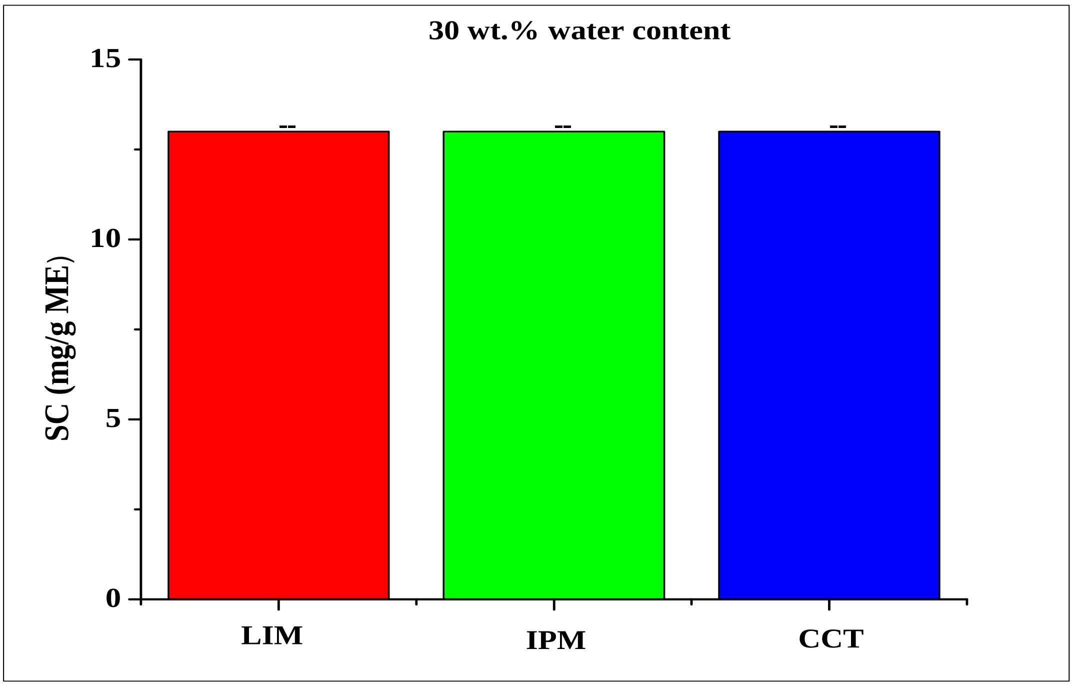


Figure 5.85: The solubilization capacity (SC) of cefuroxime axetil (mg/g microemulsion) system: W/O1570/T-MAZ 80/oils with different three types of oils (LIM, IPM and CCT) at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity.

Table 5.93 and figure 5.86 shows the variation in the solubilization capacity (SC) at 50% water content of microemulsion system: W/O1570/T-MAZ 80/oils with different three types of oils (LIM, IPM and CCT) at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity.

	SC (mg/g)
Oil	**25ºC**
LIM	8
IPM	8
CCT	12

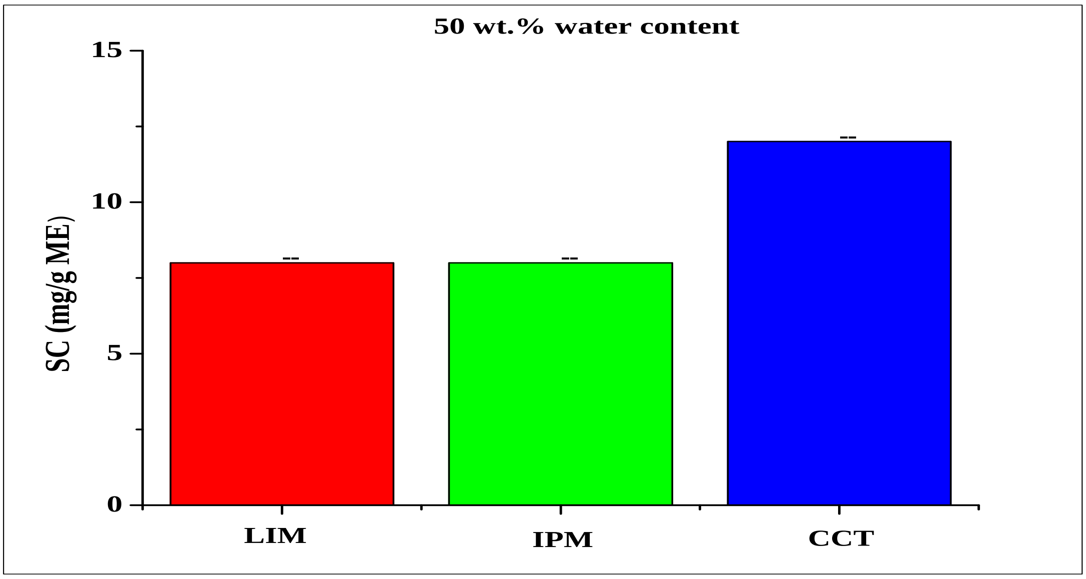


Figure 5.86: The solubilization capacity (SC) of cefuroxime axetil (mg/g microemulsion) system: W/O1570/T-MAZ 80/oils with different three types of oils (LIM, IPM and CCT) at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity.

Figures 5.83, 5.84, 5.85 and 5.86 which presented above shows that CCT oil have the maximum solubilization capacity of cefuroxime axetil compared to other oil studied, because CCT oil has the highest value of molecular volume. This gives low viscus, low motion and high stability microemulsion that causes increase in solubilization capacity of cefuroxime axetil.

Despite of the lowest molecular volume of LIM oil compared to IPM and CCT oils, and able to penetrate more easily in the surfactant palisade layer, it gives a lower solubilization capacity because it forms a very viscus microemulsion, thus the structure is more network which hindered the mobility and penetration of that oil resultant of lower solubilization capacity.

5.3.2 Drug solubilization capacity of cefuroxime axetil in mixed surfactants with oils + co-surfactants systems

5.3.2.a Drug solubilization capacity of the system W/O1570/T-MAZ 80/LIM + EtOH at ratio 1/1 (w/w) between mixed surfactants

The solubilization capacity (SC) of cefuroxime axetil at 25ºC as a function of water content along the dilution line N65 is presented in table 5.93 and figure 5.87.

Table 5.94: SC (mg/g) for the system W/O1570/T-MAZ 80/LIM + EtOH at different water content. The weight ratio is 1/1 (w/w) between mixed surfactants.

	SC (mg/ g microemulsion)
Water content (wt. %)	**25ºC**
0	10
10	12
20	12
30	12
40	13
50	13
60	10

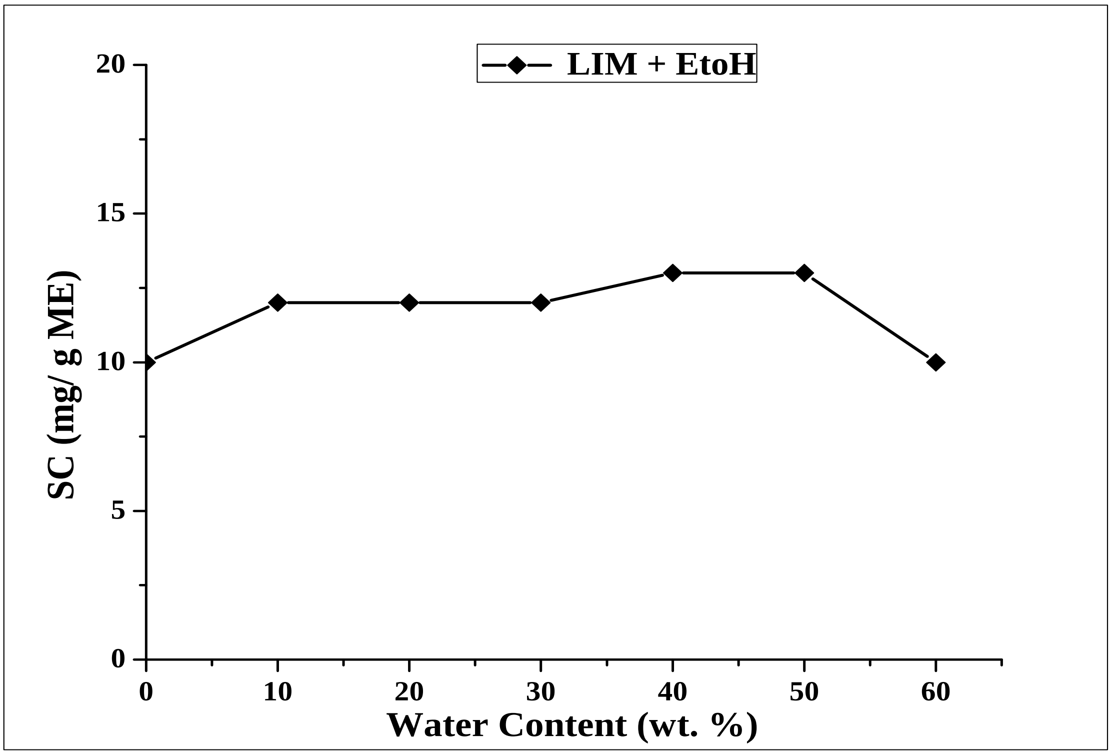


Figure 5.87: The solubilization capacity (SC) of cefuroxime axetil (mg drug/g microemulsion) as a function of water content in the system: W/ O1570/ T-MAZ 80/ LIM + EtOH at ratio 1/1 (w/w) between mixed surfactants along the dilution line N65.

The solubilization capacity increase from 10mg/g microemulsion at water content equal 0% to 12mg/g microemulsion at 10% water content, then the solubilization capacity value stability of 12mg/g until reach 30% water content. The solubilization again increase to 13mg/g microemulsion from 40% to 50% water contents then decrease to 10mg/g microemulsion at 60% water content.

5.3.2.b Drug solubilization capacity of the system W/O1570/T-MAZ 80/IPM + EtOH at ratio 1/1 (w/w) between mixed surfactants

The solubilization capacity (SC) of cefuroxime axetil at 25ºC as a function of water content along the dilution line N65 is presented in table 5.94 and figure 5.88.

Table 5.95: SC (mg/g) for the system W/O1570/T-MAZ 80/IPM + EtOH at different water content. The weight ratio is 1/1 (w/w) between mixed surfactants.

	SC (mg/ g microemulsion)
Water content (Wt. %)	**25ºC**
0	10
10	10
20	12
30	13
40	13
50	13
60	13

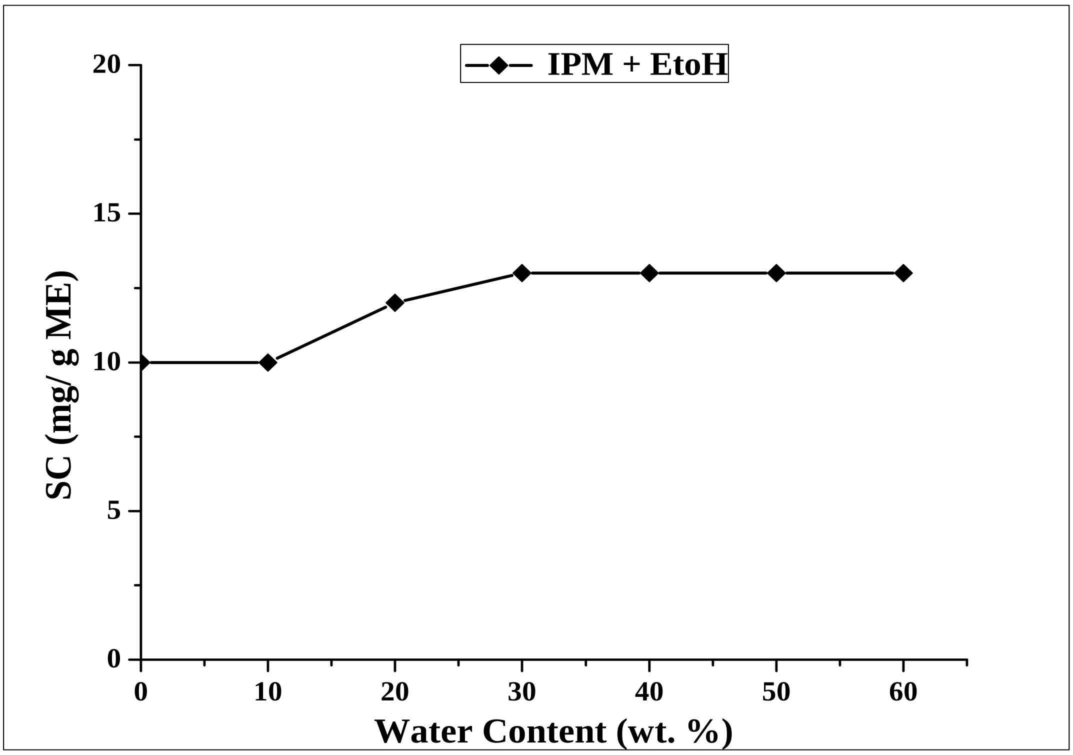


Figure 5.88: The solubilization capacity (SC) of cefuroxime axetil (mg drug/g microemulsion) as a function of water content in the system: W/ O1570/ T-MAZ 80/ IPM + EtOH at ratio 1/1 (w/w) between mixed surfactants along the dilution line N65.

From 0% to 10% water content the solubilization capacity are equal 10mg/g microemulsion and increase to 12mg/g microemulsion at water content equal 20% and then to 13mg/g microemulsion at water content equal 30%. The solubilization capacity become stability of equal amount of drug solubilization capacity equal 13mg/g microemulsion from 30% to 60% water content.

5.3.2.c Drug solubilization capacity of the system W/O1570/T-MAZ 80/CCT + EtOH at ratio 1/1 (w/w) between mixed surfactants

The solubilization capacity (SC) of cefuroxime axetil at 25ºC as a function of water content along the dilution line N65 is presented in table 5.95 and figure 5.89.

Table 5.96: SC (mg/g) for the system W/O1570/T-MAZ 80/CCT + EtOH at different water content. The weight ratio is 1/1 (w/w) between mixed surfactants.

	SC (mg/ g microemulsion)
Water content (wt. %)	**25ºC**
0	10
10	12
20	12
30	12
40	12
50	13
60	14

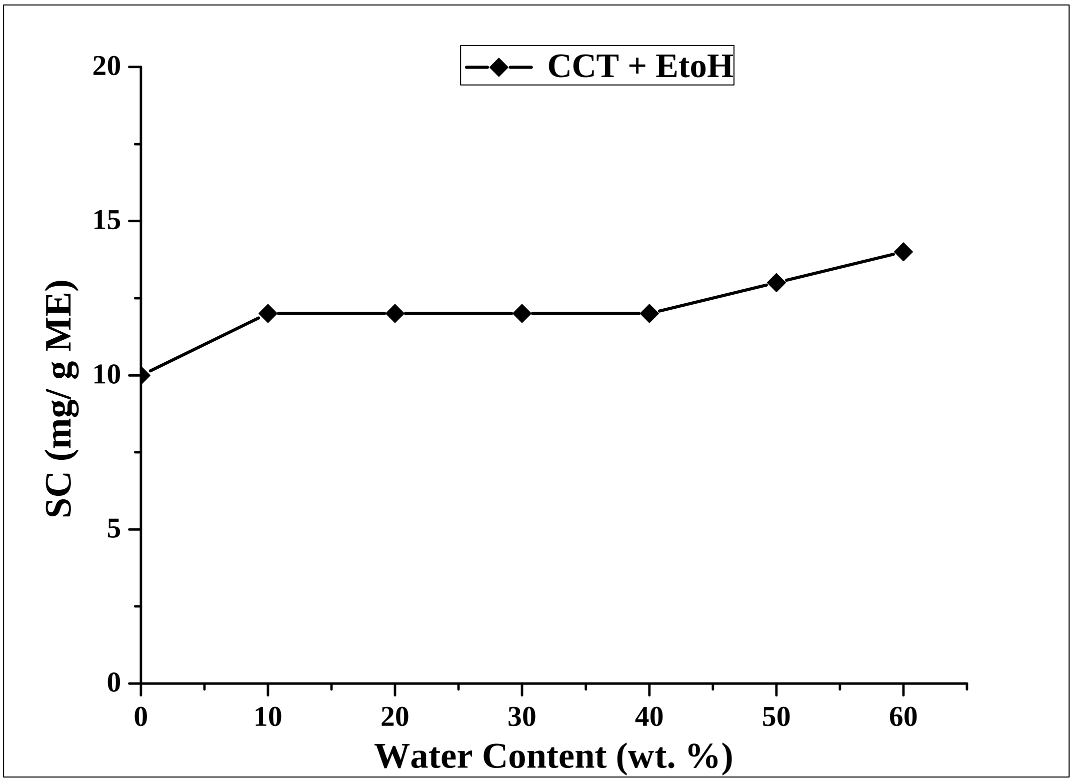


Figure 5.89: The solubilization capacity (SC) of cefuroxime axetil (mg drug/g microemulsion) as a function of water content in the system: W/ O1570/ T-MAZ 80/ CCT + EtOH at ratio 1/1 (w/w) between mixed surfactants along the dilution line N65.

From table 5.95 and figure 5.89, the solubilization capacity increases form 10mg/g microemulsion at water content 0% to 12mg/g microemulsion at water content equal 10%, then the solubilization capacity stability from 12mg/g microemulsion at water content equal 10% to water content 40%. The solubilization capacity of cefuroxime axetil increase twice to 13mg/g and 14mg/g microemulsion at water content equal 50% and 60% respectively.

Table 5.97 and figure 5.90 shows the variation in the solubilization capacity (SC) between different types of oils (LIM, IPM and CCT) with co-surfactant EtOH in mixed nonionic surfactants systems at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity.

Water content (wt. %)	SC (mg/g)		
	25°C		
	LIM + EtOH	IPM + EtOH	CCT + EtOH
0	10	10	10
10	12	10	12
20	12	12	12
30	12	13	12
40	13	13	12
50	13	13	13
60	10	13	14

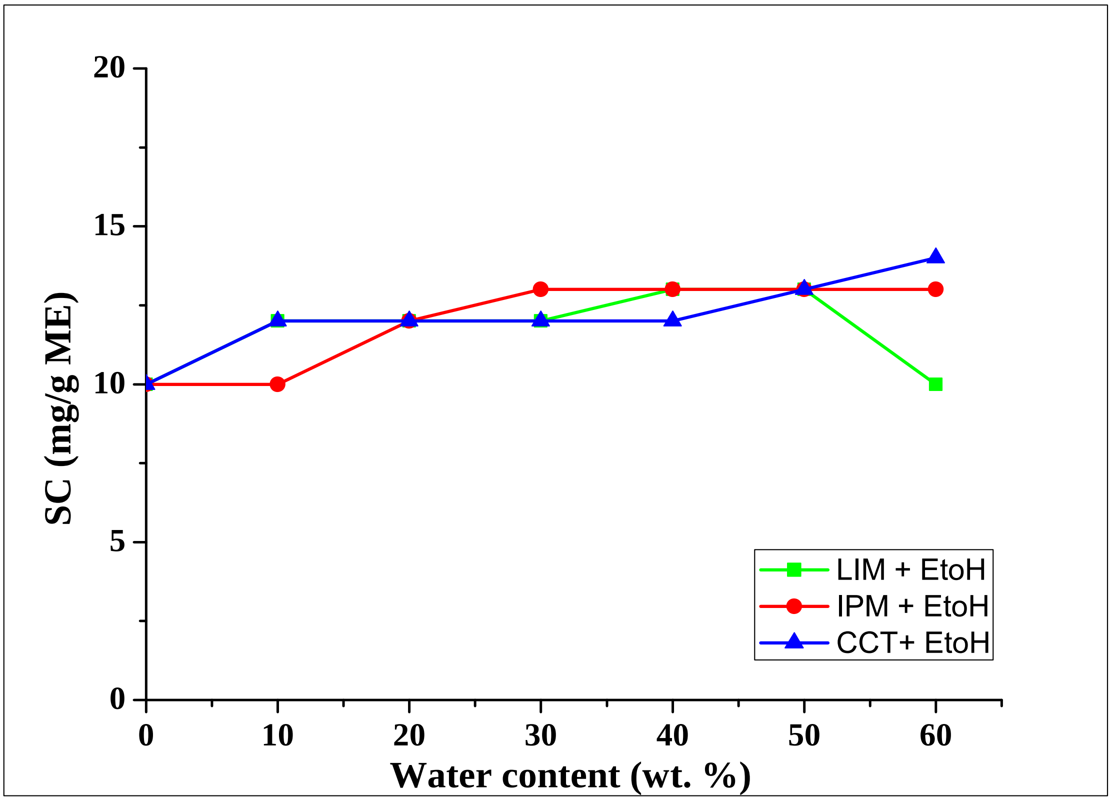


Figure 5.90: The variation in the solubilization capacity (SC) between different types of oils (LIM, IPM and CCT) with co-surfactant EtOH in mixed nonionic surfactants systems at temperature 25°C along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity.

Table 5.98 and figure 5.91 shows the variation in the solubilization capacity (SC) at 0% water content of microemulsion system: W/O1570/oils + EtOH with different three types of oils (LIM, IPM and CCT) at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity.

	SC (mg/g)
Oil	**25ºC**
LIM + EtOH	10
IPM + EtOH	10
CCT + EtOH	10

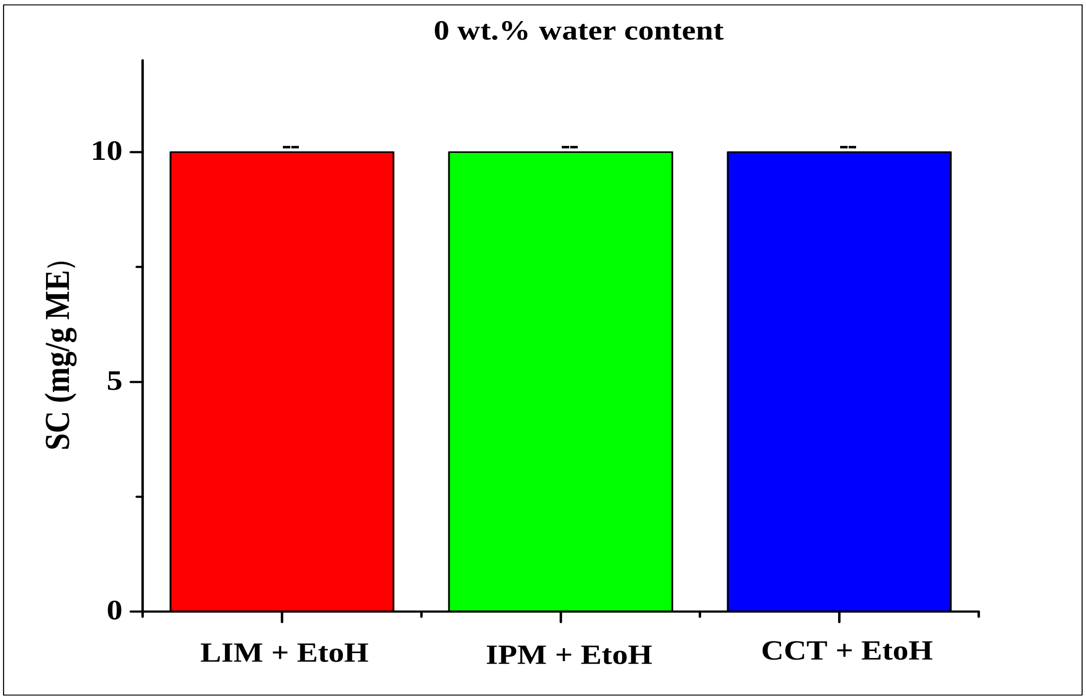


Figure 5.91: The solubilization capacity (SC) of cefuroxime axetil (mg/g microemulsion) at 0% water content of microemulsion system: W/O1570/T-MAZ 80/oils + EtOH with different three types of oils (LIM, IPM and CCT) at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity.

Table 5.99 and figure 5.92 shows the variation in the solubilization capacity (SC) at 30% water content of microemulsion system: W/O1570/oils + EtOH with different three types of oils (LIM, IPM and CCT) at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity.

	SC (mg/g)
Oil	**25ºC**
LIM + EtOH	12
IPM + EtOH	13
CCT + EtOH	12

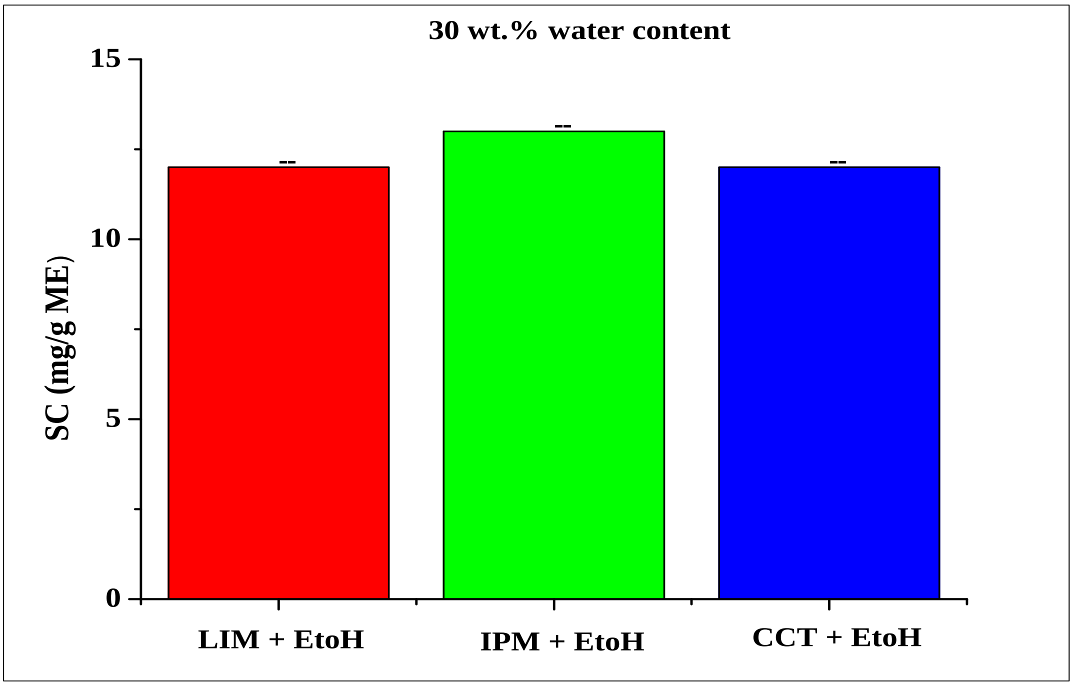


Figure 5.92: The solubilization capacity (SC) of cefuroxime axetil (mg/g microemulsion) at 30% water content of microemulsion system: W/O1570/T-MAZ 80/oils + EtOH with different three types of oils (LIM, IPM and CCT) at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity.

Table 5.100 and figure 5.93 shows the variation in the solubilization capacity (SC) at 60% water content of microemulsion system: W/O1570/T-MAZ 80/oils + EtOH with different three types of oils (LIM, IPM and CCT) at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity

	SC (mg/g)
Oil	**25ºC**
LIM + EtOH	10
IPM + EtOH	13
CCT + EtOH	14

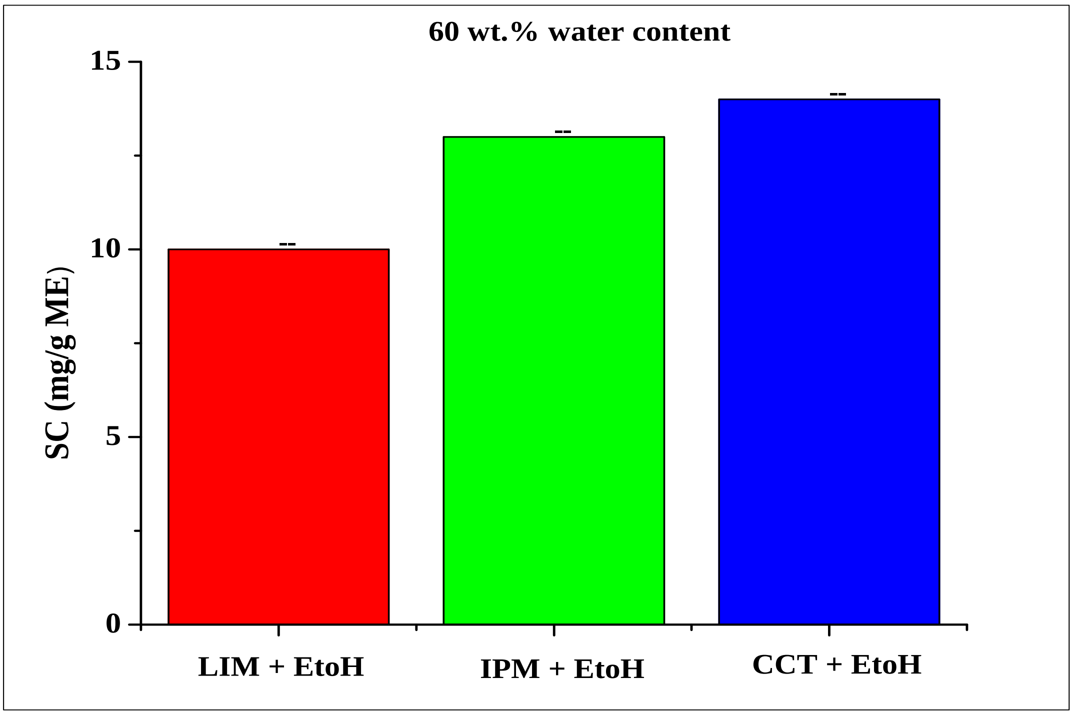


Figure 5.93: The solubilization capacity (SC) of cefuroxime axetil (mg/g microemulsion) at 60% water content of microemulsion system: W/O1570/T-MAZ 80/oils + EtOH with different three types of oils (LIM, IPM and CCT) at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity.

From tables and figures which illustrated above (Figure 5.90, 91, 92, 93 and related tables) shows that the IPM and CCT oils has a maximum solubilization capacity with little preference to CCT oil. The roles of ethanol (EtOH) in microemulsion systems are destabilization of liquid crystalline phase which extended the microemulsion region, and increase the fluidity of the interfacial film that enhance of motion and penetration of aqueous phase in the surfactant palisade layer, hence increase the entrapment of active pharmaceutical ingredient in the interfacial layer. Moreover EtOH have hydroxyl group (OH) which interact with water molecules forming hydrogen bond and therefore increase the stability of microemulsion systems.

In addition IPM and CCT are polar oils that have large tendency to penetrate in the surfactant palisade layer carrying the drug molecules which encapsulating with these oils in the interfacial layer, in the contrary to LIM oil that have low solubilization capacity because of viscus microemulsion systems formulate among this oil. As we refers previously in this section, the viscus microemulsion forms more network structures that hindered mobility of this oil and hence decrease of solubilization capacity of cefuroxime axetil.

5.3.2.d Drug solubilization capacity of the system W/O1570/T-MAZ 80/LIM + PG at ratio 1/1 (w/w) between mixed surfactants

The solubilization capacity (SC) of cefuroxime axetil at 25ºC as a function of water content along the dilution line N65 is presented in table 5.100 and figure 5.94.

Table 5.101: SC (mg/g) for the system W/O1570/T-MAZ 80/LIM + PG at different water content. The weight ratio is 1/1 (w/w) between mixed surfactants.

	SC (mg/ g microemulsion)
Water content (wt. %)	**25ºC**
0	13
10	12
20	12
30	12
40	12
50	12
60	10

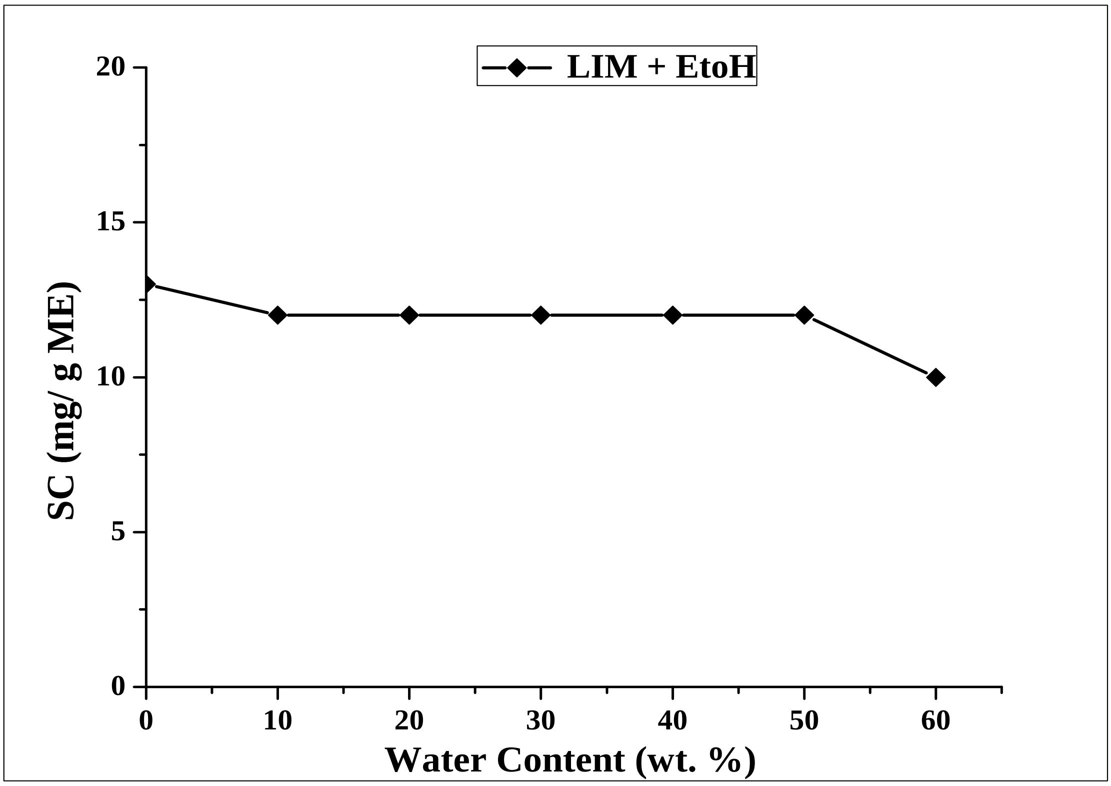


Figure 5.94: The solubilization capacity (SC) of cefuroxime axetil (mg drug/g microemulsion) as a function of water content in the system: W/ O1570/ T-MAZ 80/ LIM + PG at ratio 1/1 (w/w) between mixed surfactants along the dilution line N65.

The drug solubilization capacity decreases from 13mg/g microemulsion at water content equal 0 wt. % to 12mg/g microemulsion at water content equal 10 wt. %, then the solubilization capacity stability from 12mg/g microemulsion from 10% water content to 50% water content. At water content 60% the solubilization capacity of cefuroxime axetil decrease to 10mg/g microemulsion.

5.3.2.e Drug solubilization capacity of the system W/O1570/T-MAZ 80/IPM + PG at ratio 1/1 (w/w) between mixed surfactants

The solubilization capacity (SC) of cefuroxime axetil at 25ºC as a function of water content along the dilution line N65 is presented in table 5.101 and figure 5.95.

Table 5.102: SC (mg/g) for the system W/O1570/T-MAZ 80/IPM + PG at different water content. The weight ratio is 1/1 (w/w) between mixed surfactants.

	SC (mg/ g microemulsion)
Water content (wt. %)	**25ºC**
0	12
10	12
20	12
30	14
40	10
50	10
60	8

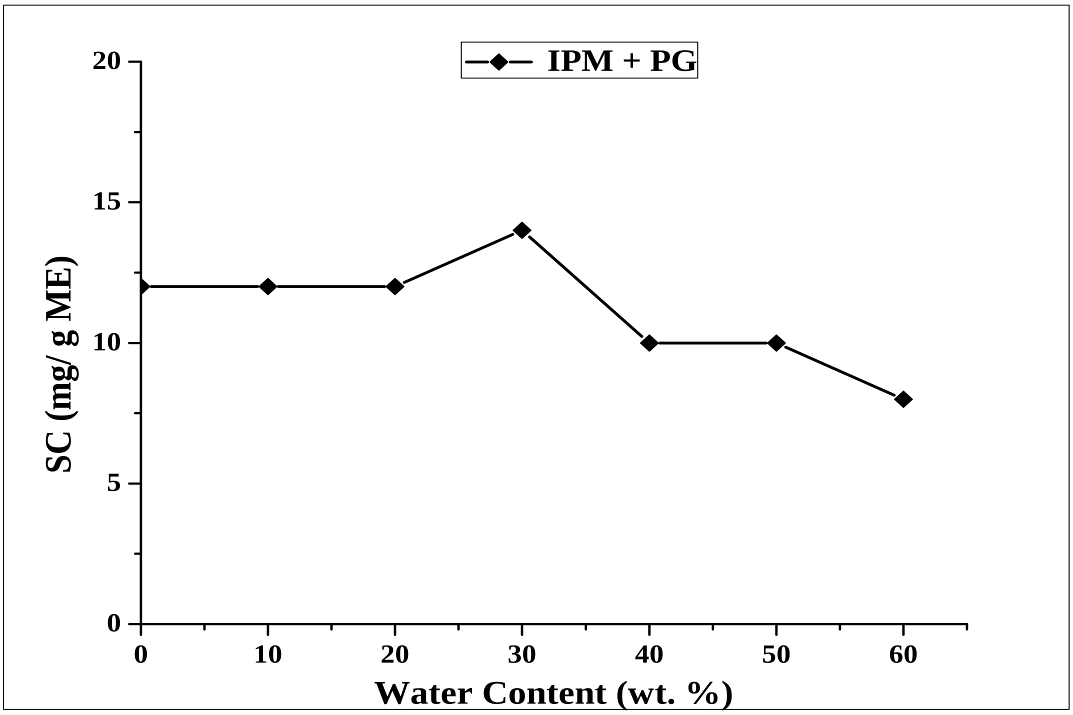


Figure 5.95: The solubilization capacity (SC) of cefuroxime axetil (mg drug/g

microemulsion) as a function of water content in the system: W/ O1570/ T-MAZ 80/ IPM + PG at ratio 1/1 (w/w) between mixed surfactants along the dilution line N65.

The solubilization capacity stability from 12mg/g microemulsion at water content equal 0% to water content equal 20%, the solubilization capacity increase to 14mg/g microemulsion at water content equal 30% then the solubilization capacity decreases again to 10mg/g and 8mg/g microemulsion at water content 40% and 60% respectively.

5.3.2.f Drug solubilization capacity of the system W/O1570/T-MAZ 80/CCT + PG at ratio 1/1 (w/w) between mixed surfactants

The solubilization capacity (SC) of cefuroxime axetil at 25ºC as a function of water content along the dilution line N65 is presented in table 5.102 and figure 5.96.

Table 5.103: SC (mg/g) for the system W/O1570/T-MAZ 80/CCT + PG at different water content. The weight ratio is 1/1 (w/w) between mixed surfactants.

	SC (mg/ g microemulsion)
Water content (wt. %)	**25ºC**
0	12
10	12
20	12
30	12
40	12
50	10
60	8

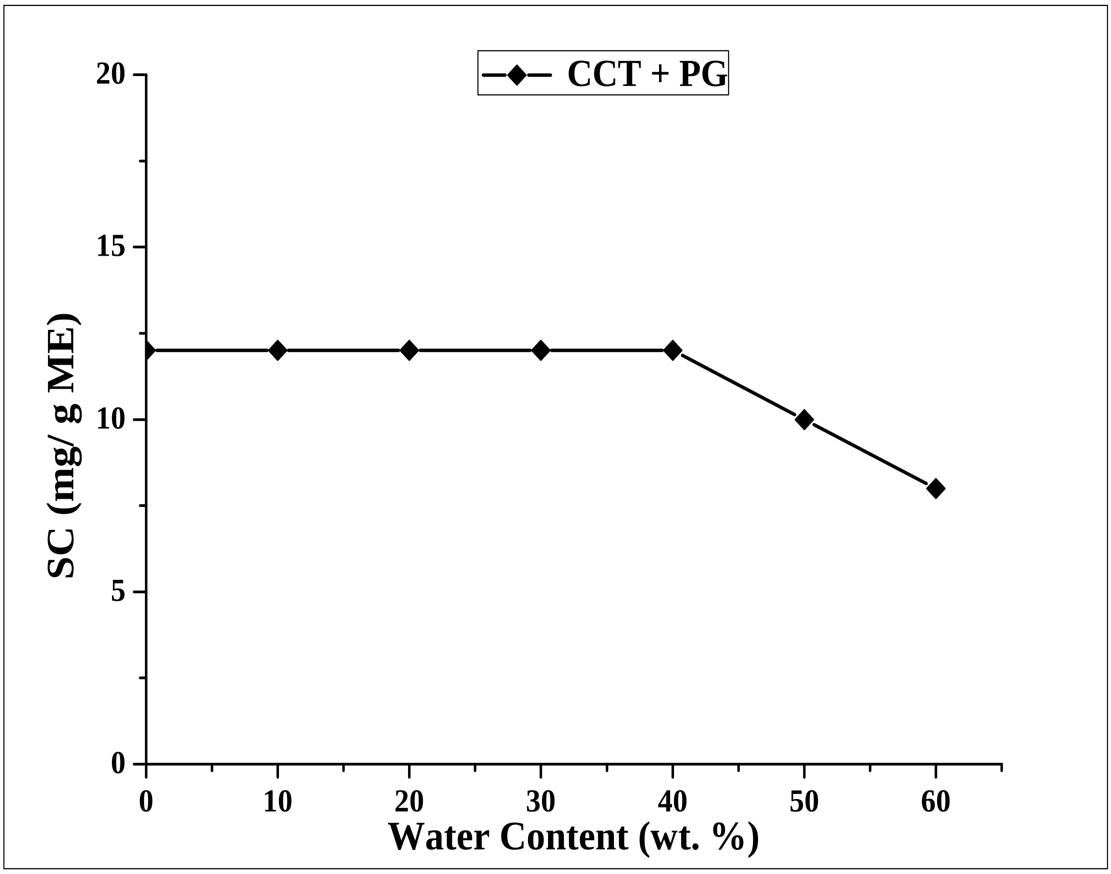


Figure 5.96: The solubilization capacity (SC) of cefuroxime axetil (mg drug/g microemulsion) as a function of water content in the system: W/ O1570/ T-MAZ 80/ CCT + PG at ratio 1/1 (w/w) between mixed surfactants along the dilution line N65.

From figure 5.96 which printed above, we can divided the figure into two regions according to the solubilization capacity of cefuroxime axetil, at the first region the solubilization capacity stability form 12mg/g microemulsion at water content equal 0% to water content equal 40%, at the second region the solubilization capacity decrease to 10mg/g microemulsion and then to 8mg/g microemulsion at water content 50% and 60% respectively.

Table 5.104 and figure 5.97 shows the variation in the solubilization capacity (SC) between different types of oils (LIM, IPM and CCT) with co-surfactant PG in mixed nonionic surfactants systems at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity.

Water content (wt. %)	SC (mg/g)		
	25°C		
	LIM + PG	IPM + PG	CCT + PG
0	13	12	12
10	12	12	12
20	12	12	12
30	12	14	12
40	12	10	12
50	12	10	10
60	10	8	8

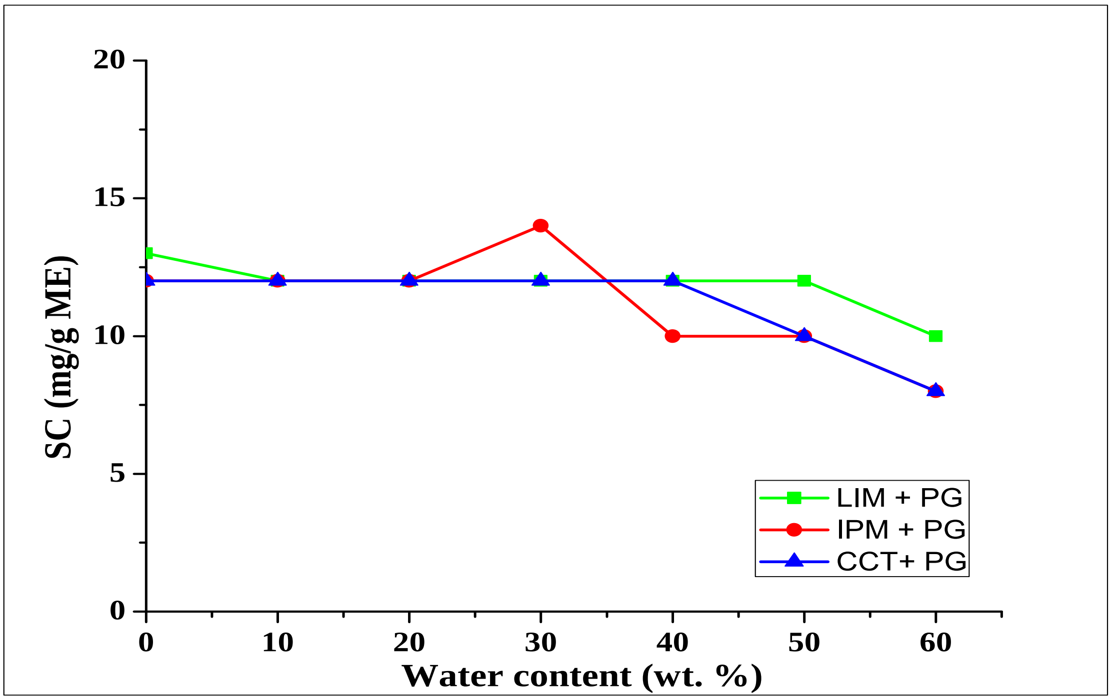


Figure 5.97: The variation in the solubilization capacity (SC) between different types of oils (LIM, IPM and CCT) with co-surfactant PG in mixed nonionic surfactants systems at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity.

Table 5.105 and figure 5.98 shows the variation in the solubilization capacity (SC) at 0% water content of microemulsion system: W/O1570/T-MAZ 80/oils + PG with different three types of oils (LIM, IPM and CCT) at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity

	SC (mg/g)
Oil	**25ºC**
LIM +PG	13
IPM + PG	12
CCT + PG	12

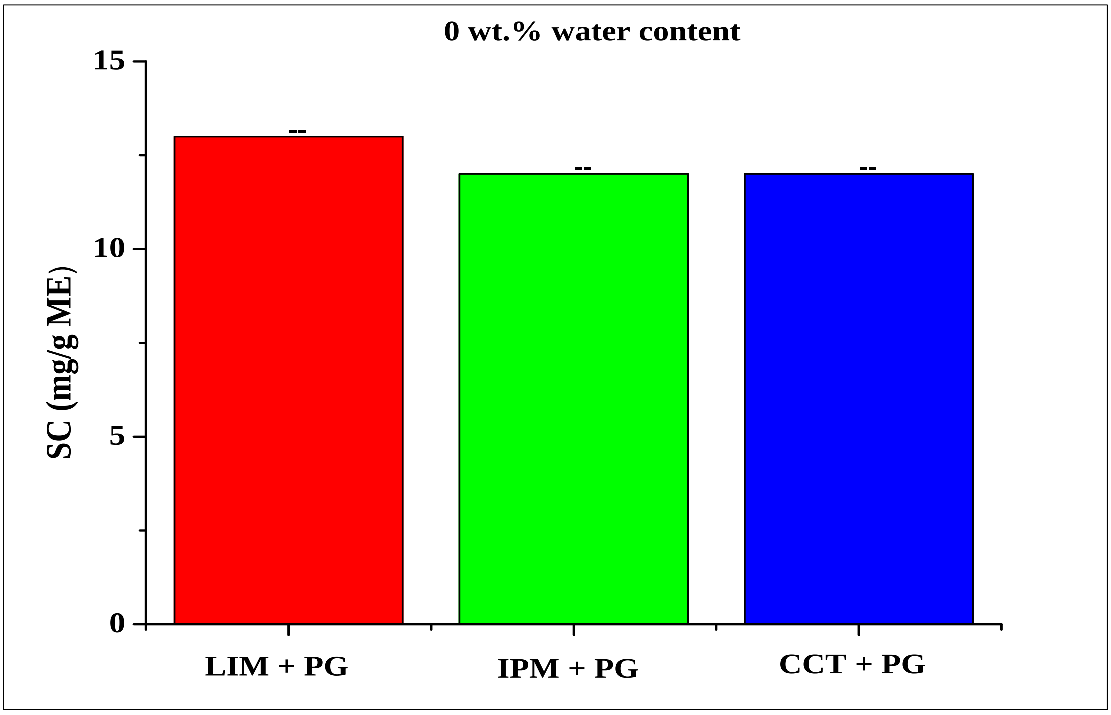


Figure 5.98: The solubilization capacity (SC) of cefuroxime axetil (mg/g microemulsion) at 0% water content of microemulsion system: W/O1570/T-MAZ 80/oils + PG with different three types of oils (LIM, IPM and CCT) at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity.

Table 5.106 and figure 5.99 shows the variation in the solubilization capacity (SC) at 60% water content of microemulsion system: W/O1570/T-MAZ 80/oils + PG with different three types of oils (LIM, IPM and CCT) at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity

	SC (mg/g)
Oil	**25ºC**
LIM +PG	10
IPM + PG	8
CCT + PG	8

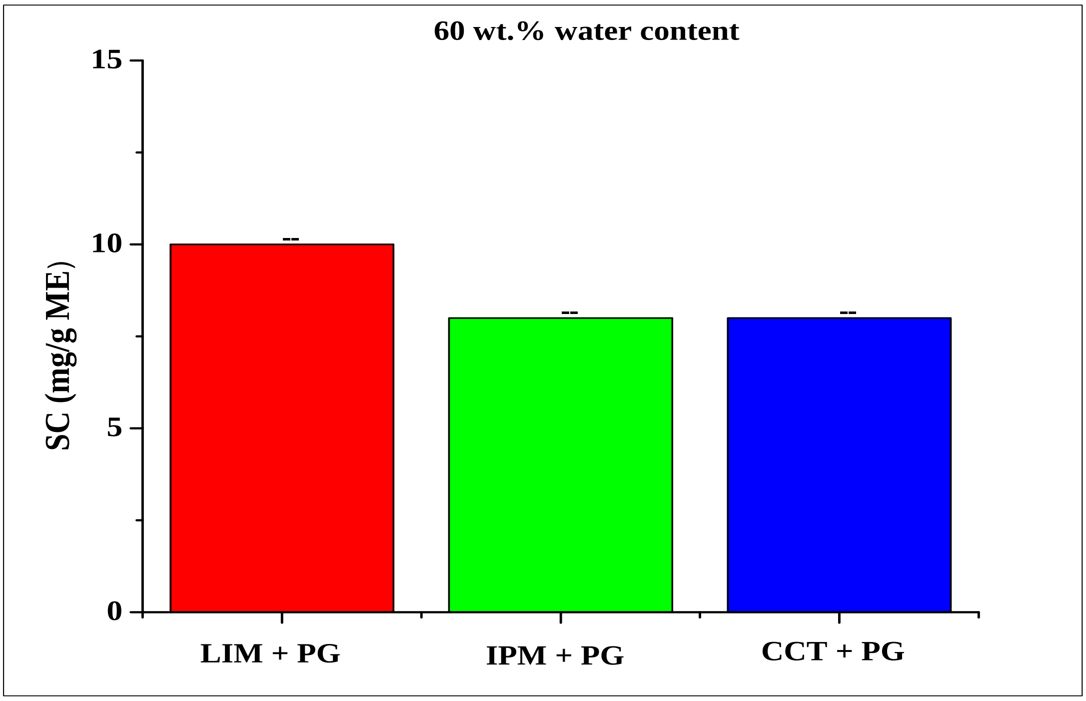


Figure 5.99: The solubilization capacity (SC) of cefuroxime axetil (mg/g microemulsion) at 60% water content of microemulsion system: W/O1570/T-MAZ 80/oils + PG with different three types of oils (LIM, IPM and CCT) at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity.

Propylene glycol (PG) is organic solvent behave like water to form hydrogen bond, and when added to microemulsion systems their resulting penetration into the surfactant interface leads to smaller or no liquid crystalline phase. In addition PG used in microemulsion systems as tuning parameter to change the surfactant layer curvature and increase the flexibility of the interfacial film and hence increase the oil penetration in the interfacial film by connecting the aqueous phase and oil phase together, these properties of PG can form a viscus microemulsion systems as observed experimentally, which more network microstructure are observed. Therefore LIM oil with lower molecular volume compared to other oils studied gives higher solubilization capacity, for this reason of lower molecular volume of LIM oil allowto penetrate more easily in the surfactant palisade layer, beside LIM has a spherical shape help him in more penetration tendency.

The second oil in solubilization capacity is IPM oil which is linear structure have ketone functional head group that soluble in water make a hydrogen bond with water molecules. This linearity increase the interaction of ketone group with water on the side, and on the other side the tail interact with the hydrophobic parts in microemulsion systems resultant of increase the penetration in the surfactant palisade layer. Thus IPM oil used as penetration enhancer in microemulsion systems.

From all of the above, we can arrange the studied oils decreasing according to the solubilization capacity of cefuroxime axetil in the system: W/O1570/T-MAZ 80/ oils + PG, where the oils are LIM, IPM and CCT as follows: LIM + PG> IPM + PG > CCT + PG.

5.3.3 Drug solubilization capacity of cefuroxime axetil in mixed surfactants with mixed oils

5.3.3.a Drug solubilization capacity of the system W/O1570/T-MAZ 80/LIM + IPM at ratio 1/1 (w/w) between mixed surfactants

The solubilization capacity (SC) of cefuroxime axetil at 25ºC as a function of water content along the dilution line N65 is presented in table 5.106 and figure 5.100.

Table 5.107: SC (mg/g) for the system W/O1570/T-MAZ 80/LIM + IPM at different water content. The weight ratio is 1/1 (w/w) between mixed surfactants.

	SC (mg/ g microemulsion)
Water content (wt. %)	**25ºC**
0	10
10	10
20	12
30	10
40	10
50	10

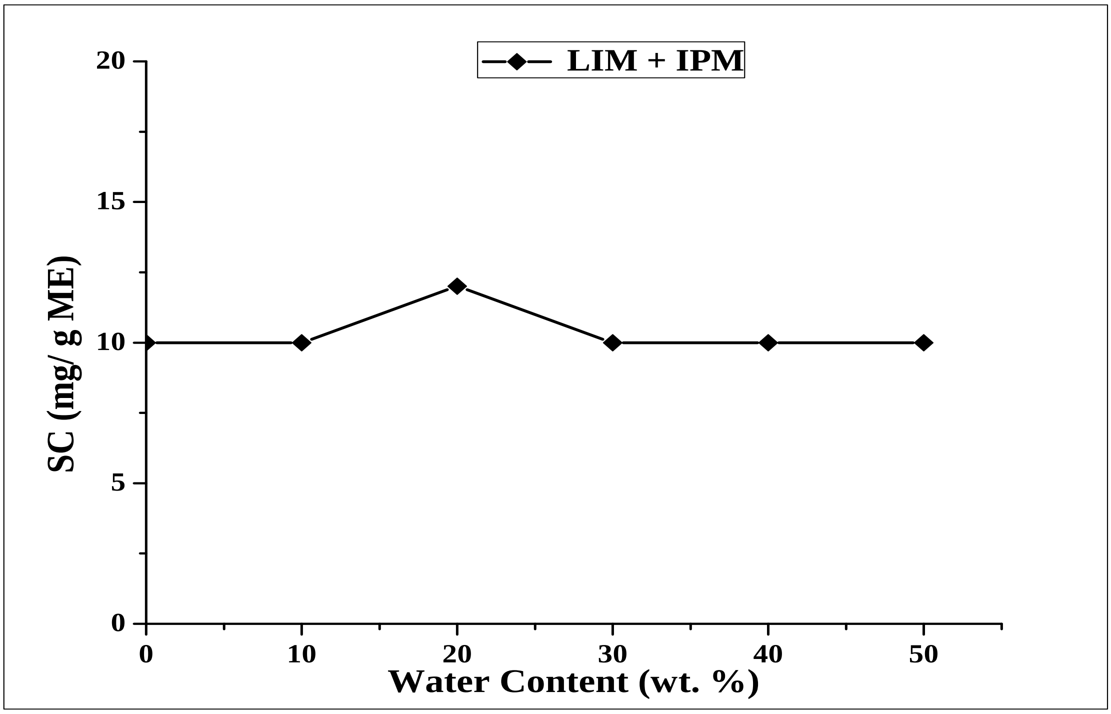


Figure 5.100: The solubilization capacity (SC) of cefuroxime axetil (mg drug/g microemulsion) as a function of water content in the system: W/ O1570/ T-MAZ 80/ LIM + IPM at ratio 1/1 (w/w) between mixed surfactants along the dilution line N65.

The solubilization capacity increase from 10mg/g microemulsion at water content 0% and 10% to 12mg/g microemulsion at water content equal 20%, then the solubilization capacity decrease to 10mg/g and become stability of this value until reach 50% water content.

5.3.3.b Drug solubilization capacity of the system W/O1570/T-MAZ 80/LIM + CCT at ratio 1/1 (w/w) between mixed surfactants

The solubilization capacity (SC) of cefuroxime axetil at 25ºC as a function of water content along the dilution line N65 is presented in table 5.107 and figure 5.101.

Table 5.108: SC (mg/g) for the system W/O1570/T-MAZ 80/LIM + CCT at different water content. The weight ratio is 1/1 (w/w) between mixed surfactants.

	SC (mg/ g microemulsion)
Water content (wt. %)	**25ºC**
0	10
10	13
20	12
30	12
40	10
50	8

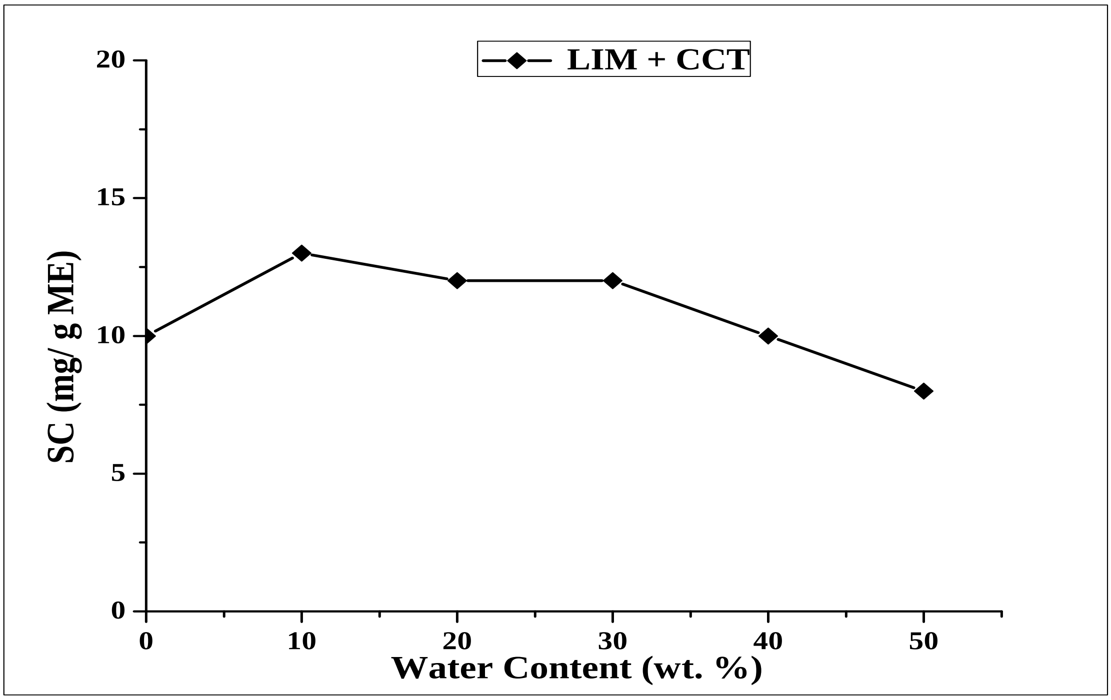


Figure 5.101: The solubilization capacity (SC) of cefuroxime axetil (mg drug/g microemulsion) as a function of water content in the system: W/ O1570/ T-MAZ 80/ LIM + CCT at ratio 1/1 (w/w) between mixed surfactants along the dilution line N65.

As shown in figure 5.101, the solubilization capacity increase form 10mg/g microemulsion at water content equal 0 wt. % to 13mg/g microemulsion at water content equal 10 wt. %, the solubilization capacity stability from 12mg/g microemulsion from water content 20 wt. % to water content 30 wt. % and then decrease to 10mg/g and to 8mg/g microemulsion at water content equal 40 wt. % and 50 wt. % respectively.

Table 5.109 and figure 5.102 shows the variation in the solubilization capacity (SC) between different mixed oils (LIM + IPM and LIM + CCT) in mixed nonionic surfactants systems at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity.

Water content (wt. %)	**LIM + IPM**	**LIM + CCT**
0	10	10
10	10	13
20	12	12
30	10	12
40	10	10
50	10	8

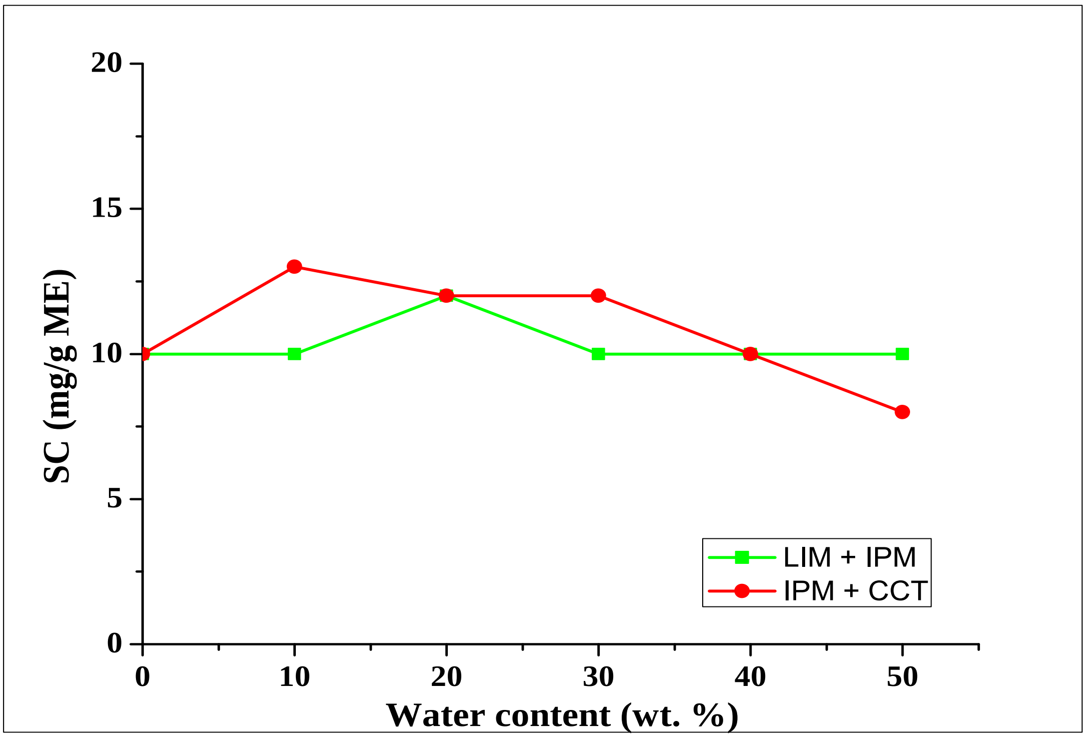


Figure 5.102: The variation in the solubilization capacity (SC) between different mixed oils (LIM + IPM & LIM + CCT) in mixed nonionic surfactants systems at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity.

Table 5.110 and figure 5.103 shows the variation in the solubilization capacity (SC) at 0% water content of microemulsion system: W/O1570/T-MAZ 80/mixed oils at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity

	SC (mg/g)
Oil	**25ºC**
LIM +IPM	10
LIM + CCT	10

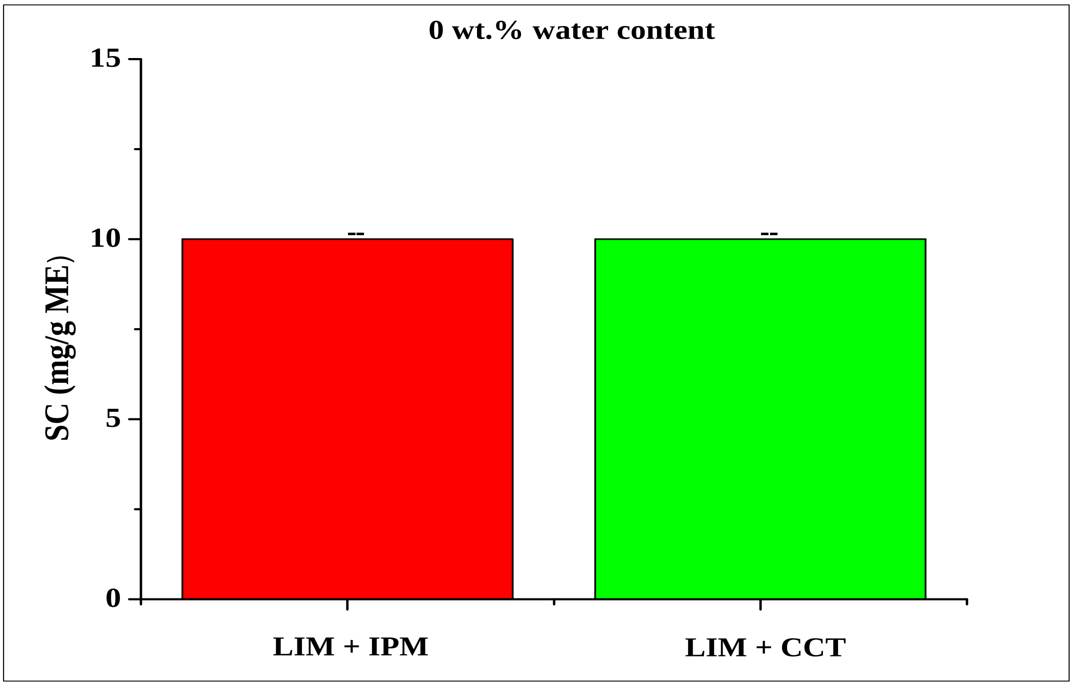


Figure 5.103: The solubilization capacity (SC) of cefuroxime axetil (mg/g microemulsion) at 0% water content of microemulsion system: W/O1570/mixed oils at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity.

Table 5.111 and figure 5.104 shows the variation in the solubilization capacity (SC) at 10% water content of microemulsion system: W/O1570/T-MAZ 80/mixed oils at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity

	SC (mg/g)
Oil	**25ºC**
LIM +IPM	10
LIM + CCT	13

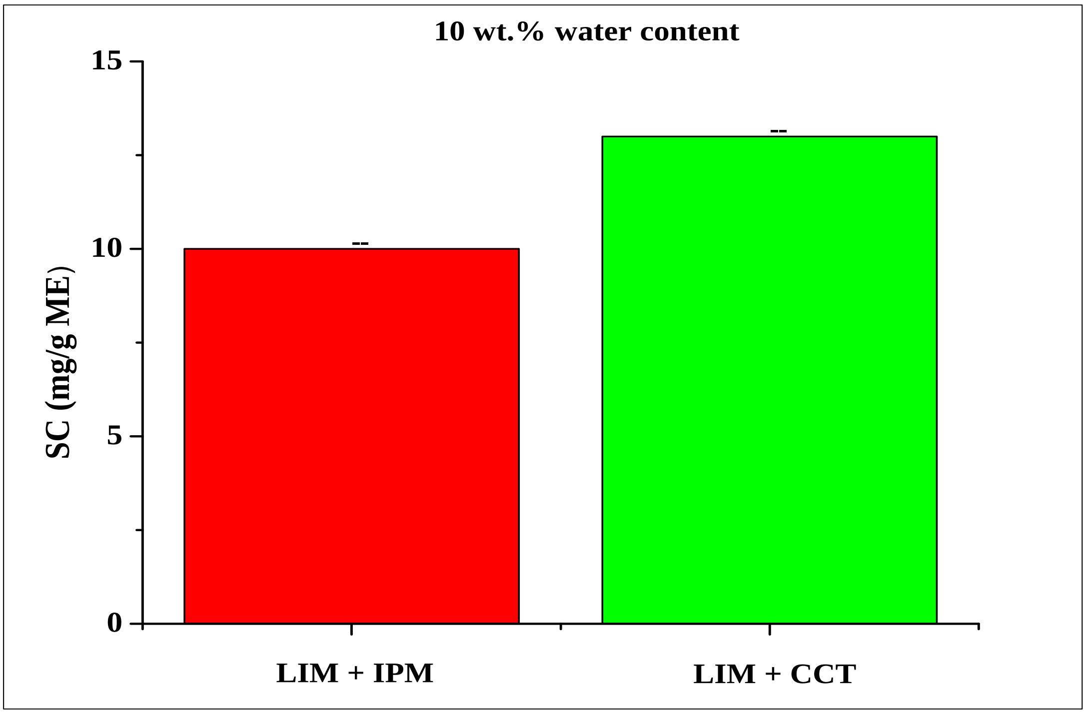


Figure 5.104: The solubilization capacity (SC) of cefuroxime axetil (mg/g microemulsion) at 10% water content of microemulsion system: W/O1570/mixed oils at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity.

Table 5.112 and figure 5.105 shows the variation in the solubilization capacity (SC) at 50% water content of microemulsion system: W/O1570/T-MAZ 80/mixed oils at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity

	SC (mg/g)
Oil	**25ºC**
LIM +IPM	10
LIM + CCT	8

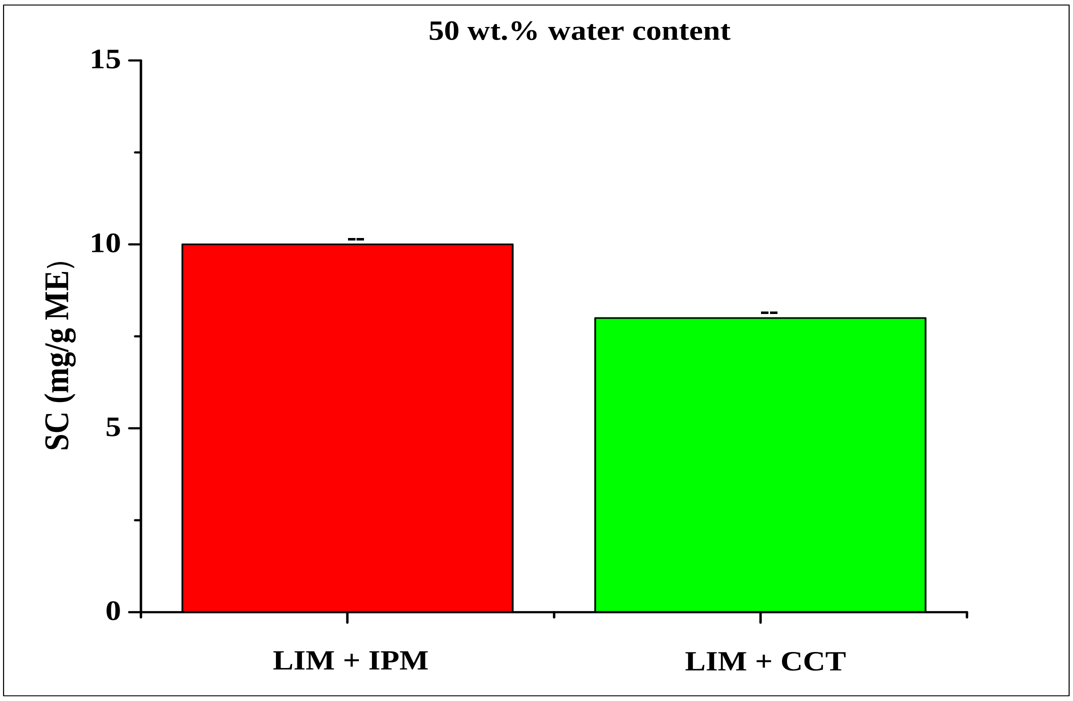


Figure 5.105: The solubilization capacity (SC) of cefuroxime axetil (mg/g microemulsion) at 50% water content of microemulsion system: W/O1570/mixed oils at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity.

From figures 5.102, 5.103, 5.104 and 5.105 which presented above shows that the mixed oils of LIM + CCT gives a maximum solubilization capacity. IPM and CCT oils are polar oils that have large tendency to penetrate in the surfactant palisade layer, the polarity of these oils increase the partitioning these oils in the interfacial layer. The chain length compatibility of microemulsion systems play a key role in determining the interfacial properties and stability of microemulsions formed, therefore LIM + CCT oils have more compatibility to form stable and ordered microemulsion system than LIM + IPM system in mixed nonionic microemulsions.

Also we observed from the figure 5.102 which illustrated above that microemulsion system of LIM + IPM have a higher stability of equal amount of drug solubilization capacity, because as we referred previously in this section IPM oil have carbonyl compound soluble in water which in turn make a hydrogen bond with water molecules and increase the stability of microemulsion system, thus IPM oil used in microemulsion systems as penetration enhancer.

Tables 5.113, 5.114 and 5.115 which presented below shows a comparative study of different three types of oils (LIM, IPM and CCT) with and without co-surfactants (EtOH, PG) for each type of oil, in order to study the effect of these parameters in the solubilization capacity of cefuroxime axetil.

Table 5.113 and figure 5.106 shows the variation in the solubilization capacity (SC) between LIM, LIM + EtOH and LIM + PG in mixed nonionic surfactants systems at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity.

Water content (wt. %)	**SC (mg/g)**		
	25°C		
	LIM	**LIM + EtOH**	**LIM + PG**
0	8	10	13
10	12	12	12
20	13	12	12
30	13	12	12
40	8	13	12
50	8	13	12
60	8	10	10

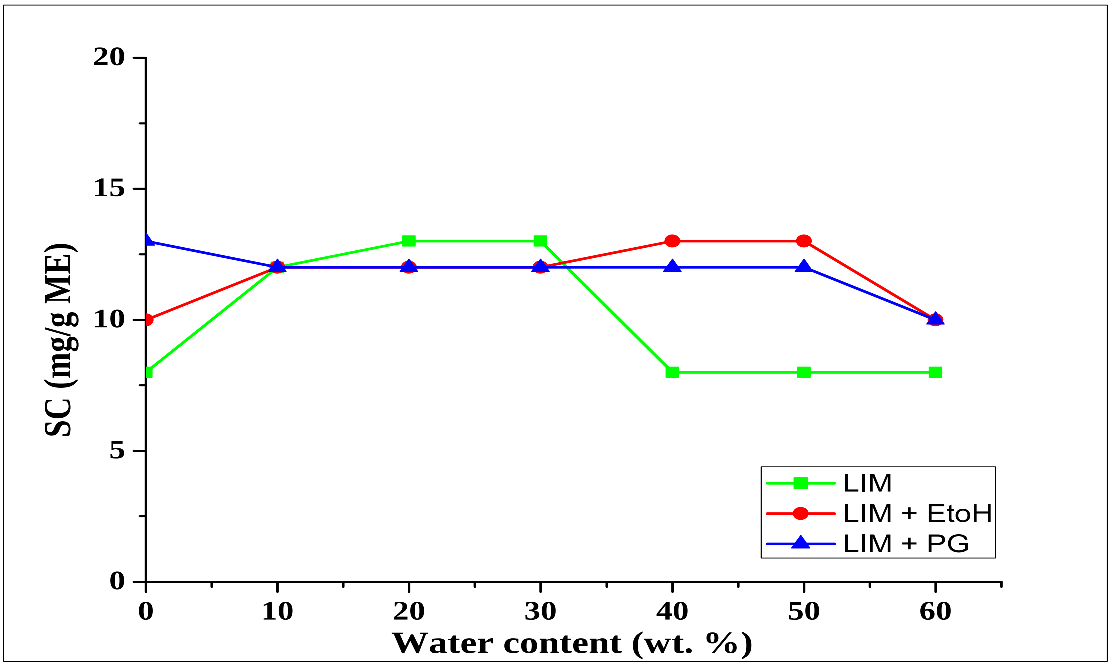


Figure 5.106: The variation in the solubilization capacity (SC) between LIM, LIM + EtOH and LIM + PG in mixed nonionic surfactants systems at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity.

Table 5.114 and figure 5.107 shows the variation in the solubilization capacity (SC) between IPM, IPM + EtOH and IPM + PG in mixed nonionic surfactants systems at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity.

Water content (wt. %)	**SC (mg/g)**		
	25°C		
	IPM	**IPM + EtOH**	**IPM + PG**
0	8	10	12
10	12	10	12
20	13	12	12
30	13	13	14

40	8	13	10
50	8	13	10
60	8	13	8

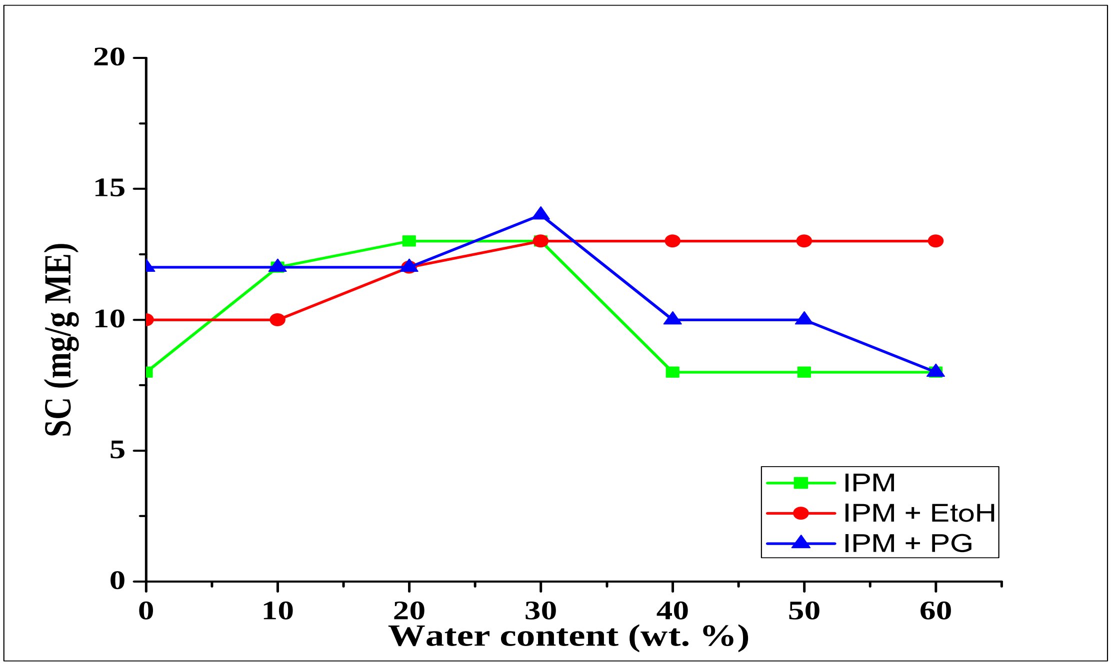


Figure 5.107: The variation in the solubilization capacity (SC) between IPM, IPM + EtOH and IPM + PG in mixed nonionic surfactants systems at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity.

Table 5.115 and figure 5.108 shows the variation in the solubilization capacity (SC) between CCT, CCT + EtOH and CCT + PG in mixed nonionic surfactants systems at temperature 25ºC along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity.

Water content (wt. %)	**SC (mg/g)**		
	25ºC		
	CCT	**CCT + EtOH**	**CCT + EtOH**
0	10	10	12

10	12	12	12
20	13	12	12
30	13	12	12
40	13	12	12
50	12	13	10
60	10	14	8

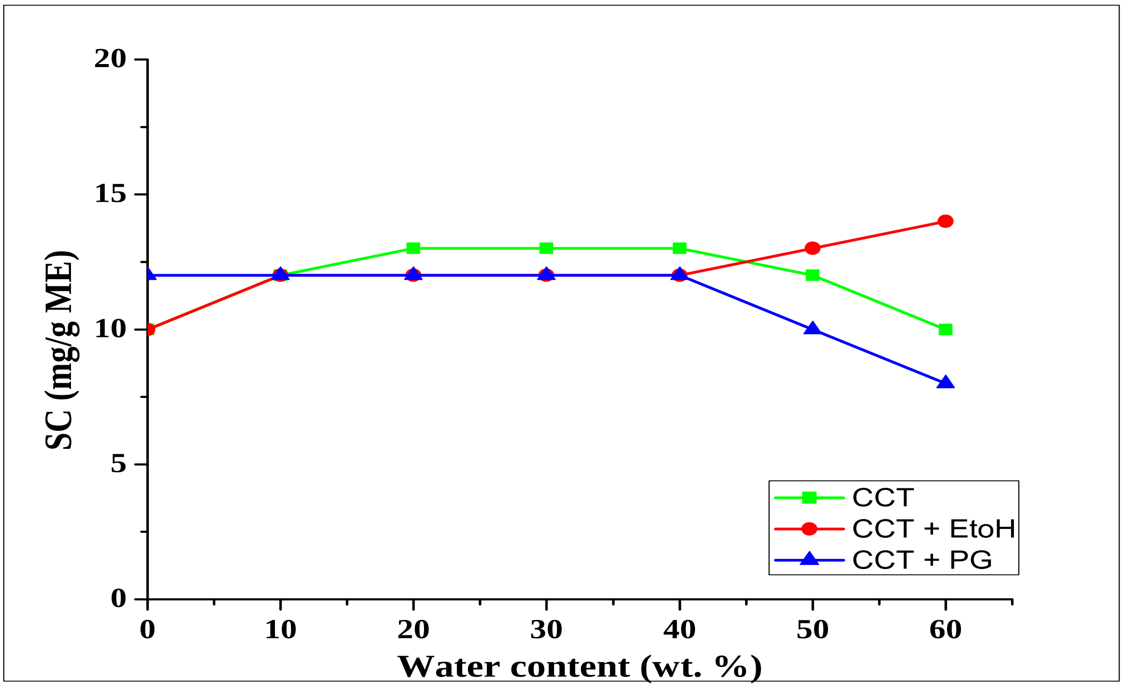


Figure 5.108: The variation in the solubilization capacity (SC) between CCT, CCT + EtOH and CCT + PG in mixed nonionic surfactants systems at temperature 25°C along the dilution line N65, were the mixing ratio between mixed surfactants are of equal unity.

It is obvious form the figures above that different types of oils (LIM, IPM and CCT) with ethanol (EtOH) gives a maximum solubilization capacity of cefuroxime axetil, which indicate the role of ethanol in microemulsion systems that destabilization of liquid crystalline phase and increase the fluidity of interfacial film. This increasing in the fluidity of interfacial film adjust the interfacial layer curvature which in turn allows the oils of more penetration carrying a pharmaceutical ingredients with it.

In the second one is oils (LIM, IPM and CCT) alone, and the third one with propylene glycol (PG), because PG is a polyol compound that strongly combined with water molecules resulting of viscus microemulsion systems. This viscosity hindered mobility of micro molecules in microemulsion systems that decease the penetration tendency of oils in the surfactant palisade layer, hence decrease of solubilization capacity.

- About drug solubilization

In this section we was studied the solubilization capacity of poorly water soluble drug, cefuroxime axetil and try to benefit from a unique properties of microemulsion systems that included the mutual solubilization of water and oil to solubilize active pharmaceutical ingredients by dissolving it in these microemulsion systems, also we examined different factors that influenced on the solubilization capacity of cefuroxime axetil, and noted these observations:

- From all systems studied in this section, the drug solubilization capacity are strongly influenced with water content, as we observed experimentally. At low water content (0 wt. % to 30 wt. %) the solubilization capacity reach a maximum values and the microemulsion system is micelles or reverse micelles (w/o). This highest values of solubilization capacity in this region is due to a high surface area and high oil content. At water content 40 wt. % to 60 wt. % the solubilization capacity become constant, because it is suggested that the microemulsion systems converted to bicontinuous, and the system formulate different types of microemulsions with low stability. Above 60 wt. % of water content have a lower solubilization capacity suggested that o/w microemulsion was formed, and the oil content will be decreased, resulting of modification of surfactant layer curvature. A small amount of oil exists in the core of the droplets and the interfacial layer convex towered oil phase resulting in low solubility in the core and poor accommodation of the drugs at the hydrophilic interface.

Some of exception will be found in the presence of ethanol in microemulsion systems studied, such as W/O1570/T-MAZ 8/CCT + EtOH microemulsion, that the solubilization capacity will be increased more than the systems of free ethanol, because ethanol increase the fluidity of the interfacial film and alter the surfactant layer curvature, thus increase of oil penetration resultant of increase solubilization capacity. On the contrary to the presence of propylene glycol (PG), the solubilization capacity will decreased. A possible explanation for this deceases in solubilization capacity that PG have two hydroxyl groups (OH) interacts with water molecules make a viscus microemulsions which in turn increase the elasticity of the interfacial film and decrease the oil penetration in the surfactant layer, thus decrease of solubilization capacity.

- We study the effect of different types of oils on the solubilization capacity of cefuroxime axetil. The LIM oil is cyclic mono-terpene that have low molecular volume and effective carbon number also it have a spherical shape, the IPM oil have linear and moderate molecular volume and higher effective carbon number than LIM, CCT oils, and of rod shape in three dimentional arrangement. The third one is CCT that have highest molecular volume, and higher effective carbon number than LIM oil, the shape is plate- like (see tables 5.33 and 5.34). Effective carbon number (ECN) of these oils plays a major role in determining the solubilization capacity, so as the increase of effective carbon will be increase the interaction between oils and surfactant results of more compatible microemulsion systems, hence increase of solubilization capacity as shown experimentally. Moreover we observed from this study that the molecular volume is not a driving role in determination of solubilization capacity, this can be interpreted in terms of synergistic effects between nonionic surfactants within and the mixed surfactants with oils will increase the attractive interdroplet interaction, therefore increase the mutual solubility.

5.4 Drug permeability study

Permeability is the ability of a molecules or ion species to diffuse from one side to another through a membrane barriers by passive diffusion in order to calculate the amount of permeant in which it passes through this barriers.

The Franz diffusion Cell is an in vitro skin permeation assay frequently used in formulation development. The Franz Cell apparatus consists of two primary chambers separated by a membrane. The test product is applied to the membrane via the top chamber. The bottom chamber contains fluid from which samples are taken at regular intervals for analysis. This testing determines the amount of active that has permeated the membrane at each time point. The Franz cell assay cannot necessarily predict the efficacy of a drug formulation; it does allow formulators to determine whether a particular formulation delivers an active agent through the skin. As such, generic manufacturers typically rely on Franz cell analysis during the formulating process to try to devise a vehicle that matches the penetration rates of an innovator. The “optimal” formulation identified is then subject to the in vivo assay.

Transdermal is a route of administration more advantageous over other traditional routes; because it avoids chemically hostile gastrointestinal environment, provides adequate absorption of drugs, increases patient compliance, avoids first-pass effect, allows effective use of drugs with short biological half-lives, provides controlled plasma levels of potent drugs and interrupts drug input promptly when toxicities occur [Ranade. V, 1991], according to these advantages many authors [Addicks. W,Flynn. G,Weiner. N, 1987], [Shah.V, et al, 1989], [Madhav. N, Raina. D, Mala. M, 2015] try to make new formulations of transdermal routes in order to solve the issue of water insoluble drugs like CFA and other class II, class IV drugs.

HPLC analysis

- Reference standard

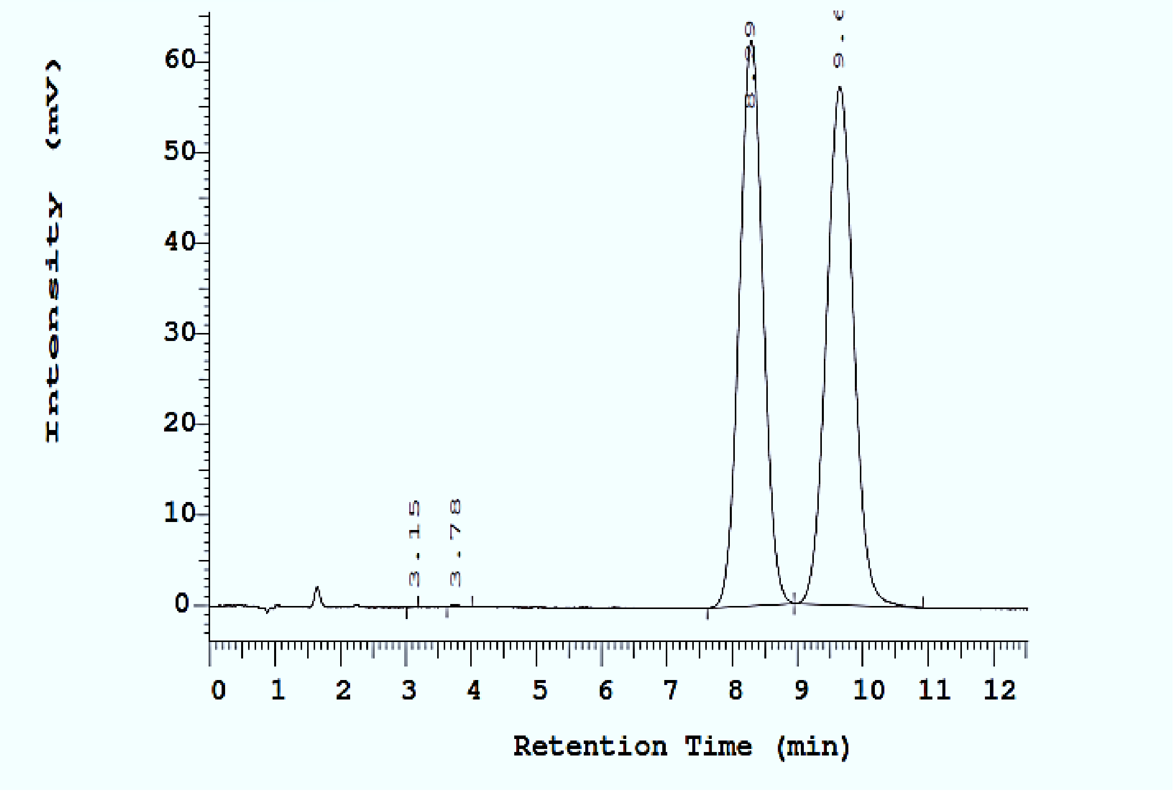


Figure 5.109: Monograph of CFA standard sample

- W/O1570/T-MAZ 80/IPM

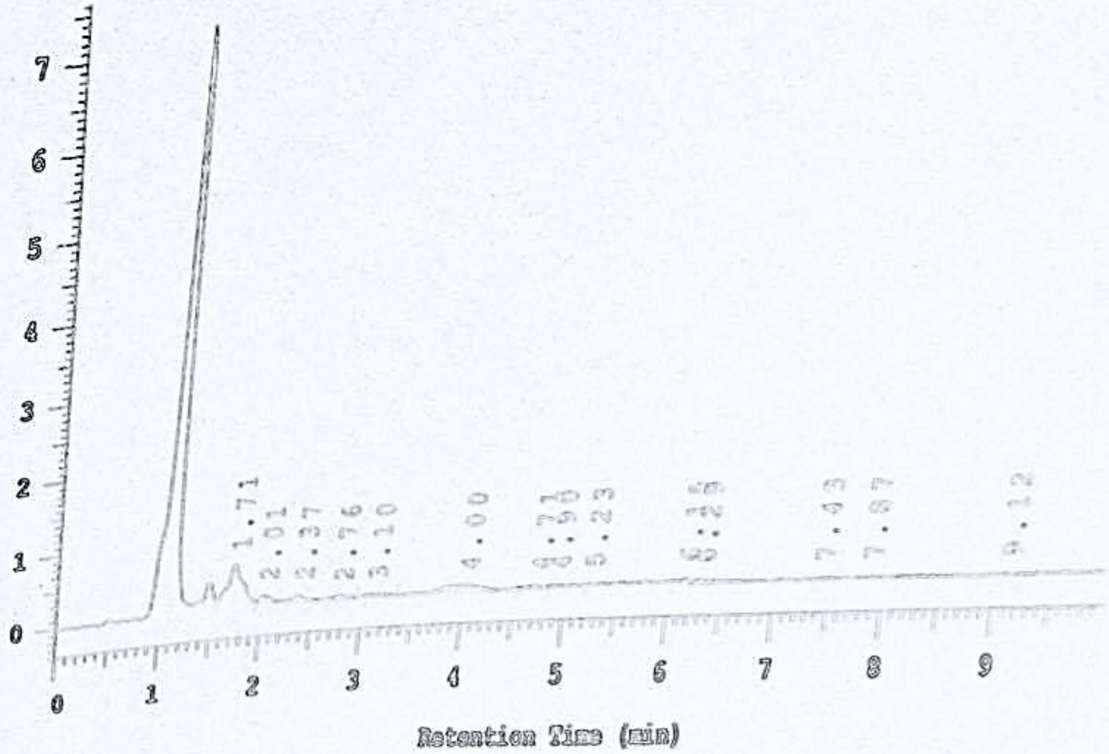


Figure 5.110: Monograph of CFA for system: W/O1570/T-MAZ 80/IPM

- W/O1570/T-MAZ 80/ LIM

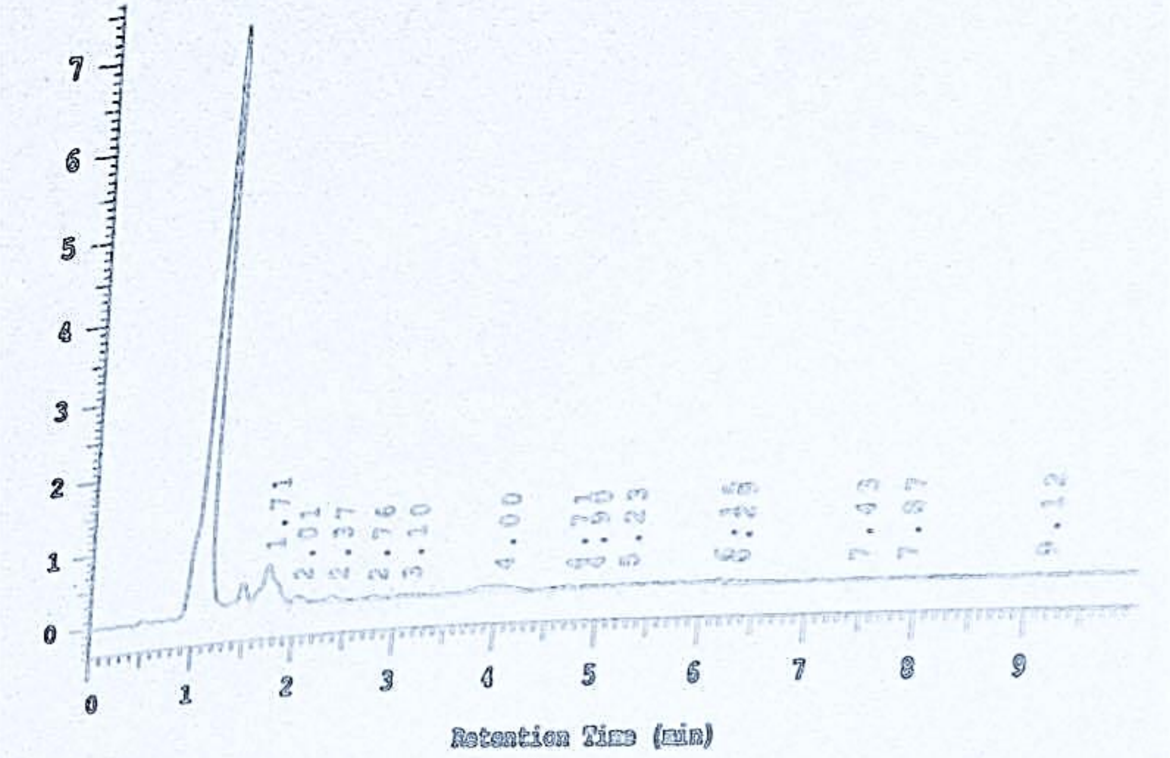


Figure 5.111: Monograph of CFA for system: W/O1570/T-MAZ 80/LIM

- W/O1570/T-MAZ 80/ CCT

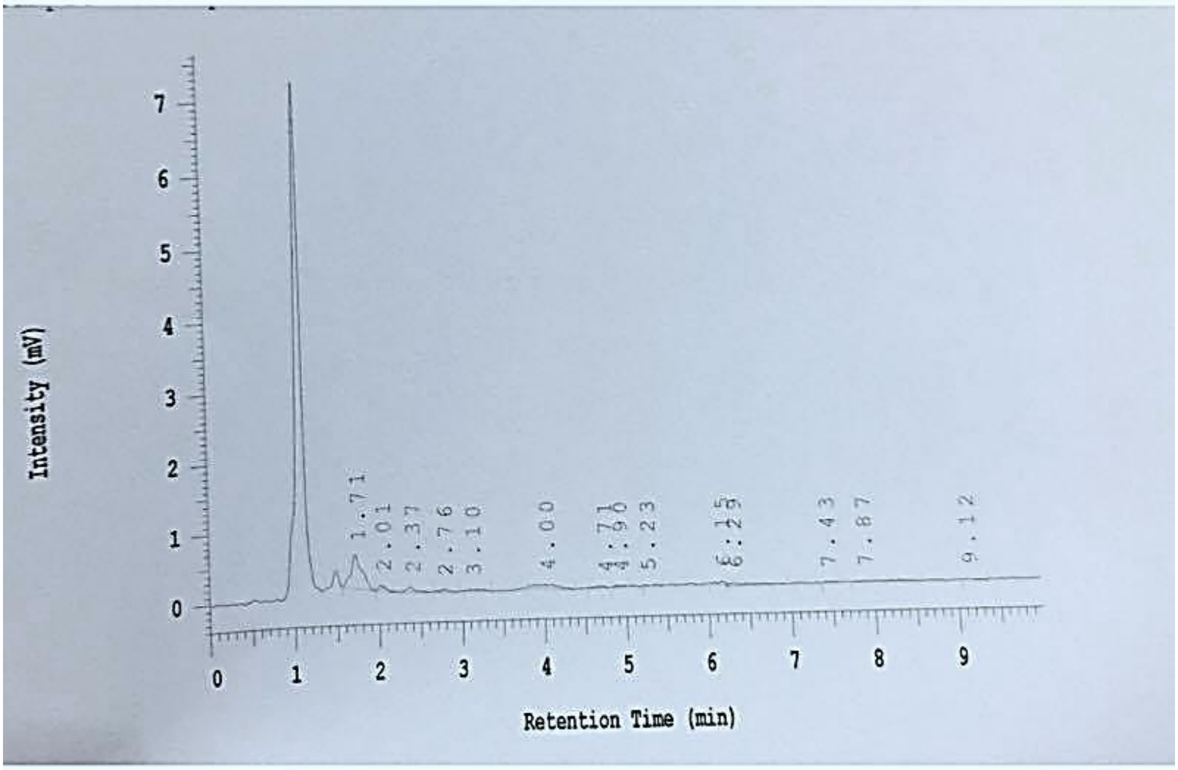


Figure 5.112: Monograph of CFA for system: W/O1570/T-MAZ 80/CCT

From all of figures presented above, it is clear that there are no response seen in all system studied except the standard reference sample, and it mayexplained as follows:

1. The active pharmaceutical ingredients (CFA) was dissolved in complex nonionic microemulsion systems haven't any clear procedure for permeability studies.

2. The membrane in franz diffusion analysis may not be suitable for complex microemulsion systems studied.
3. The quantity of CFA solubilized in microemulsion systems may not be enough to give a suitable permeation and hence not enough to give a response on HPLC analysis.
4. Another materials may need to be add in microemulsion systems to be suitable for franz cell analysis.

Finally, further extensive study should be done on permeability to solve the issues faced in this part of study.

Chapter Six

Conclusion

In this study, new microemulsion systems were developed using different types of oils, such as food grade single surfactant, sucrose oleate (O1570) and natural oils, R (+)-Limonene oil, isopropyl myristate oil and common edible oil caprylic-capric triglyceride. In additionit is used different types of co-surfactants (EtOH, PG, PrA and GLY) to formulate proper microemulsion systems, these co-surfactants could help to bring down the interfacial tension to a very low values in a combination of surfactant molecule. The phase behavior of mixed nonionic surfactants, O1570 + T-MAZ 80 with single oil and co-surfactant or with mixed oils were studied. Microemulsions formulated according to these strategies have advantages of very high microemulsification capacity, low surfactant residue, and low cost. This approach may reduce the cost and improve the performance of several industrial applications. Similarly, interfacial chemical reactions can be facilitated using microemulsionforming surfactants, in combination with indigenous cosurfactants.

Co-surfactants play an important role in solubilization of microemulsion systems. The role of alcohol like ethanol is to increase the fluidity of the interfacial layer by delay the occurrence of liquid crystalline phase and modify the curvature to less positive or negative, hence increase the cross-sectional area per surfactant molecule, in addition the presence of polyol molecules like propylene glycol and glycerol extended the water solubilization capacity; because polyols act as tuning parameters in microemulsion systems. It has hydroxyl group (OH) that strongly combined with water molecules by hydrogen bonds and increase the stability of microemulsions formed.

The water solubilization capacity study showed that the mixed nonionic microemulsion systems improve solubilization capacity to very high values compared to the microemulsion systems based on single surfactant. This improvement of solubilization capacity in mixed nonionic surfactants indicating of synergistic effect between mixed surfactants, this phenomena may be result of better mixed surfactants orientation around the oil droplets and allow to enhance the penetration in the interfacial film, the mix surfactants depends on the weight ratio and HLB value.

This study showed that different factors affecting on the water solubilization capacity and the total monophasic area A_T %, these factors are:

- Chain length compatibility (empirical BSO equation).
- Effective carbon number (ECN).
- Molecular volume of oil.
- Types of co-surfactants being involved in microemulsion systems.
- The chemical structures of oils.

The empirical BSO (Bansal, Shah and O'Connell) equation which was derived as empirical conditions for maximum water solubilization capacity in microemulsion systems stabilized by anionic surfactants in relation to the cosurfactant, alcohol, and oil chain lengths, i.e. $N_S = N_O + N_A$, where N_S, N_O, N_A are the surfactant chain lengths, oil and alcohol, respectively, was re-examined for this type of surfactants. This study demonstrates that a maximum water solubilization is obtained when the $N_S = (N_O \pm 3) + N_A$ for N_S is greater than 14; when N_S is less than 14, this equation cannot predict the maximum water solubilization. They concluded that the maximum amount of water which may be solubilized in such a microemulsion is reached when the oil chain length (carbon number), N_O, added to that of the co-surfactant (alcohol) chain length, N_A, is equal to the surfactant chain length, N_S, i.e. $N_S = N_O + N_A$. In the following, this is known as the BSO equation.

On single surfactant microemulsion systems (section 5.1.1), the chain length compatibility (BSO equation) plays a major role in determining the maximum water solubilization capacity; in this part, the IPM and CCT oils showed a maximum compatibility in variation according to type of co-surfactant used in microemulsions. Also we observed another important parameter that has affect on the water solubilization capacity, this parameter is the effective carbon number (ECN) of oils, co-surfactants and of surfactant, so the ECN and chain length compatibility (BSO equation) are strongly related to each other. The IMP and CCT oils has ECN values higher than LIM oil, for this reasons the IPM and CCT oils tends to have higher maximum water solubilization capacity compared to LIM oil.

On the contrary, the mixed nonionic microemulsion systems were studied (section 5.1.2) showed that the main driving factor is molecular volume of oil. Thus we observed that LIM oil give higher total monophasic area (A_T %) in all systems studied in this section, because LIM oil has the smallest molecular volume compared to IPM and CCT oils, moreover the synergistic effect between surfactants in mixed microemulsion systems may results of better solubilization capacity, these two reasons were consider the differences in results obtained from single surfactant and of mixed surfactants microemulsion systems.

The chemical structure of the oil affects its penetration in the surfactants palisade layer and determines the extent of water solubilization. We studiedthree different types of oils according to its structure, i.e., cyclic oil (LIM), linear oil (IPM) and triglyceride oil (CCT), the tendency of these oils to penetrate in the interfacial layer varied according to the structure of the oil, the LIM oil has more affinity to penetrate in the surfactant palisade layer; because it has sphere-like shape in three dimentional point of view, and IPM oil which has rod-like shape can penetrate in the interfacial film but with less affinity comparing to LIM oil, and the third one in penetration tendency is CCT oil that has plate-like shape in three dimentional arrangement. This shape hindered the ability of that oil to penetration in the surfactant palisade layer, and hence decrease the total monophasic area (A_T%) of microemulsion systems based on this oil.

Properties of microemulsions can be determined using various techniques such as electrical conductivity. The results of electrical conductivity was examined the structural transition of microemulsion systems along the dilution line N65 as a function of temperature and water volume fraction. Along the aqueous dilution line examined, electrical conductivity measurements confirm that the system undergoes a continuous structural transition of microemulsions from W/O via bicontinuous phase to O/W.

It can be concludes that the electrical conductivity values increase with the increase in temperature at a given dispersed phase volume fraction, due to the fact that increase in temperature will increase in kinetic energy which increase the collision between droplets and increase movement of ions. By increasing temperature, the collisions between droplets increases and the opening and reforming of droplets will increase the mobility of water and the electrical conductivity will gain rises with temperature. In addition, the possibility of percolation become larger and the formation of water channels will increase the electrical conductivity of the systems, also we indicated that the electrical conductivity values increased as a function of water content increased. This increase in electrical conductivity is due to the interaction between droplets and therefore ion exchanges are resulting by fraction of ionized droplets that are not enclosed in the core of microemulsion systems. at low water content, the electrical conductivity have low values indicates micelles microemulsions which in turn converted to water-in-oil microemulsion system by addition of water, so the droplets become contact to each other forming a clusters of droplet. This clusters generates a network produced by short range attractive interaction leads to important changes of the transport properties, such as droplet size, the rate of exchange of materials between droplets and electrical conductivity.

The phenomena has been described in terms of percolation. According to percolation model, the conductivity suddenly raising to give the high value at certain water volume fraction at constant temperature or at certain temperature with constant water volume fraction, however as the water volume fraction increase to reach the percolation threshold volume fraction the droplets contact to each other forming clusters, these clusters allow to exchange ions among droplet or from droplet to another by opening channels resulting of high electrical conductivity values.

The solubility of cefuroxime axetil in these microemulsion systems was investigated by dissolving in microemulsion. Microemulsion has unique properties that include high mutual solubilization of water and oil, that increase the solubility of active pharmaceutical ingredients cefuroxime axetil, the mixing of different types of oils with cosurfactant enhanced the solubilization capacity significantly. This interesting observation was explained by a hypothesis assuming non-ideal mixing of the oil and their penetration into surfactant layers. These formulations should help to improve the bioavailability of low soluble drugs.

The solubilization capacity of cefuroxime axetil in microemulsion systems was higher than any single component that formed the microemulsion. It was found that the solubilization curves for cefuroxime axetil showed different regions, a region at low water content (0 wt. % to 30 wt. %) the solubilization capacity reach a maximum values and the microemulsion system is micelles or reverse micelles (w/o). This highest values of solubilization capacity in this region is due to a high surface area and high oil content. At water content 40 wt. % to 60 wt. % the solubilization capacity become constant, because it is suggested that the microemulsion systems converted to bicontinuous, and the system formulate different types of microemulsions with low stability. Above 60 wt. % of water content have a lower solubilization capacity suggested that o/w microemulsion was formed, and the oil content will be decreased, resulting of modification of surfactant layer curvature. A small amount of oil exists in the core of the droplets and the interfacial layer convex towered oil phase resulting in low solubility in the core and poor accommodation of the drugs at the hydrophilic interface.

The solubilization capacity of cefuroxime axetil highly depends on the composition of the microemulsion system. The presence of alcohol as a cosurfactant and the oil type and its penetration at the interface both greatly affect the degree of cefuroxime axetil solubilization. The solubilization capacity of cefuroxime axetil depends on the microstructure, which means that the microemulsion type strongly influenced by the extent of cefuroxime axetil solubilization.

The drug interacts at the interface with the microemulsion components at any specific microstructure of the investigated vehicles and affects the water contents at which the transitions from w/o to bicontinuous to o/w microemulsions, so the drug release kinetics from these microemulsions should be affected. The drug remains solubilized at the interface upon dilution with water and is oriented with its hydrophilic part facing the water. In many of the formulations the drug is soluble in the concentrated capsule, but it precipitates at once if diluted with water. Our formulations are based on nonionic surfactants and therefore are more resistant to low pH and can survive the stomach dilution and acidity.

From all the above, we can conclude:

1. Microemulsion are thermodynamically stable mixture of at least two immiscible liquids (water, oil) imparted by surfactant (surface-active ingredients) forming films that separate these phases.

2. Microemulsions could be prepared by using oil, nonionic surfactant and water without Co-surfactant or using these components with cosurfactant and the optimum amount of water in this case increased with increasing the cosurfactant content.

3. Generally, the solubilization capacity for aqueous phase in case of using mix (O1570 + T-MAZ 80) as surfactant was higher than that in case of using of single surfactant systems.

4. The total monophasic region A_T % of cyclic oil is more than A_T % to triglyceride oils and linear oil in the case of mixed surfactants systems, and A_T % of triglyceride oils and linear oilare higher than cyclic oil in single surfactant microemulsion systems.

5. Increase the molecular volume causes a decrease in water solubilization and (the total monophasic region A_T %).

6. Increase in chain length compatibility and effective carbon number will increase the total monophasic area A_T %.

7. The maximum water solubilization obtained in this study was when the system contains water + mixed surfactants (O1570 + T-MAZ 80) + propylene glycol as a co-surfactant and LIM as oil.

8. The minimum water solubilization obtained in this study was when the system contains water + mixed surfactants (O1570 + T-MAZ 80) and CCT oil at weight ratio 2/1 (w/w) between mixed surfactants.

9. Solubility of cefuroxime axetil in microemulsions containing oil + cosurfactant as lipophilic phase was markedly higher than that in single oil without presence of cosurfactant, we concluded that the presence of ethanol as co-surfactant gives better solubility higher than in the presence of propylene glycol.

Finally, Microemulsions that have unique properties of high mutual solubility of oil and water will help in improvement of poorly water soluble drug and enhance the solubility of these drugs to be more efficient.

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المستحلبات الدقيقة المبنية على اساس خليط من مواد فعالة سطحيا: تحضير، تشخيص، إذابة السيفوركسيم آكستل، ودراسة النفاذية.

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الملخص

تهدف هذه الدراسة الى انشاء مستحلبات دقيقة (Microemulsions) ذات جزيئات صغير جدا تقل عن 100 نانوميتر عن طريق خلط مادتين لا يختلطا ببعضهما البعض (الزيت والماء) وذلك بإضافة خوافض التوتر السطحي (Surfactants) ومساعدات خوافض التوتر السطحي (Co–surfactants) مما يجعل هذه المواد تبدو بالعين المجردة كأنها حالة واحدة. تتميز المستحلبات الدقيقة بأنها شفافة، قليلة اللزوجة، ذات توتر سطحي صغير وثابتة لمدة طويلة من الزمن (thermodynamic stable)، حيث انه من خلال هذه الخصائص الفريدة التي تتمتع بها هذه المستحلبات الدقيقة يمكن استخدامها في العديد من التطبيقات العملية كالصناعات الغذائية والدوائية والعلوم المختلفة.

تناولت هذه الدراسة عدة انظمة تختلف فيما بينها في التركيب والنوعية ونسب المواد المضافة، حيث تم تشكيل نوعين من الانظمة والتي تختلف في نوع خافض التوتر السطحي المستخدم وهما الانظمة التي تعتمد على خافض توتر سطحي منفرد وتحتوي على (ماء/خوافض توتر سطحي منفرد/ مساعدات خوافض التوتر السطحي/ زيت)، اما النوع الثاني فيتكون من خوافض توتر سطحي مختلطة وتحتوي على (ماء/خوافض توتر سطحي مختلطة/ مساعدات خوافض التوتر السطحي/ زيت).

خوافض التوتر السطحي التي استخدمت في هذه الدراسة هي سكروز الاوليات (O1570) والسوربتان مونواوليت (T–MAZ 80) وتعتبر هذه خوافض توتر سطحي لا ايونية تختلف فيما بينها في التركيب البنائي ومدى قدرتها على الذوبان في الماء، اما مساعدات خوافض التوتر السطحي فقد تم استخدام مواد تدخل في الصناعات الغذائية والدوائية ومواد التجميل وهي الايثانول (EtOH)، البروبلين جلايكول (PG)، وحامض البربوبايونيك (PrA) والذي يستخدم في الصناعات الدوائية كمضاد للبكتيريا والجليسيرول (GLY) الذي يزيد من لزوجة الانظمة المشكلة، واما الزيوت المستخدمة التي تم استخدمها في هذه الدراسة فكانت: اولا زيوت عطرية حلقية مثل زيت الليمونين (LIM)، ثانيا زيوت خطية التركيب مثل زيت الايزوبروبل ميريستات (IPM) وثالثا زيوت ثلاثية الجليسيرايد مثل الكابريلك–كابرك ثلاثي الجلسريد (CCT).

في هذه الدراسة وجد ان المستحلبات الدقيقة المبنية على خوافض التوتر السطحي المختلطة (السكروز اولييت و السوربيتان مونواوليت) تعطي اكبر مساحة وحيدة الحالة (Total monophasic area) من تلك الانظمة المبنية على خافض توتر سطحي منفرد (O1570)، كما وجد ان المستحلبات الدقيقة المبنية على خليط من خوافض التوتر السطحي (السكروز اولييت و السوربيتان مونواوليت) وبوجود مساعدات خوافض التوتر السطحي (PG) وزيت الليمونين(LIM) في النظام (ماء/السكروز اولييت/السوربيتان مونواوليت/ زيت الليمونين/ البروبلين غلايكول) عند الخلط بنسبة 1:1 يعطي اعلى مساحة وحيدة الحالة بالمقارنة مع جميع الانظمة التي تم دراستها، ايضا وجد من خلال هذه الدراسة ان زيت الليمونين (LIM) يعطى اكبر مساحة وحيدة الحالة في جميع الانظمة المبنية على خوافض توتر سطحي مختلطة وبنسب متفاوتة، ايضا تم دراسة تاثير النسب في الخلط على المساحة وحيدة الحالة، حيث وجد ان النسبة 1:1 تعطي افضل مساحة وحيدة الحالة في الانظمة المبنية على خليط من خوافض التوتر السطحي (السكروز اولييت والسوربيتان مونواوليت) بالمقارنة مع النسب 1:2 و 2:1.

ومن الأهداف الأخرى لهذه الدراسة هو تبيان و توضيح البناء الجزيئي الدقيق للمنطقة المكونة من طبقة واحدة وذلك باستخدام جهاز التوصيل الكهربائي، حيث وجد أن التوصيل الكهربائي للمستحلبات الدقيقة والمبنية من مركب مستحلب خليط تعتمد بشكل أساسي على محتوى الماء داخل المستحلبات الدقيقة.كذلك وجد أن أعلى قيمة للتوصيل الكهربائي للمستحلبات الدقيقة التي تم دراستها تحدث عندما تزيد كمية الماء على الزيت مما يدل على تحول في شكل التركيب الداخلي للمستحلب الدقيق من (ماء في زيت) الى (زيت في ماء)، كما لوحظ انه بزيادة درجة الحرارة تزداد قيم التوصيل الكهربائي وتقل عند تحولها الى (زيت في ماء) بشكل قليل.

من اهم اهداف هذه الدراسة هو استكشاف مدى قدرة هذه المستحلبات الدقيقة (Microemulsions) على اذابة العقاقير الدوائية ذات القدرة المنخفضة جدا على ذوبانها في الماء وذلك بسبب القدرة الفريدة لهذه المستحلبات في اذابة العقاقير ذات الذائبية المنخفضة في الماء، كما انها ثابتة لمدة طويلة من الزمن وشفافة. تم استخدام دواء السيفوركسيم اكستل وهو دواء يصنف بانه قليل الذائبية في الماء حيث وجد أن سعة الذائبية للعقاقير المستخدمة في الدراسة تقل مع زيادة محتوى الماء في المستحلب الدقيق وهذا دليل على حدوث تغير في التركيب الداخلي للمستحلبات الدقيقة.