

Phase behavior, Microstructure and Solubilization Capacity
Studies of Nonionic Surfactants Microemulsion Systems

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Thesis Approval

DEDICATION

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by wife Dr. Sahar

by Mother and

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Declaration

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

Signed.....

Samer Ibrahim Abdelqader Mudalal

Date...24/06/2007

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Abstract

The phase behaviors of microemulsions composed of peppermint oil, benzaldehyde, sesame oil, olive oil as non-polar phase and sucrose ester surfactants (sucrose monolaurate, dilaurate, palmitate, stearate), sorbitan ester (sorbitan monooleate, Polyoxyethylene sorbitan monooleate), ethoxylated mono-diglycerides (EMDG) as amphiphilic compounds were studied at different temperature (25, 37, 45 °C) with and without propylene glycol as cosolvent. The largest one phase regions were for microemulsion systems based on peppermint oil. The effect of mixing ethoxylated mono-diglycerides with sucrose ester surfactants on total mono phasic area (A_T) was examined. Mixed microemulsion systems showed larger total mono phasic area (A_T) than single microemulsion systems. Conductivity and viscosity has been measured to study the microstructural transitions of single microemulsion (sucrose monolaurate and dilaurate) with peppermint and benzaldehyde, and mixed microemulsion systems (ethoxylated mono-diglycerides + Sucrose mono laurate) at different ratios (50:50, 75:25, and 25:75). The electrical conductivity for single and mixed microemulsion systems depends mainly on water content and sharp increase in conductivity were occurred at nearly equal amount of oil and water in which indicating on the first structural transition (w/o to bicontinuous structure). Viscosity of single and mixed microemulsion systems showed small increase at the beginning of the curve that represents water content versus viscosity and then decrease with increase in water

content. On the other hand, solubilization capacity of Celecoxib and Azithromycin drugs (low water solubility drugs) in single microemulsion systems based on sucrose monolaurate and peppermint oil and in mixed microemulsion system (EMDG+L1695) in presence of ethanol as cosurfactant or propylene glycol as cosolvent or the combination of the two were studied. The solubilization capacity of these drugs decrease with water content increase, introducing propylene glycol increase solubilization capacity while ethanol decreases solubilization capacity.

الملخص

يهدف هذا البحث إلى دراسة سلوك مراحل المستحلبات الدقيقة المكونة من زيت النعناع و زيت اللوز و زيت السمسم و زيت الزيتون كوسط غير قطبي و من مركبات مستحلبة مثل: ايسترات السكروز (سكروز مؤستر من : أحادي اللوريك، ثنائي اللوريك، بالمتيت، ستيريت) ، ايسترات السوربتان (سوربيتان أحادي اوليت، سوربيتان متعدد اوكسيد الايثلين)، جليسيريد احادي و ثنائي اوكسيد الايثلين على درجات حرارة مختلفة (٢٥،٣٧،٤٥م°) بوجود أو عدم وجود البروبيلين جليكول كمذيب مساعد، من خلال الدراسة وجد أن المستحلبات الدقيقة المبنية في تركيبها على زيت النعناع تعطي اكبر مساحة وحيدة الحالة في رسومات الحالات للمستحلب الدقيق من أي زيت اخر، كذلك تم دراسة اثر استخدام خليط من المركبات المستحلبة مثل : ايسترات السكروز و جليسيريد أحادي و ثنائي اوكسيد الايثلين بنسب مختلفة عوضا عن مركب منفرد في تكوين المستحلبات الدقيقة حيث وجد أن استخدام خليط من هذه المركبات يعطي مساحة وحيدة الحالة على منحنى الرسم اكبر بالمقارنة مع استخدام مركب منفرد، التوصيل الكهربائي و اللزوجة تم قياسهما للمستحلبات الدقيقة المبنية في تركيبها على ايسترات السكروز و جليسيريد أحادي و ثنائي اوكسيد الايثلين كمركبات مستحلبة سواء كانت منفردة أو ممزوجة بنسب مختلفة و زيت النعناع و اللوز كوسط غير قطبي لدراسة أنواع أشكال التراكيب الدقيقة و تغيراتها، حيث وجد أن التوصيل الكهربائي للمستحلبات الدقيقة سواء كانت مبنية من مركب مستحلب منفرد أو مزيج من المستحلبات تعتمد بشكل أساسي على محتوى الماء داخل المستحلبات الدقيقة. كذلك وجد أن أعلى قيمة للتوصيل الكهربائي للمستحلبات الدقيقة التي تم دراستها تحدث عندما تتساوى كمية الماء و الزيت مما يدل على تحول في شكل التركيب الدقيق من تركيب منفصل (ماء في زيت) إلى تركيب متصل من الماء و الزيت، وجد أن اللزوجة التي تم قياسها للمستحلبات الدقيقة سواء كانت مبنية من مركب مستحلب منفرد أو مزيج أنها تزيد في بداية المنحنى الذي يمثل العلاقة بين اللزوجة و محتوى الماء و بعد ذلك تبدأ اللزوجة بالانخفاض مع زيادة محتوى الماء، من ناحية أخرى تم دراسة سعة الذائبة لعقاقير (ذات ذائبة منخفضة جدا في الماء) مثل السيليكوكسيب و الازيثروميسين في مستحلبات دقيقة مبنية في تركيبها على مركب مستحلب منفرد (سكروز أحادي اللوريك) و كذلك على مزيج من المركبات المستحلبة (السكروز أحادي اللوريك و جليسيريد أحادي و ثنائي اوكسيد الايثلين) بوجود الايثانول كمستحلب مساعد أو البروبيلين جليكول كمذيب مساعد أو من الاثنين معا حيث وجد أن سعة الذائبة للعقاقير المستخدمة في الدراسة تقل مع زيادة محتوى الماء في المستحلب الدقيق و تزيد بوجود البروبيلين جليكول و تنخفض بوجود الايثانول في تراكيب المستحلبات الدقيقة.

CHAPTER ONE

INTRODUCTION

1. Introduction:

Microemulsions are isotropic, transparent fine dispersions of two immiscible phases (water and oil) stabilized by amphiphilic compounds (surfactants) in the form of small droplets. Surfactants form flexible interfacial film with low interfacial tension values. Microemulsion structures can be obtained in three forms: oil in water (O/W), water in oil (W/O), and bicontinuous structure [1, 2].

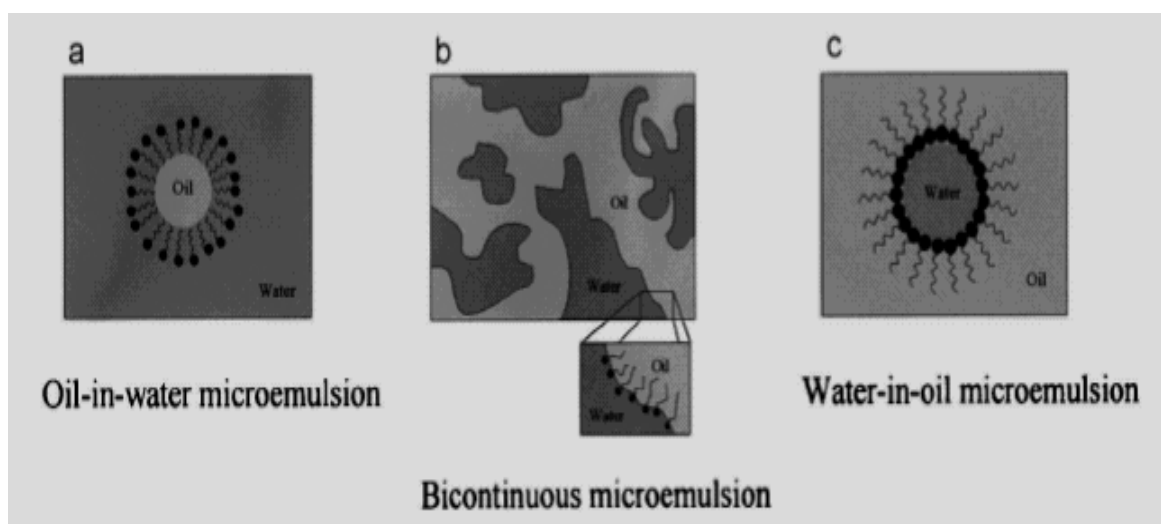


Figure 1.1: Schematic representation of the three most commonly encountered microemulsion microstructure: (a) oil-in-water (b) bicontinuous and (c) water-in-oil microemulsion [2].

Microemulsions that are formed from: 1)- oil, 2)- water, and 3)- surfactant only called ternary systems. But in many cases, microemulsions cannot be formed without co-surfactants (alcohol) or co-solvents or the two in the same time. In this case microemulsions are called pseudo- or quaternary systems. Co-surfactants decrease the interfacial tension on the interface of surfactants film between oil and water. A long alcohol chain increases the interfacial rigidity, and shorter alcohols are favorable to a disordered interfacial film [3, 4].

The advantages of microemulsions over emulsions or other solutions are either improved stability or solubility characteristics. Microemulsions also have the potential ability to solubilize both lipophilic and hydrophilic agents, which allows for a variety of flavouring and coloring materials having vastly different physical properties to be dissolved in the system. An additional important feature of phospholipid-based microemulsions is in their ability to solubilize larger guest molecules [8, 19, 30].

The most characteristic difference between an emulsion and a microemulsion is their appearance. An emulsion is turbid while the microemulsion is almost transparent. The reason for this difference in appearance is the size of the droplets. For an emulsion the droplets are similar or greater than the wave length of light and light is reflected off their droplets. The emulsion, hence, appears turbid because the light cannot penetrate through it. On the other hand the size of microemulsion droplets is smaller than the wave length of light, and the interaction with light is limited to scattering. The light beam passes through with little loss; consequently the microemulsion appears transparent. The microemulsions are thermodynamically stable with few exceptions, but the emulsions are not thermodynamically stable because the interfacial energy is positive and dominant in total free energy, where its droplet is of a size that the bending energy is negligible and the surface free energy is large and positive; a few mN/m. The surface tension of the microemulsion has two components stretching (positive contribution) and bending (negative contribution). The two cancel each other and the total surface free energy is extremely small about 10^{-3} mN/m. Moreover, the microemulsions form spontaneously or need gentle shaking for short time (few minutes) to miscible the components [20, 21, 25, 29, 30].

Microemulsions characteristic enable them to be used as drug carriers for topical, oral, and parenteral administration. Due to the small size of the droplets (less than 100 nm) and high surface area, microemulsion may be used as microreactors for different chemical and biochemical reactions. Microemulsion droplets may work as packaging material for food ingredients that are sensitive to light, oxygen, heat, and microorganisms. The use of microemulsions have rapidly grown as solvent flooding liquids in enhanced oil recovery process, in skin and body care products, in nano-particles synthesis, and effective drug delivery systems [1,3,10,11,18].

Hydrophilic-Lipophilic number (HLB) of the surfactant have great effect on the type and phase behavior of the microemulsions. If the HLB increases, the hydrophilic part of the surfactant will increase, and the surfactants will have strong affinity to water phase forming O/W- microemulsion such as mono and di-ester of sucrose, and if the HLB decreases, the lipophilic part of the surfactant will increase, and the surfactants will have strong affinity to oil phase forming W/O microemulsions such as polyester of sucrose [5, 6].

The phase behavior and microstructure of microemulsions can be determined by spontaneous curvature (H_0) of the surfactant monolayer at the oil-water interface. Hydrophilic surfactants produce oil-in-water (O/W) microemulsions ($H_0 > 0$), whereas lipophilic surfactants produce water-in-oil (W/O) microemulsions ($H_0 < 0$). When the hydrophilic-lipophilic properties of the surfactant monolayers at the oil-water interface are balanced, bicontinuous-type microemulsions are formed ($H_0 = 0$). Maximum solubilization of water and oil with the minimum amount of surfactant is achieved at balanced conditions ($H_0 = 0$). The bicontinuous microemulsion phase may coexist with excess water and oil phases and ultra low interfacial tensions between the coexisting phases are attained [5, 12].

Type of microemulsion which is formed in a given system can be predicted by the surfactant packing parameter which is defined by Israelachvili et al. as $V/a_0 L_c$ where v is the surfactant molecular chain volume, a_0 the area per surfactant head group and L_c the surfactant alkyl chain length. This parameter relates the properties of the surfactant film. For $V/a_0 L_c < 1$, the surfactant prefers curvature toward oil, whereas for $V/a_0 L_c > 1$ it prefers to curve toward the water. For quantitative analysis, however, it is advantageous to consider the spontaneous curvature H_0 as the basic property of a film [5, 8].

Microemulsions systems which are consisted of nonionic surfactant, water, and oil with or without co-surfactant and their phase diagrams behavior, solubilization capacity, and types of microstructure have been studied by many scientists. Most of these researches concentrated on ethoxylated alcohols, acids, fats, etc. but small number of researches studied polyol types of nonionic surfactants, such as ethers (sucrose glycosides) or ester (sucrose ester). Most studies and research efforts have focused on the progress of microemulsions with standard surfactants that are prohibited in foods formulations, such as, polyoxyethylene-type nonionic surfactants, alkyl sulfates, quaternary ammonium salts and dialkyl sulfosuccinate [5, 9, 12].

The first application of microemulsions in food has been described through number of papers by Schulman and Hoar in 1943 [33]. Duxbury studied the fortification of milk by vitamin A solubilized in a microemulsion. Dissolving essential oils in microemulsions to be used in beverage industry has been studied by Wolf and Havekotte [33]. Using microemulsion to increase the lipase efficiency or activity to hydrolyze milk fat in dairy industry has been studied by Chen and Pai. The ability of microemulsion to increase vitamin C stability and decreasing oxidation rate have been studied by Gallarate et al [33]. They found that the rate of oxidation of linolic and ethyl linoleate in microemulsion decrease and their result

showed that the structure of interface protect the systems from autooxidation [4, 19, 30].

In general, applications of microemulsions in food industry are very limited due to many reasons: firstly, is the cost and quantity of surfactant used in microemulsion. Secondly, level of surfactant used in microemulsion may not comply with FDA regulations. Thirdly the difficulty to prepare microemulsion from oils and fats used in foods [4, 19, 30].

Today, the new studies and researches are being focused on the formulation of microemulsion based on food-grade surfactants that are limited in their number and structure. Among the hydrophobic surfactants one can find mono- and diglycerides of fatty acids; sorbitan esters, polyglycerol esters, such as polyglycerol polyricinoleate (PGPR) and sucrose ester (sucrose polystearate). Among the hydrophilic surfactants, the selection is somewhat larger, and emulsifiers such as ethoxylated sorbitan esters, polyglycerol esters, sodium stearyl lactylate and sucrose esters, are food-grade compounds [5, 6].

Sucrose esters surfactants have unique properties (biodegradable, nontoxic and capable of forming temperature-insensitive microemulsions), which make them suitable for a variety of food-based and pharmaceutical application. Sucrose contains in its structure eight-hydroxyl groups that can be esterified. If the esterification degree increases on the hydroxyl groups by fatty acids, the hydrophobicity will increase. Partial esterification will produce sucrose ester with amphiphilic properties. Mono, di and tri ester of sucrose usually used as emulsifier in foods, cosmetic, detergent, etc. sucrose ester molecule has the following structure [5, 11].

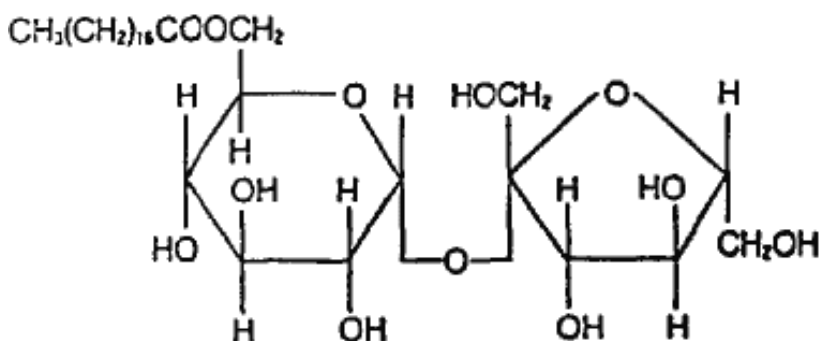


Figure 1.2: Chemical structure of sucrose monostearate

Sucrose-esters have unique emulsification properties such as any hydrophilic-lipophilic balanced can be produced, hydrophilic and lipophilic balance of sucrose esters do not change with temperature on contrast to ethoxylated derivatives. Sucrose ester which is produced commercially although much improved in consistency, are complex mixtures of various internal compositions of different chain lengths of fatty acids, mono-, di-, tri- or polysubstitutions on the hydroxyl groups, free fats or fatty acids, etc. Sucrose esters are tasteless, odorless, nontoxic, non irritant to eyes and skin, biodegradable and approved as food, pharmaceutical and cosmetics emulsifiers in most countries of the world. These surfactants offer a full range of Hydrophilic-Lipophilic Balance (HLB) values from 1 to 16 [5, 9, 15].

Sorbitan fatty acid esters are non-ionic surfactant-active agents that typically find use as emulsifiers, stabilizers and thickeners in foods, cosmetics, medical products, lubricants and other applications. Chemically, the sorbitan esters category is comprised of substances that are ester derivatives of sorbitan (which is derived from sorbitol - a natural carbohydrate sweetener) and monoacids (derived from natural fatty acids). The natural fatty acids may include lauric, stearic, oleic acids and coconut fatty acids (mainly lauric and myristic acids). Thus, sorbitan esters can be regarded as carbohydrate-derived esters with ester linkage(s) to the hydroxyl group(s) of sorbitan. Although there are four hydroxyl groups in sorbitan available for esterification, most of the sorbitan esters list on HVP (high

production volume) under EPA (Environmental Protection Agency) is monoester derivatives. Metabolism of the sorbitan esters in animals has been reported to occur initially via enzymatic hydrolysis, leading to sorbitan and the corresponding natural fatty acids [4, 8].

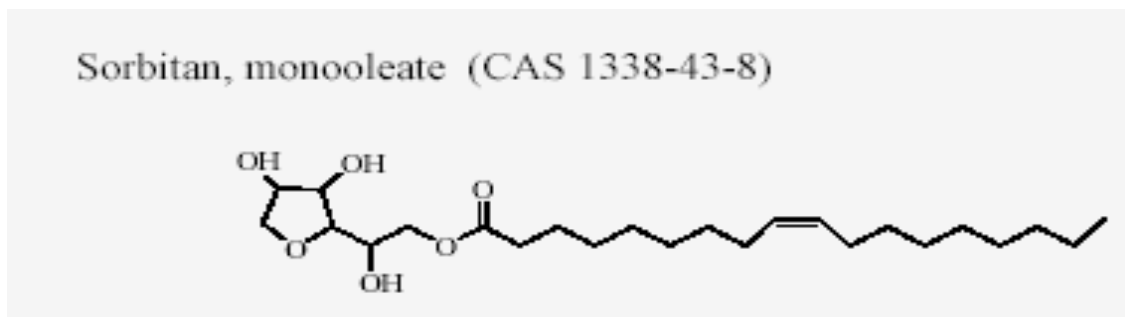


Figure 1.3: Structure of sorbitan monooleate (SMAZ80)

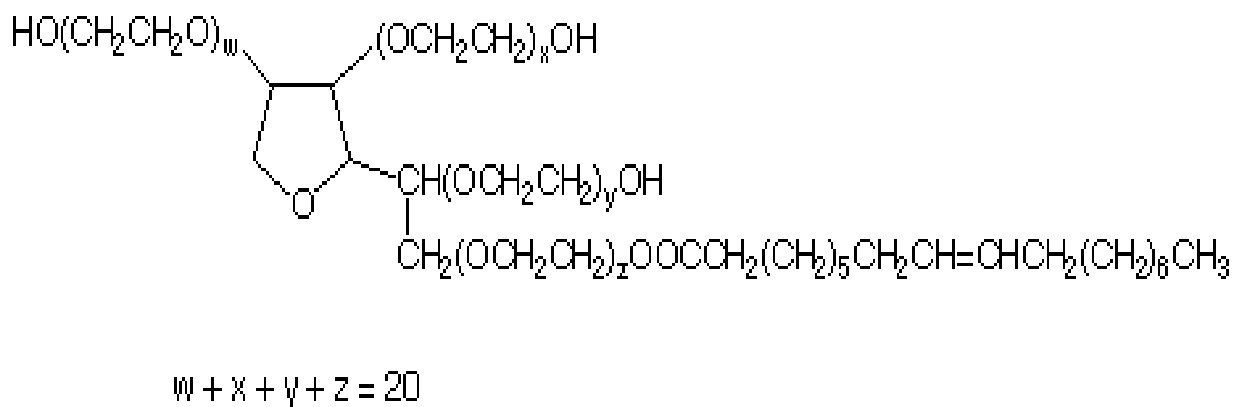


Figure 1.4: Sorbitan Polyethylene oxide structure (TMAZ80).

Ethoxylated fatty alcohols are generally recognized as the least toxic of the nonionic surfactants for industrial applications. The choice of suitable surfactants for the formation of food grade O/W microemulsions is very limited. Polyoxyethylene sorbitan esters (Tweens) are probably the most widely used, commercially inexpensive, and readily available food grade surfactants. They have bulky polyoxyethylene head groups attached to a sorbitan ring, which increases the hydrophilicity of sorbitan fatty ester [4, 8].

Most commercially available surfactants are composed of a mixture of surfactants. Understanding the mixed surfactants behavior in the presence of water and oil is an important issue for the development and the optimal design of mixed surfactants based microemulsions for industrial applications. Mixed surfactant systems are of great importance for the reasons: many technical grade surfactants are mixture of chain lengths or isomers and the surface activity of a mixture of surfactants is not being as the individual components. These reasons beside the fact that in industrial applications it may be necessary to obtain microemulsions in a given range of composition or temperature with given oil or surfactant. Adding second surfactant can tune the phase behavior in the desired direction. The properties and applications of mixed surfactant systems have much been studied in the recent years [13, 14, 15].

Static or dynamic light scattering, dielectric relaxation, time-resolved fluorescence or phosphorescence quenching, an electric field or temperature jump, a small angle X-ray scattering (SAXS), a small-angle neutron scattering (SANS), nuclear magnetic resonance (NMR) techniques have been developed recently to study the microstructure of microemulsions. these techniques can give valuable information about the core and surface monolayer structure, the polydispersity, the particle size distribution, the droplet clustering and diffusion dynamics, the interdroplet exchange rate and the monolayer fluidity [6,7, 8, 16,17, 30].

In industrial applications, there is an interest in formulating nonionic, nontoxic, biodegradable microemulsions with high solubilization power and temperature insensitivity. Increasing aqueous solubility of pharmaceutical active ingredients improves their efficacy, allow a reduction in the total dose needed, and minimize their toxic side effects. Solubilization of drugs by surfactant systems as

microemulsions can be useful as a new pharmaceutical dosage forms for overcoming solubility problems [19, 20].

In this study we aim firstly to explore the phase behavior of pharmaceutical grade microemulsion based on nonionic sucrose esters (SE) , sorbitan ester, and ethoxylated mono-diglycerides in the presence of water (W), peppermint oil (MNT), benzaldehyde oil, ethanol (EtOH) and propylene glycol (PG) in order to determine the regions of microemulsion phase, secondly, probe the microstructure of the formed microemulsions using electrical conductivity, dynamic viscosity and finally, solubilization of Azithromycin a pharmaceutical active ingredient used in the acni vulgaris treatment in the formulated microemulsions and also Celecoxib, and determining the correlation between the microstructure of microemulsions and the quantity of solubilized material [24,30].

Formulating microemulsions composed from food grade components with minimum amount of surfactant and maximum amount of water was one of the major directions in recent researches. Using of these microemulsions systems to solubilize a wide spectrum of lipophilic and hydrophilic compounds such as drugs, vitamins, colors, etc. studying the correlation between solubilization and microstructure of microemulsion was the second major direction in recent studies [8, 12, 19].

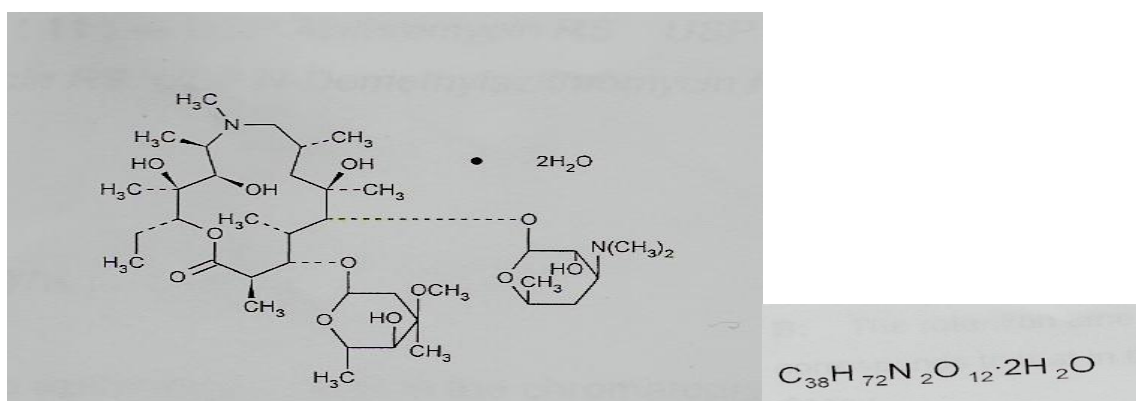
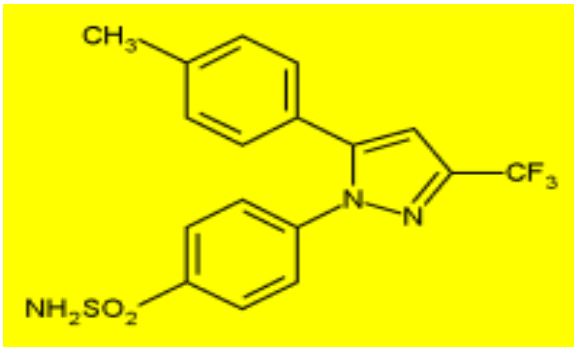


Figure 1.5: Azithromycin structure



Chemical formula C₁₇H₁₄F₃N₃O₂S

Figure 1.6: Celecoxib structure

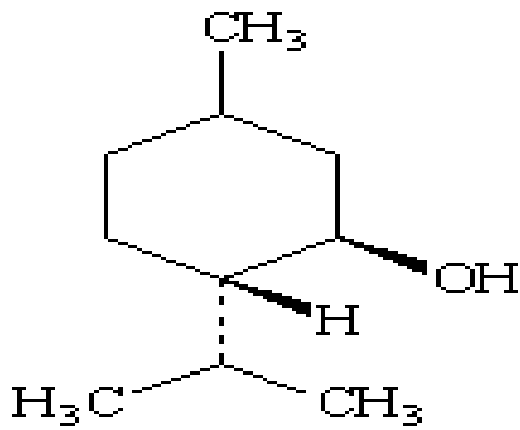


Figure 1.7: Menthol Major Compound of peppermint oil.

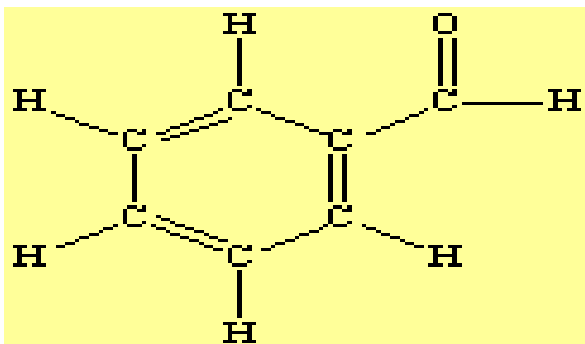


Figure 1.8: Benzaldehyde structure.

CHAPTER TWO

OBJECTIVES

2. Objectives

Our research aim to study the two directions. The first is formulating microemulsions composed of food grade surfactants with minimum amount of surfactants and maximum amount of water and investigating physicochemical properties for these formulation. The second is using these formulations to solubilize drugs concentrating on specific types of nonionic surfactants and oils. Our objectives can be summarized as:

1. Study of the phase behavior of microemulsion systems based on single and mixed nonionic food and pharmaceutical grade surfactant, co-surfactant, co-solvent and vegetable oils in order to determine the microemulsion phase regions. This is accomplished by the investigation of multi components system phase diagrams (ternary, psuedoternary, and quaternary systems).
2. Evaluation of the water solubilization capacity of the prepared microemulsion systems.
3. Exploring the microstructures of the formed microemulsion by electrical conductivity and viscosity measurements. These techniques will be used to study how changes in the relative amounts of the surfactant and in the chain length of the surfactants or oil, the presence of co-surfactant and the addition of water influence the microemulsion microstructure within the one-phase region.

4. Solubilization of pharmaceutical active ingredients (Celecoxib and Azithromycin) in the dispersed phase of the microemulsion and find a correlation between the microstructure of microemulsion and the quantity of solubilized materials.

CHAPTER THREE

MATERIALS AND METHODS

3. Materials and Methods

3.1 Materials

Mitsubishi-Kasei Food Corporation, Mie, Japan supplied sucrose ester surfactants. sorbitan esters and Ethoxylated mono-di glycerides were supplied by BASF Corporation-Gurnee Illinois, USA. Table 3.1 show the types of surfactants used in this study:

Table 3.1: surfactants that are used in the study with scientific and trade name, HLB numbers, and monoester percentage.

<i>Surfactants</i>	<i>Trade name</i>	<i>HLB</i>	<i>% monoester</i>
Sucrose dilaurate	L595	5	30
Sucrose mono laurate	L1695	16	80
Sucrose oleate	O1570	15	70
Sucrose palmitate	P1570	15	70
Sucrose stearate	S1570	15	70
Sucrose caprate	SM1000		
Sucrose laurate	SM1200		95
a mixture of stearate and palmitate partial esters of glycerin ethoxylated with approximately 20 moles of ethylene oxide per mole of alpha-mono-glyceride reaction mixture	EMDG	13.5	
Polyoxyethylene sorbitan monooleate	TMAZ80	17	
Sorbitan monooleate	SMAZ80	15	

Benzaldehyde , Sesame oils, Propylene glycol (99.5%) were supplied by Sigma Chemical Co/Germany. Extra virgin filtrated olive oil was supplied by Palestinian Agricultural Relief Committees. Peppermint oil and ethyl alcohol were purchased by Frutarum Co. Haifa, Israel. NaCL, double distilled water ($\sigma < 3 \mu\text{S}$).

Table 3.2: Sesame and olive oils composition

<i>Fatty acids</i>	<i>Olive oil</i>	<i>Sesame oil</i>
Oleic (18:1)	78 %	40.4-44.9%
Linoleic (18:2)	7%	37.7-43.4%
Linolenic (18:3)	1%	1%
Stearic (18:0)	2%	4.8-6.1%
Palmitic (16:0)	10%	9.1-9.8%
Others	2%	1%

Active pharmaceutical ingredients were supplied from ALEBIC (azithromycin) and IPCA Company/ India (celecoxib).

3.2 Methods

3.2.1 Construction of ternary and pseudoternary phase diagram

1 g of mixture of oils and surfactants at different ratios were weighted into screw cap tubes and stirred at high temperature (60-70 °C) by vortex until clear solution was obtained and kept in a thermostat ($\pm 0.5^\circ\text{C}$). Then phase diagrams were drawn by titrating 1g of these samples with an aliquot of double distilled-water in the case of ternary systems until the boundaries of the microemulsions zones were reached. For pseudoternary systems, 1g of these samples is titrated with a mixture of double distilled water and propylene glycol (co-solvent 67: 33). Microemulsions areas were checked visually by examination of the optical clarity and fluidity of resulting preparation. All experiments were performed at $T=25^\circ\text{C}$, $T=37^\circ\text{C}$, and $T=45^\circ\text{C}$ except for mixed surfactants systems were performed at $T=25^\circ\text{C}$ only.

Ternary Systems, which will be studied at different temperature (25, 37, 45 °C) as follow:

Table 3.3: Microemulsion systems which will be studied

<i>Oil phase</i>	<i>Surfactant</i>	<i>Co-surfactant</i>	<i>Co-solvent</i>	<i>Aqueous phase</i>
*Peppermint oil	EMDG	-	With and without propylene glycol	Double distilled water
*Benzaldehyde oil	SM1200			
	SM1000			
*Sesame oil	SMAZ80			
*Olive oil	TMAZ80			
	L595			
	L1695			
	S1570			

Quaternary systems, which will be studied, are the same of the ternary systems at the same conditions (temperatures) but in the presence of propylene glycol as co-solvent.

On other hand, quaternary systems with mixed surfactant will be studied at 25 °C as in the following table:

Table 3.4: Microemulsion systems which will be studied based on mixed surfactants

<i>Oil phase</i>	<i>Mixed surfactant</i>	<i>Aqueous phase</i>
Peppermint oil	EMDG+M1695	Double distilled water
	EMDG+L595	
	EMDG+L1695	
	EMDG+ O1570	

3.2.2- Electroconductive measurements

A long experimental path investigated, 20 samples were prepared from each microemulsion system, each sample contained 10 ml that was prepared from oil, water with 0.05 and 0.01M NaCl solution, and surfactants with different water contents (5% each step). The conductivity (σ) was measured by means of Inolab Cond Level 1, Wissenschaftlich Technische Werkstätten, D-82362 Weilheim, Germany. The conductivity meter was calibrated using standard KCL solutions at every measurement of microemulsion system. The conductivity cell was immersed in the microemulsion sample until equilibrium was reached and reading became stable. All measurements were taken within ± 0.5 °C.

3.2.3-Viscosity measurements

The same samples which were prepared for electroconductive measurements were used to measure the viscosity. Capillary viscometer was used to determine the viscosity, flow behavior, and the form of aggregation of the water/ surfactant/oil. Viscosity measurements are performed by capillary viscometer. Viscosity is determined by the following equation:

$$\eta_1/\eta_2 = (\rho_1 * t_1)/(t_2 * \rho_2)$$

Where :

η_1 : viscosity of microemulsions

ρ_1 : density of microemulsions

t_1 : time consumed for microemulsions to travel through capillary

η_2 : viscosity of distilled water at 25 °C

ρ_2 : density of distilled water at 25 °C

t_2 : time consumed for water to travel through capillary

3.2.4 Solubilization capacity

Solubilization of celecoxib and azithromycin has been studied in different microemulsion systems. 10 g of microemulsion was prepared in a test tube and a small amount of antibiotic (about 3 mg in each step) was then added and dissolution was performed by mixing through a vortex in water bath at 60°C. The dissolved amount of antibiotic was estimated by accumulated weight of antibiotic before the first precipitate nucleus of antibiotic appeared in the bottom of test tube after they hold in water bath at 25 °C for at least 24 hour.

CHAPTER FOUR

RESULTS AND DISCUSSION

4. Results and Discussion

4.1 Water solubilization

Bansal *et al.* [31, 32] reported that the conditions necessary for microemulsion formation are:

1. Large adsorption of surfactant or surfactant/co-surfactant mixture at the interface between the oil and water which achieved by choosing a surfactant mixture with proper hydrophilic lipophilic- balance (HLB).
2. High fluidity of the interface: The interfacial fluidity can be developed by using a proper cosurfactant or an optimum temperature.
3. Optimum curvature: The importance of oil penetration in the surfactant /cosurfactant film and the appropriate surfactant/cosurfactant structures.

A microemulsion that contains a relatively low content of oil confined within small isolated droplets dispersed in water is known as oil-in-water (O/W) microemulsion, while the reverse type (small amount of water dispersed in large amount of oil) is water-in-oil (W/O) microemulsion. Upon continuously increasing the water-to-oil ratio in a W/O microemulsion, phase inversion occurs. An intermediate transparent, isotropic bicontinuous structure may form during such an inversion, involving both oil and water-continuous domains separated by interfacial surfactant film. Under appropriate conditions the microemulsion system is miscible with both oil and aqueous phase. However, the microemulsion system partitions into three phases, a surfactant-rich phase, a surfactant rich aqueous phase and surfactant-rich oil phase. The surfactant-rich phase is called a middle phase microemulsion. It is in the middle phase microemulsion where a surfactant shows the greatest solubilizing power for both water and oil; here it also gives ultra small values of interfacial tensions between oil and water which

are less than 10^{-2} mN/m under proper conditions. The nature and structure of the surfactant, cosurfactant and oil are important factors in the preparation of microemulsions [31, 32].

Various microemulsion systems were prepared by using a number of natural oils as lipophilic phase such as peppermint, sesame, olive, benzaldehyde oil. A proper food surfactant such as sucrose ester, sorbitan ester, ethoxylated surfactants was used as emulsifier. The aqueous phase was either water in the absence or presence of ethanol as cosurfactant in the presence or absence of propylene glycol as co-solvent [32, 33].

Three, four, and five component systems were described on ternary and pseudo-ternary phase diagram. They were constructed at 25, 37, 45 °C for single surfactant system and just at 25 °C for mixed surfactants [22, 32].

Two suitable solubilization parameters were used in this work to compare the solubilization of different food grade nonionic surfactants: maximal amount of aqueous phase (water, and polyol) is denoted as W_m and total monophasic region, is denoted as A_T . W_m was determined from the titration with the aqueous phase (water, and polyol mixture). The relative error in the calculation of A_T (%) and W_m (wt. %) was estimated as $\pm 4\%$ [2, 32].

4.1.1 Phase Diagram

Total monophasic area was obtained from phase diagram plotted as a function of degree of monoester and surfactant chain length for all types of microemulsion systems used in this study.

4.1.1.1 Ternary system

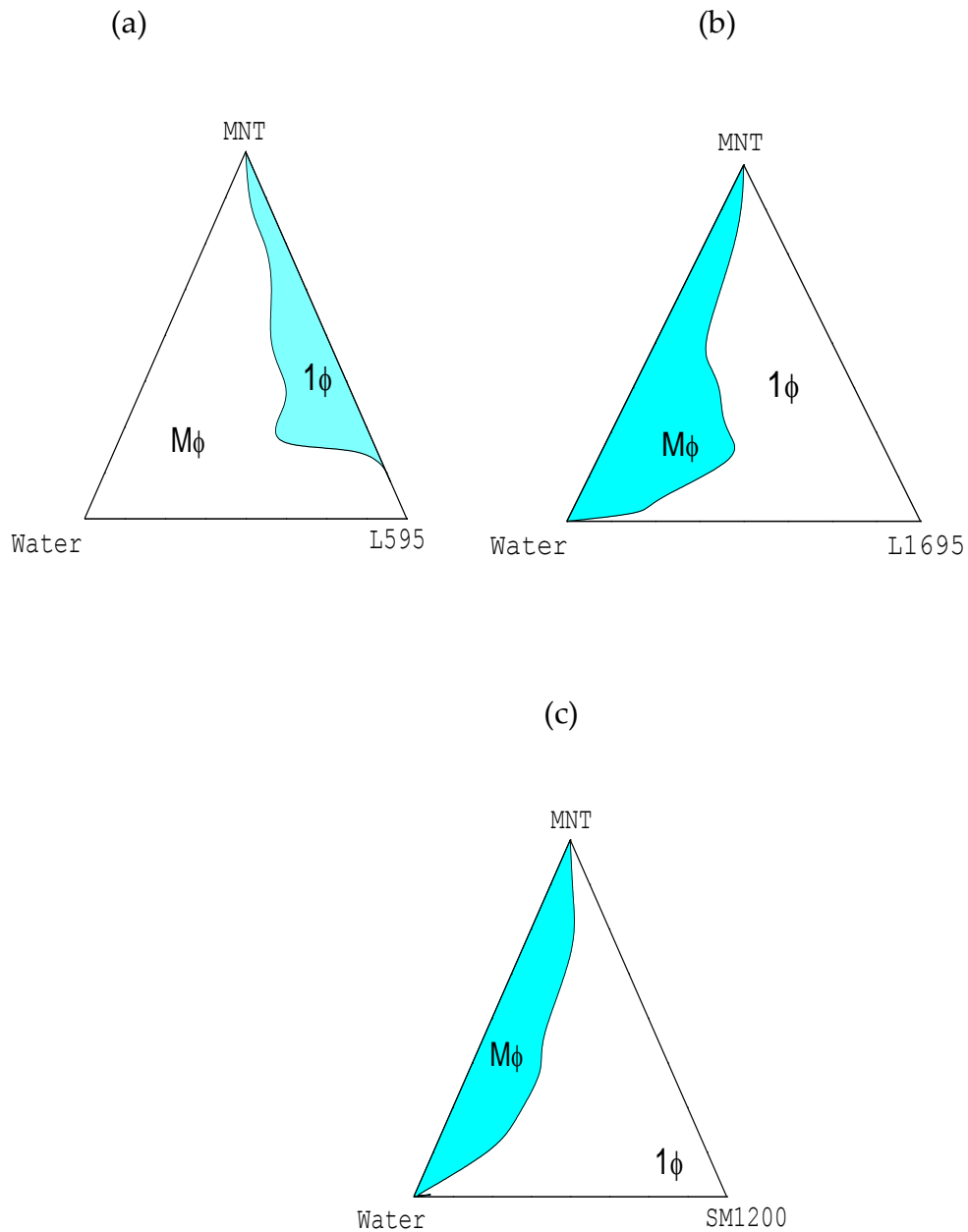


Figure 4.1: Phase diagrams of system: water/sucrose laurate/ peppermint at 25 °C. Sucrose laurate surfactants used in these diagrams were : (a) L595; (b) L1695 ;(c) SM1200.

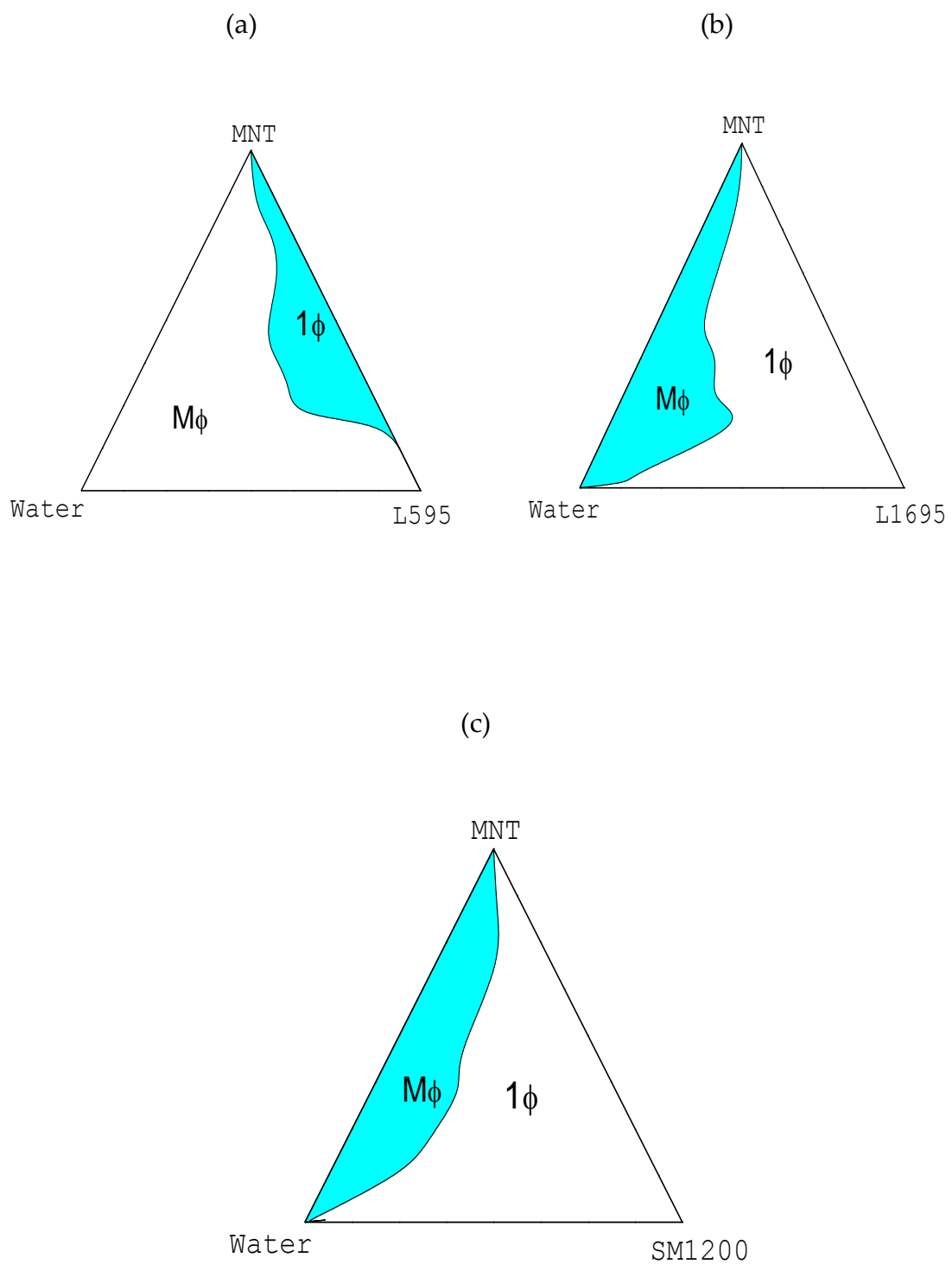


Figure 4.2: Phase diagrams of system: water/sucrose laurate/ peppermint at 37 °C. Sucrose laurate surfactants used in these diagrams were :(a) L595; (b) L1695 ;(c) SM1200.

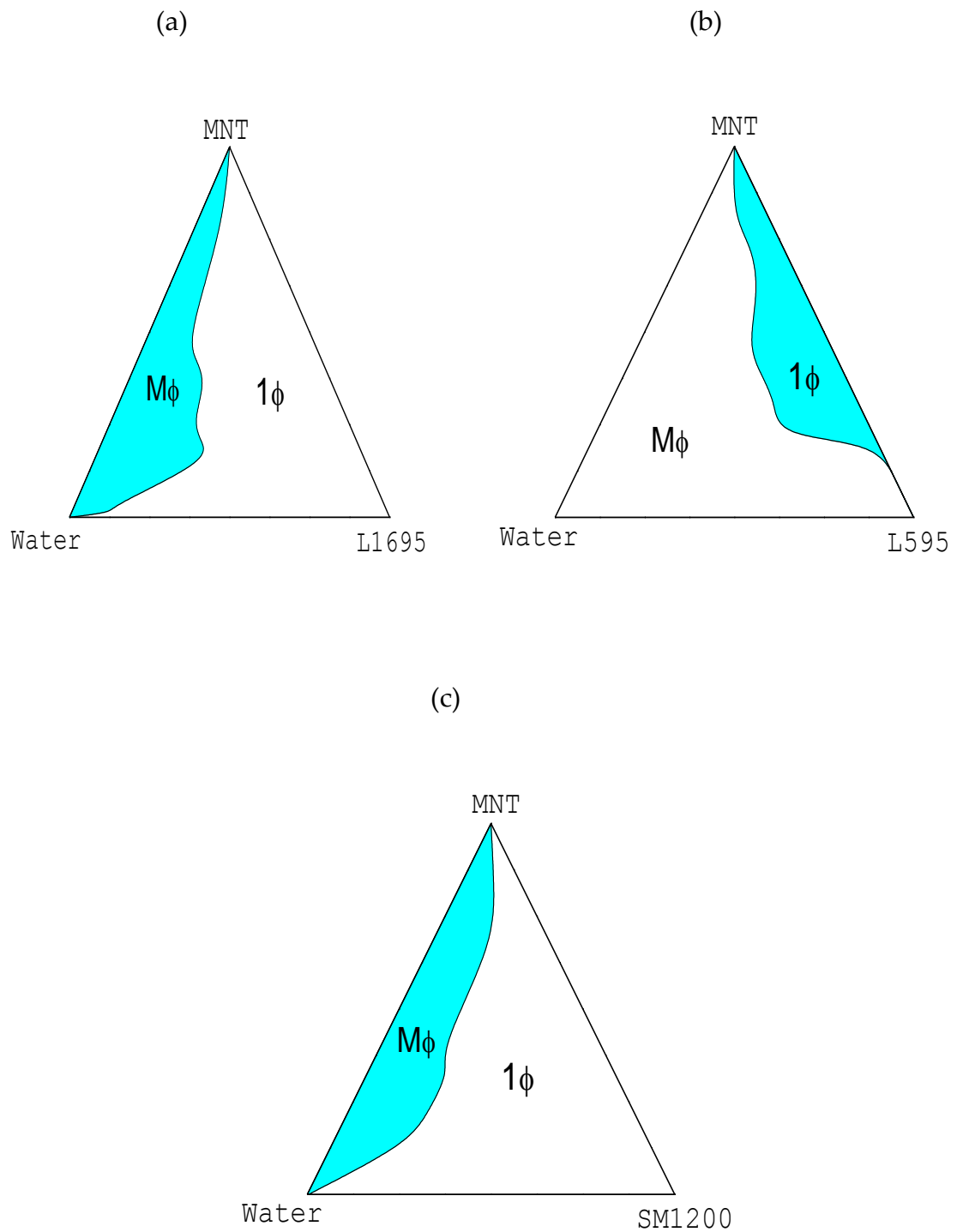


Figure 4.3: Phase diagrams of system: water/sucrose laurate/ peppermint at 45 °C. Sucrose laurate surfactants used in these diagrams were :(a) L595; (b) L1695 ;(c) SM1200.

Table 4.1: the total monophasic area (A_T) for sucrose laurate at different temperatures.

		A_T		
surfactant	Monoester%	25 °C	37 °C	45 °C
L595	30%	25.61	24.34	25.26
L1695	80%	62.32	66.32	67.9
SM1200	95%	69.6	70.61	71.99

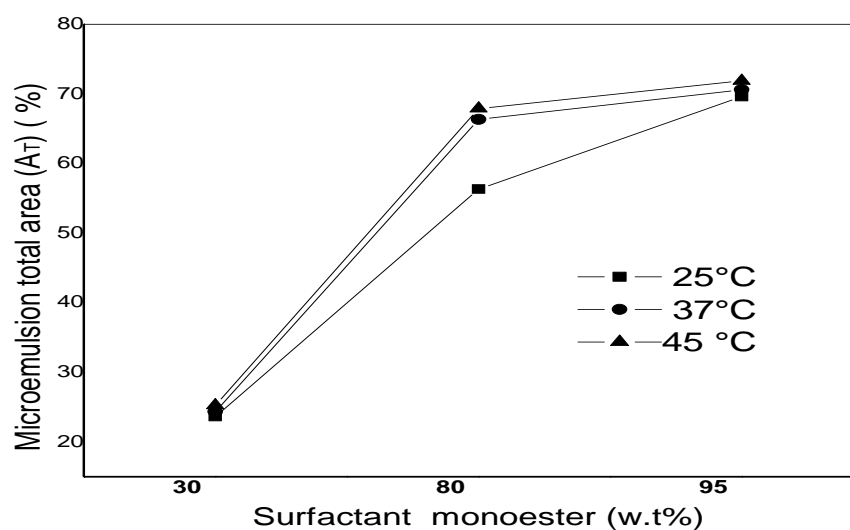


Figure 4.4: Variation of the total monophasic region (A_T) as a function of monoester percentage and temperature in the systems water/sucrose laurate/peppermint.

The total monophasic area (A_T) increased as the percentage of monoester in sucrose laurate increased in microemulsion system based on peppermint oil as shown in Fig 4.4. This trend in the relationship explained by the increase of hydrophilicity of surfactant by increasing the degree of monoester in sucrose. The increase of monoester in sucrose caused the increase of free hydroxyl group which

led to increase of hydrophilicity. Where as the total monophasic area (A_T) did not increase as temperature was increased for the same surfactant at different degree of esterification with temperature in the range 25–45 °C can be due to that the heat has no ‘disordering effect’ or no melting effect on the microemulsion systems based on sucrose laurate [31,32].

Laughlin [24] reported that this ‘melting’ effect is induced by the increase in the thermal motion of surfactant, which decreased the molecular order of surfactant in the liquid crystal. There will be an increase in the interfacial flexibility that eventually will lead to the ‘melting’ of the liquid crystal but this rule can not be subject on sucrose laurate surfactants which are heat insensitive[23,32].

4.1.1.1.1 The effect of surfactant chain length on total monophasic area

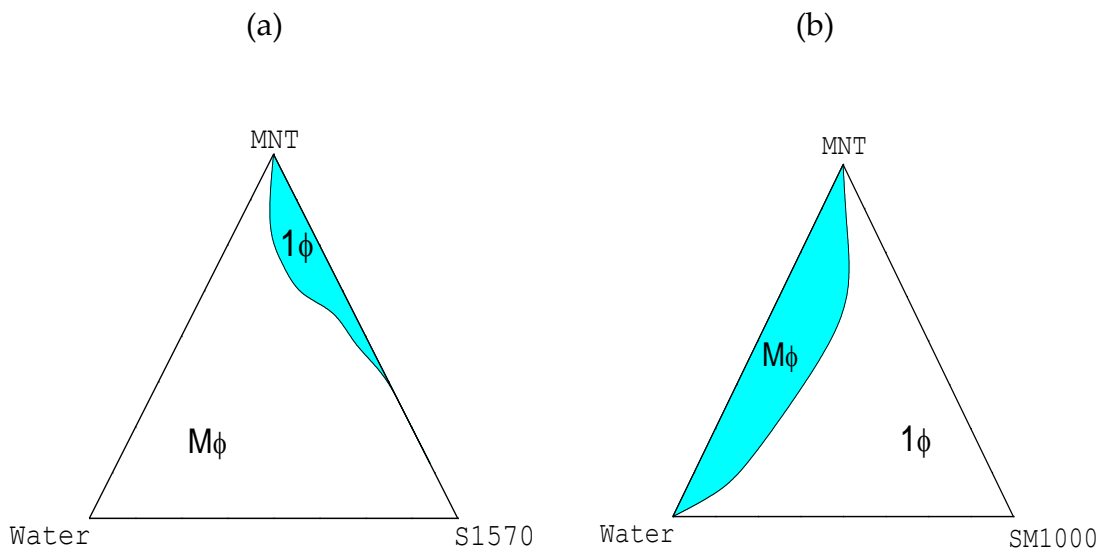


Figure 4.5: Phase diagrams of system: water/sucrose ester/ peppermint at 25 °C. Sucrose ester surfactants used in these diagrams were: (a) S1570 ;(b) SM1000

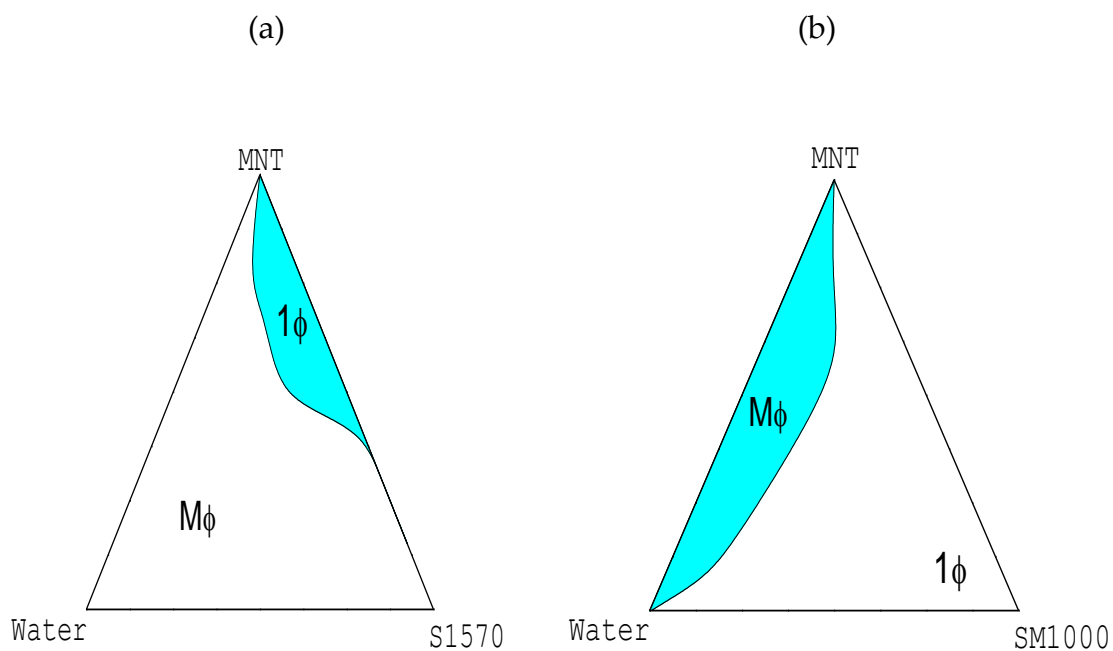


Figure 4.6: Phase diagrams of system: water/sucrose ester/ peppermint at 37 °C. Sucrose ester surfactants used in these diagrams were: (a) S1570 ;(b) SM1000.

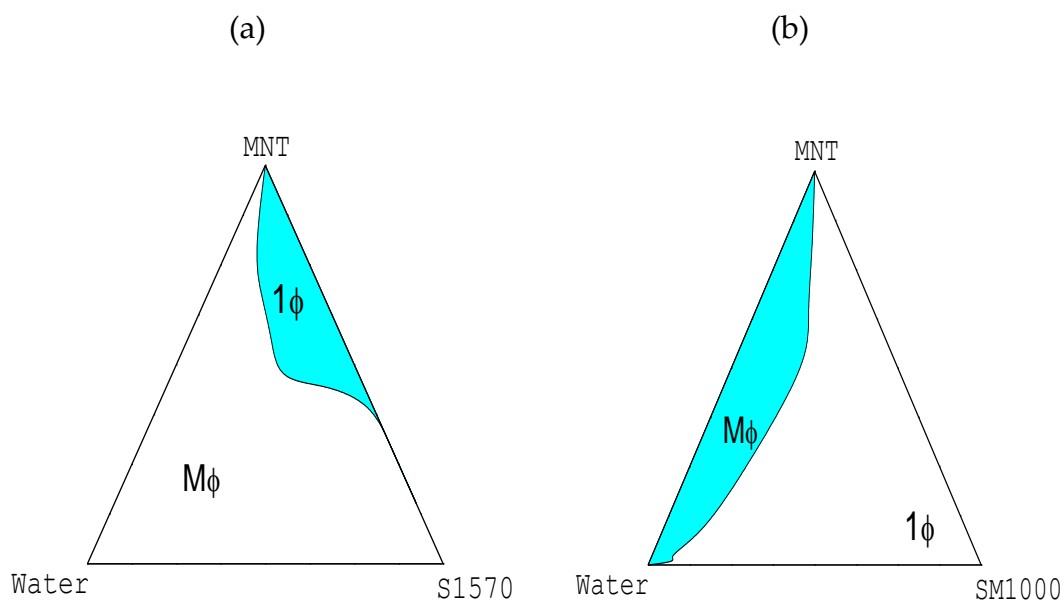


Figure 4.7: Phase diagrams of system: water/sucrose ester/ peppermint at 45 °C. Sucrose ester surfactants used in these diagrams were: (a) S1570 (b) SM1000.

Table 4.2 total monophasic area and surfactant chain length for sucrose ester at different temperatures (peppermint as oil phase).

		A_T		
surfactant	Chain length	25 °C	37 °C	45 °C
SM1000	10	70.2	70.95	73.02
SM1200	12	69.5	70.61	71.99
S1570	18	11.5	15.42	17.07

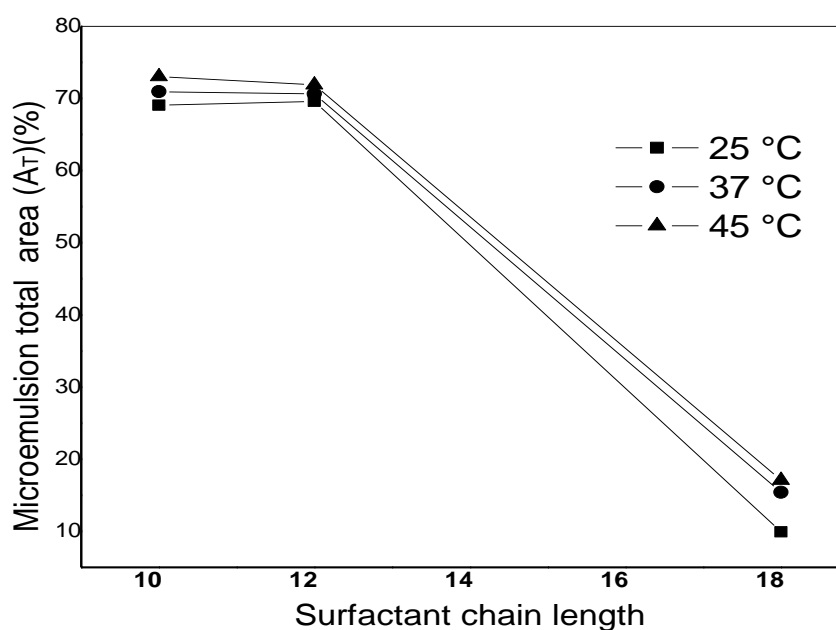


Figure 4.8: Variation of the total monophasic region (A_T) as a function of surfactant chain length of sucrose ester surfactant and temperature in the systems water/sucrose ester/ peppermint.

Figure 4.8 show that the total monophasic area (A_T) decreased as function of surfactant chain length of sucrose ester increased. There was small decrease in total monophasic area (not very clear) when carbon chain length of surfactant

changed from 10 ($A_T = 70.2\%$) to 12 ($A_T = 69.5\%$) but a sharp decrease in total monophasic area found when hydrocarbon chain length change from 12 ($A_T = 69.5\%$) to 18 ($A_T = 9.93\%$) at $25\text{ }^\circ\text{C}$. This can be due to the increase of chain length caused by an increase in ordering and the rigidity of surfactant film also because of increase in molecular volume and an increase in attractive forces. The systems based on SM1000, SM1200, and S1570 found to be temperature-insensitive in the temperature range $25\text{--}45\text{ }^\circ\text{C}$ due to that the heat has on a 'disordering effect' on the liquid crystals that are turning into an isotropic phase with increasing temperature [27, 34, 44,45].

4.1.1.1.2 The phase behaviors for microemulsions based on ethoxylated surfactants

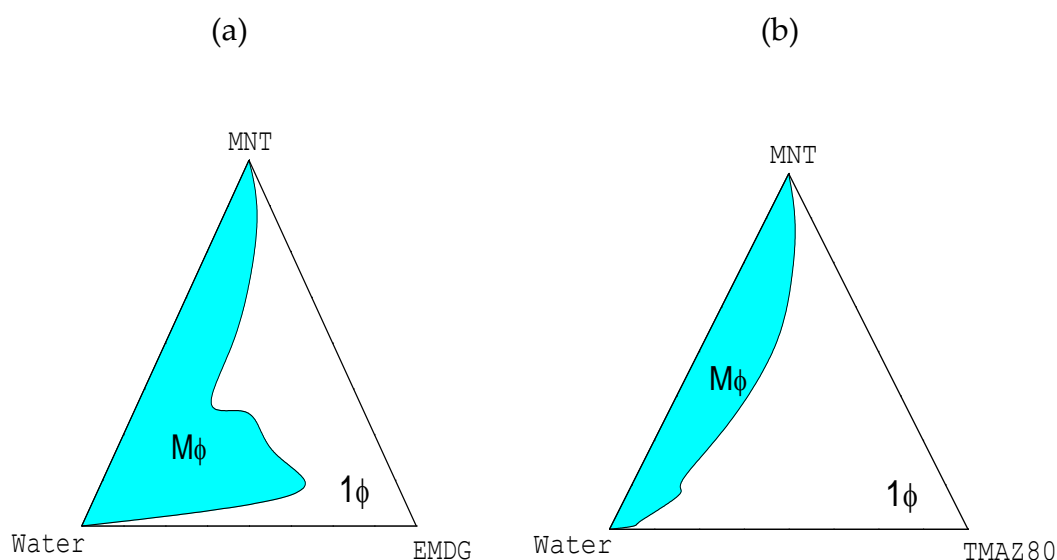


Figure 4.9: Phase diagrams of system: water/ethoxylated surfactant/ peppermint at $25\text{ }^\circ\text{C}$. Surfactants used in these diagrams were: (a) EMDG (b) TMAZ80.

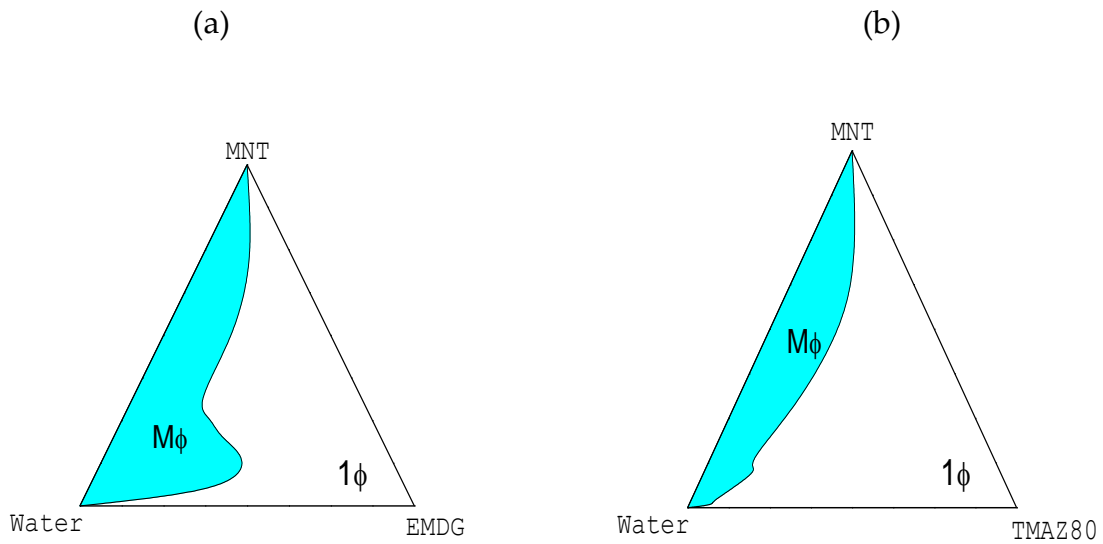


Figure 4.10: Phase diagrams of system: water/ethoxylated surfactant/ peppermint at 37 °C. Surfactants used in these diagrams were: (a) EMDG (b) TMAZ80.

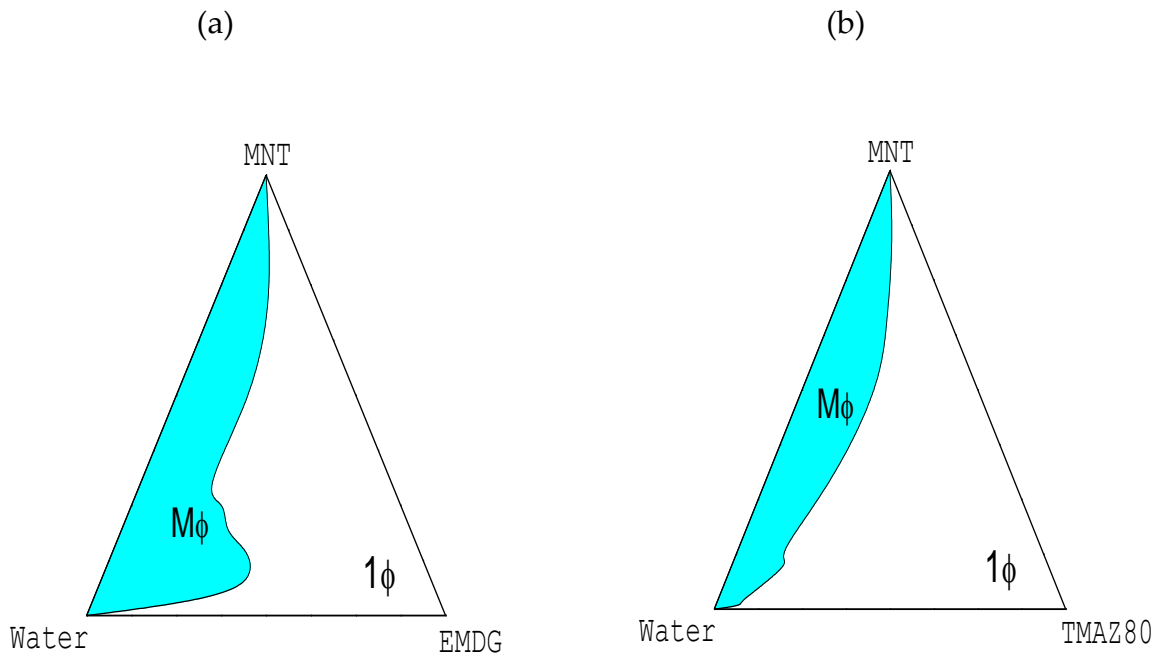


Figure 4.11: Phase diagrams of system: water/ethoxylated surfactant/ peppermint at 45 °C. Surfactants used in these diagrams were: (a) EMDG (b) TMAZ80.

Table 4.3 Total monophasic area for ethoxylated surfactant at different temperature.

surfactant	A_T		
	25 °C	37 °C	45 °C
EMDG	48.4	59.23	60.68
TMAZ80	68.1	70.27	70.83

The total monophasic area (A_T) for microemulsion system based on EMDG was less than total monophasic area based on TMAZ80 in ternary microemulsion systems based on peppermint oil as shown in the table 4.3. This is due to hydrophlicity of TMAZ80 (HLB= 17) was more than the hydrophilicity of EMDG (HLB = 13.5) due to the abundance of ethoxylated groups in TMAZ80 more than EMDG. The systems based on TMAZ80 were found to be temperature-insensitive in the temperature range 25–45 °C where the difference between total monophasic areas did not exceed 4% at different temperatures which is within the error range . This is due to the bulky shape of surfactant which prevent thermal motion during heating where as microemulsion system based on EMDG was temperature sensitive due to the ability of thermal motion upon heating and the hydrophilic-lipohilic balance of EMDG changes with temperature due to the dehydration of the polyethylene group which makes EMDG more lipophilic with increasing temperature [37, 40].

4.1.1.1.3 The effect of degree of esterification on microemulsions phase behaviors

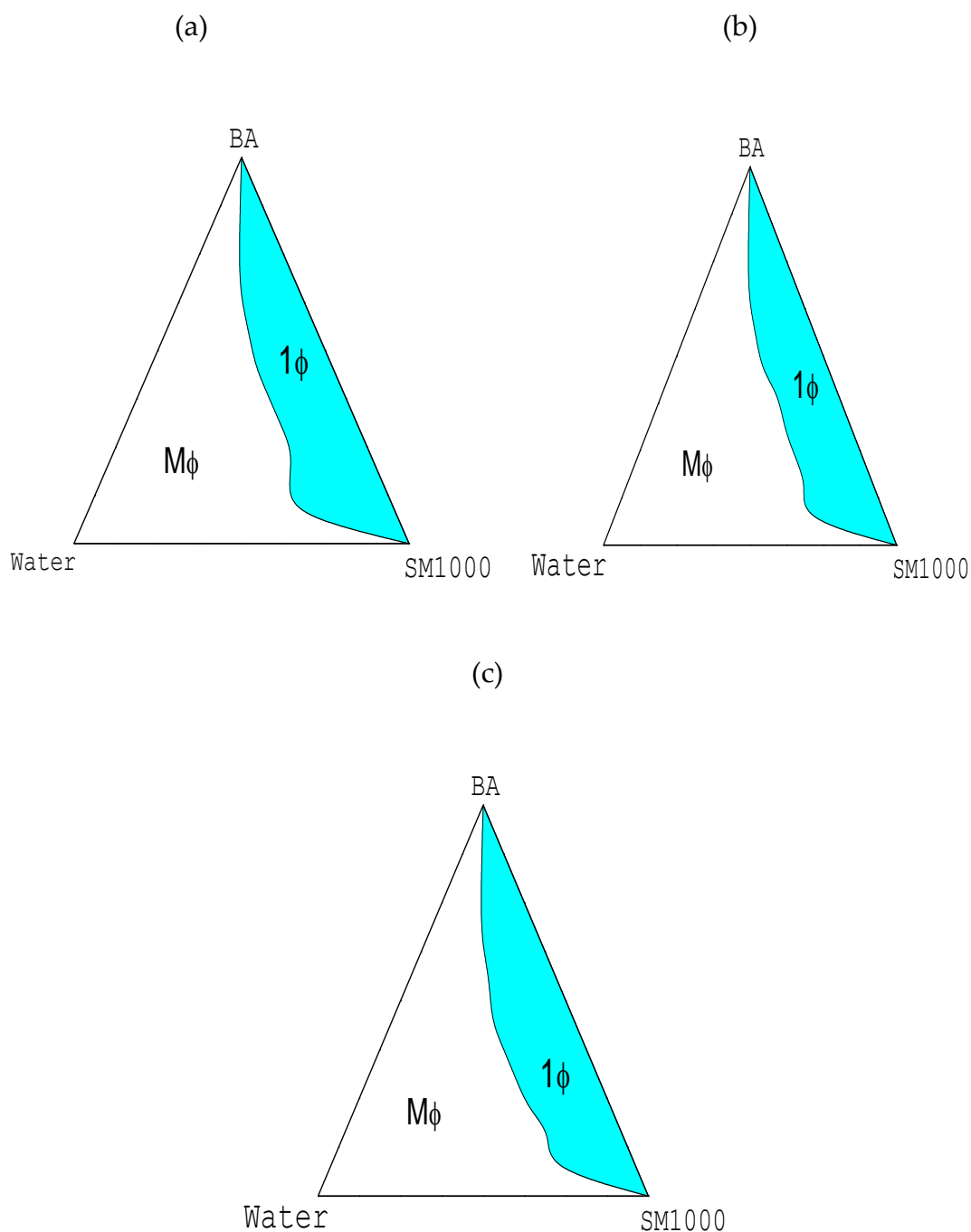


Figure 4.12: Phase diagrams of system: water/sucrose ester/ benzaldehyde. Sucrose ester surfactants used in these diagrams were: (a) SM1000 at 25 °C, (b) SM1000 at 37 °C, (c) SM1000 at 45 °C.

Table 4.4 Total monophasic area for sucrose ester at different chain length and temperatures based on benzaldehyde microemulsion system.

		A_T		
surfactant	Chain length	25 °C	37 °C	45 °C
SM1000	10	27.88	35.4	37.17
SM1200	12	69.6	70.61	71.99
S1570	18	0	0	0

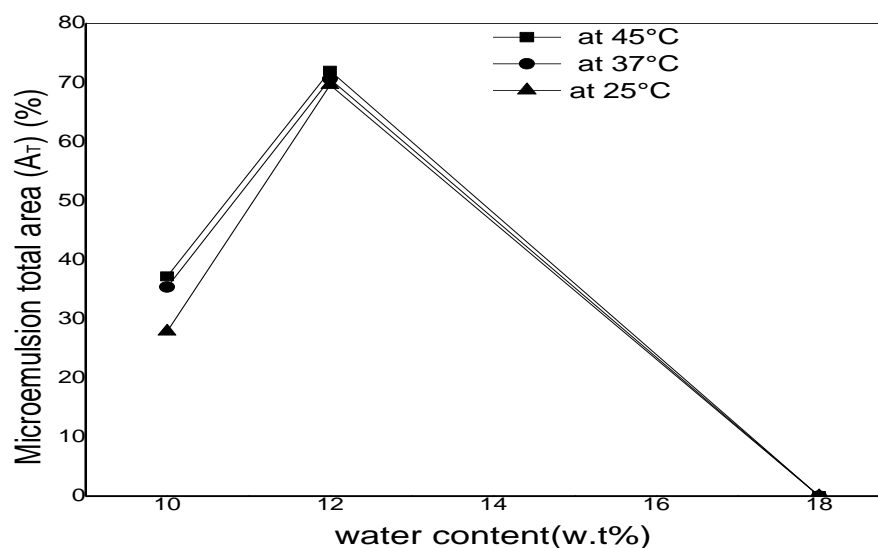


Figure 4.13: Variation of the total monophasic region (A_T) as a function of hydrocarbon chain length of surfactant and temperature in the systems water/sucrose ester/ benzaldehyde.

The total monophasic area (A_T) for microemulsion system based on benzaldehyde oil and sucrose ester surfactant was highest at surfactant chain length 12 (A_T about 70%) and then at surfactant chain length 10 (A_T about 30%) while at surfactant chain length 18 there was no monophasic area formation as shown in figure 4.13. this

was due to that the optimum hydrophilic-lipophilic balance occurred at surfactant chain length 12. This trend in the relationship was different when peppermint oil was used. All used sucrose ester surfactants was found to be temperature insensitive [26, 34, 44, 45].

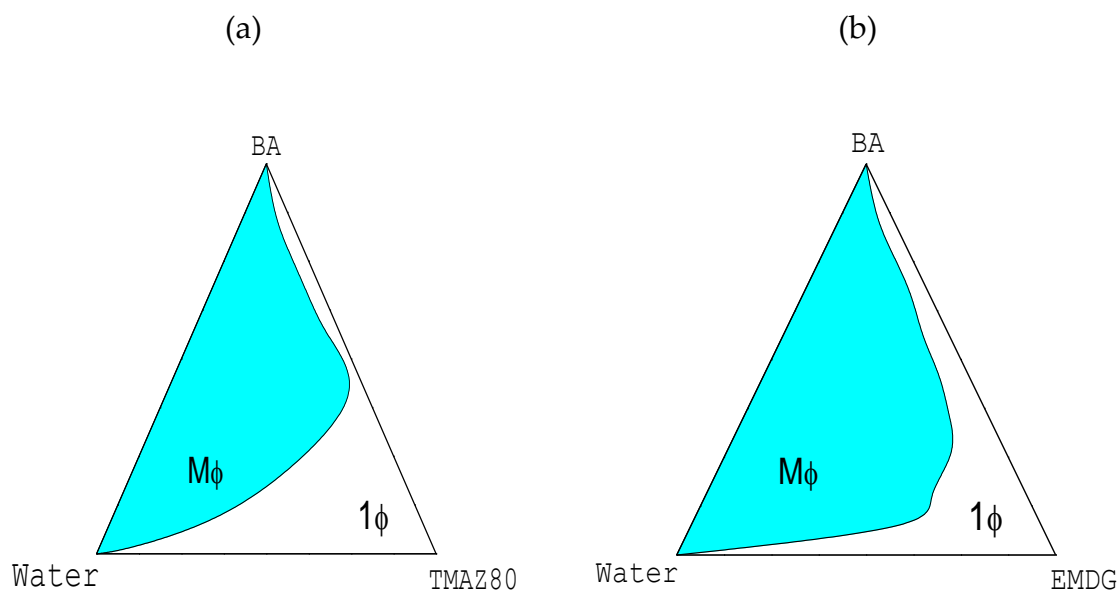


Figure 4.14: Phase diagrams of system: water/ethoxylated surfactant/benzaldehyde at 25 °C. Ethoxylated surfactants used in these diagrams were: (a) TMAZ80 (b) EMDG.

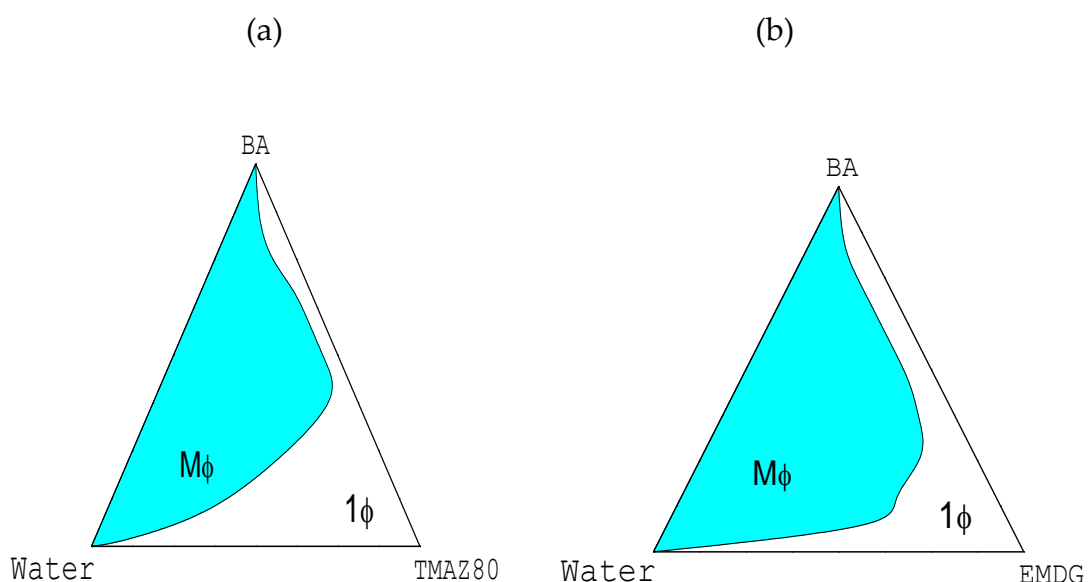


Figure 4.15: Phase diagrams of system: water/ethoxylated surfactant/benzaldehyde at 37 °C. Ethoxylated surfactants used in these diagrams were: (a) TMAZ80 (b) EMDG.

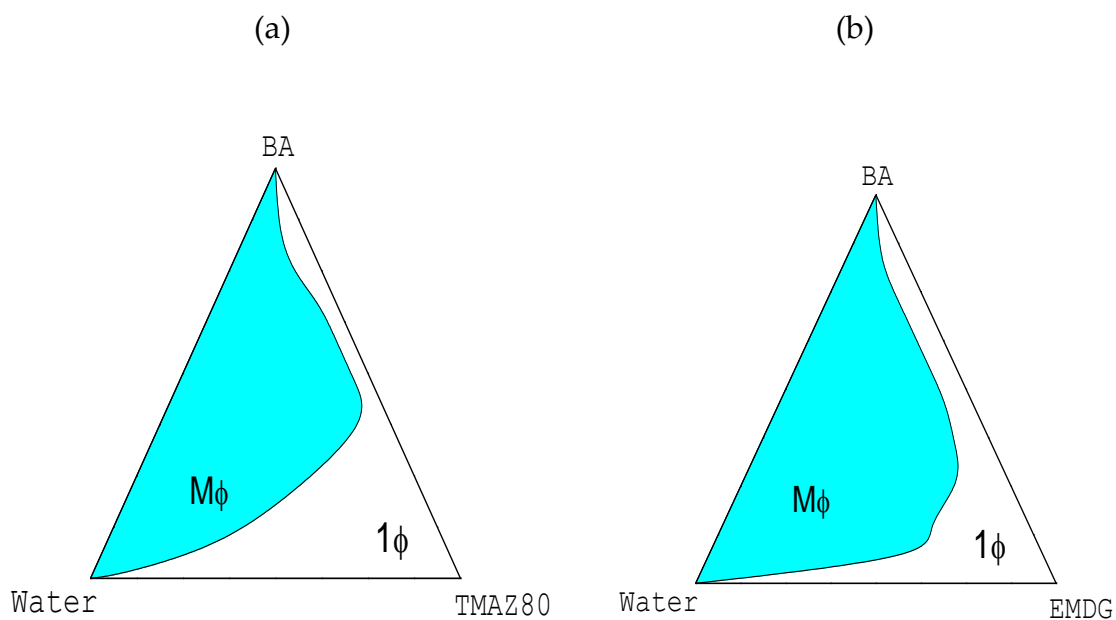


Figure 4.16: Phase diagrams of system: water/ethoxylated surfactant/benzaldehyde at 45 °C. Ethoxylated surfactants used in these diagrams were: (a) TMAZ80 (b) EMDG.

Table 4.5 Total monophasic area for ethoxylated surfactants at different temperatures in microemulsion systems based on benzaldehyde.

surfactant	A_T		
	25 °C	37 °C	45 °C
EMDG	28.3	29.2	29.95
TMAZ80	34.5	37.5	38.56

The total monophasic area (A_T) for microemulsion system based on EMDG was less than total monophasic area based on TMAZ80 this is due to the TMAZ80 is more hydrophilic. The systems based on TMAZ80 and EMDG was temperature-insensitive in the range 25–45 °C as shown in the table 4.5 this was due to the hydrophilicity of TMAZ80 (HLB =17) higher than EMDG (HLB = 13.5) [34, 43, 45].

4.1.1.1.4 The phase behavior for microemulsion systems based on benzaldehyde oil and ethoxylated surfactants

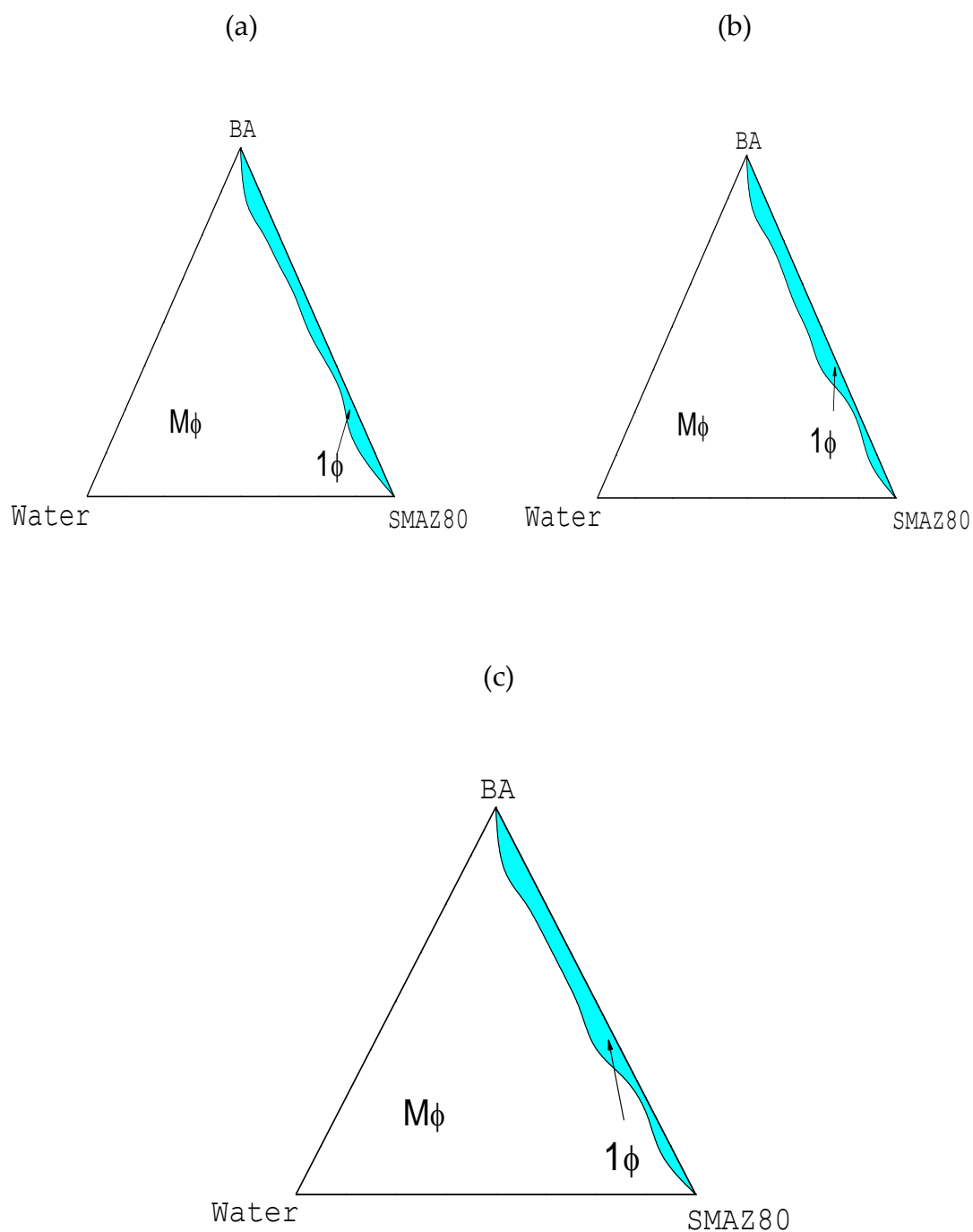


Figure 4.17: Phase diagrams of system: water/ sorbitan monooleate / benzaldehyde. Sorbitan monooleate surfactants used in these diagrams were at: (a) 25 °C (b) 37 °C, (c) 45 °C.

Table 4.6 Total monophasic area for sorbitan monooleate at different temperatures.

surfactant	A _T		
	25 °C	37 °C	45 °C
SAMZ80	8.68	9.62	10.92

Total monophasic area in microemulsion based on sorbitan monooleate and benzaldehyde have nearly the same area at different temperature within the range 25-45 °C which indicate that sorbitan monooleate surfactant was temperature insensitive as shown in table 4.6 [34, 44, 45].

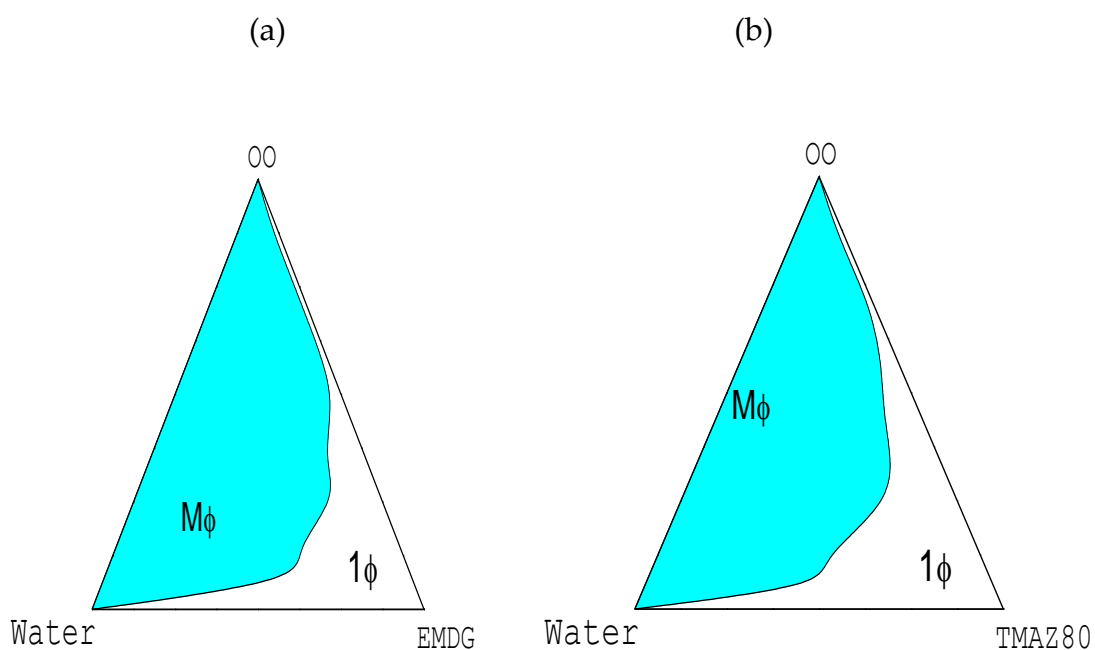


Figure 4.18: Phase diagrams of system: water/ethoxylated surfactant / olive oil at 25 °C. Surfactants used in these diagrams were: (a) EMDG (b) TMAZ 80.

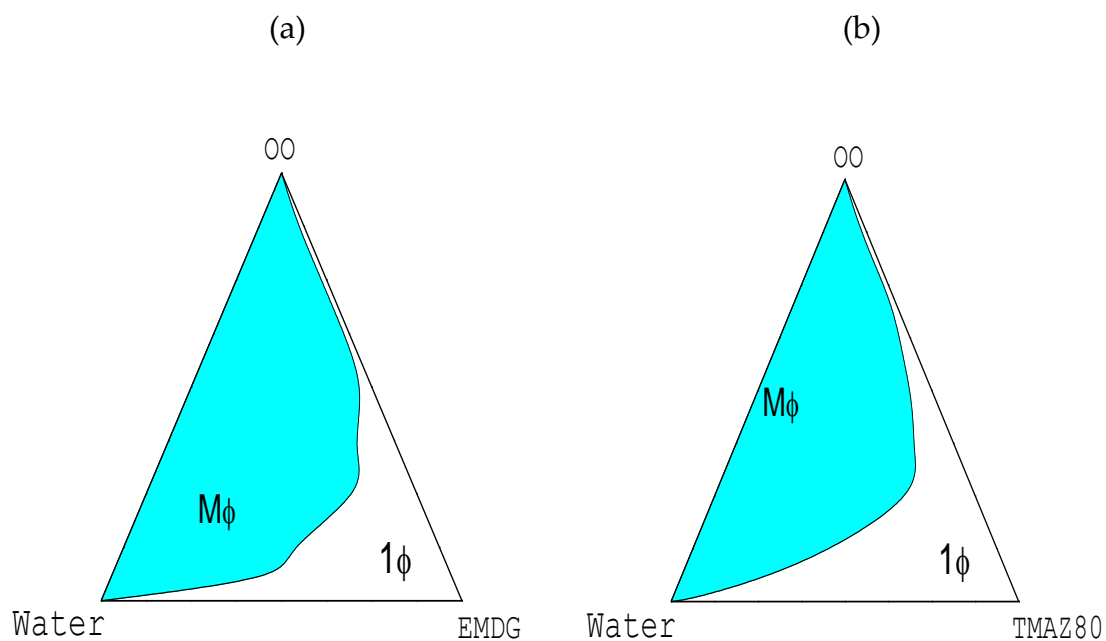


Figure 4.19: Phase diagrams of system: water/ethoxylated surfactant / olive oil at 37 °C. Surfactants used in these diagrams were: (a) EMDG (b) TMAZ 80.

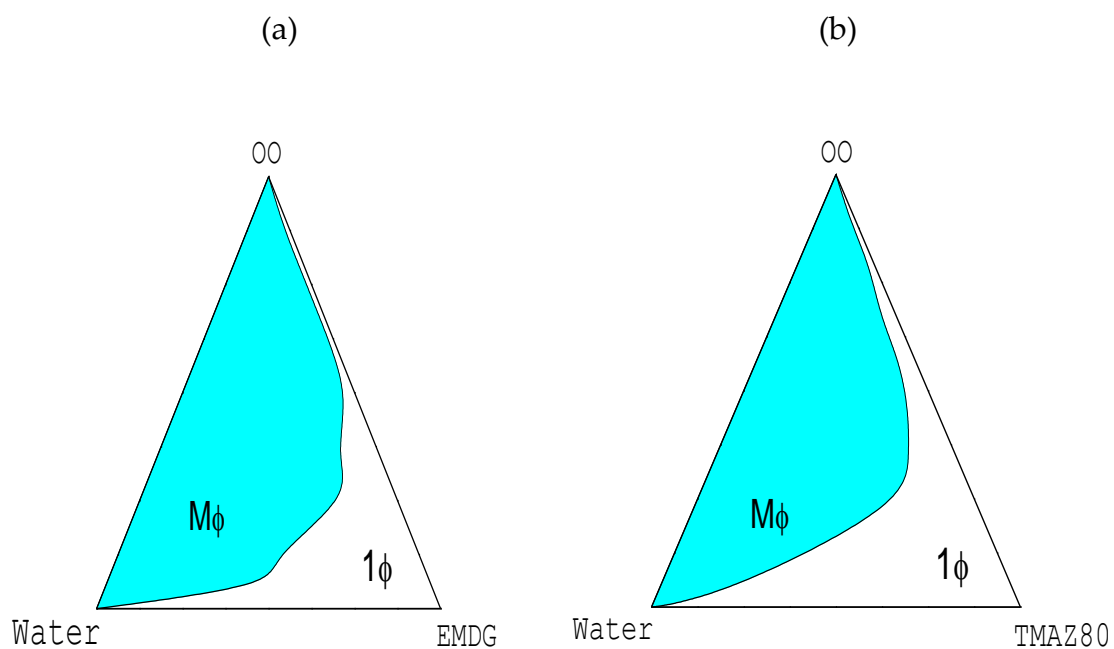


Figure 4.20: Phase diagrams of system: water/ethoxylated surfactant / olive oil at 45 °C. Surfactants used in these diagrams were: (a) EMDG (b) TMAZ 80.

Table 4.7 Total monophasic area for ethoxylated surfactant at different temperature.

surfactant	A _T		
	25 °C	37 °C	45 °C
EMDG	28	30.05	30.41
TMAZ80	31.63	32.95	34.86

The total monophasic area (A_T) for microemulsion system based on EMDG was found less than total monophasic area based on TMAZ80 when using olive oil as oil phase as shown in table 4.7. this is due to high hydrophilicity of TMAZ80 which comes from the substitution of hydroxyl group on sorbitan ring with bulky polyoxyethylene groups increased the hydrophilicity of surfactant and this case agree with peppermint and benzaldehyde oil. The systems based on TMAZ80 and EMDG was found to be temperature-insensitive in the temperature range 25–45 °C. They have bulky polyoxyethylene head groups attached to a sorbitan ring, which increased the hydrophilicity of sorbitan fatty ester [33, 42].

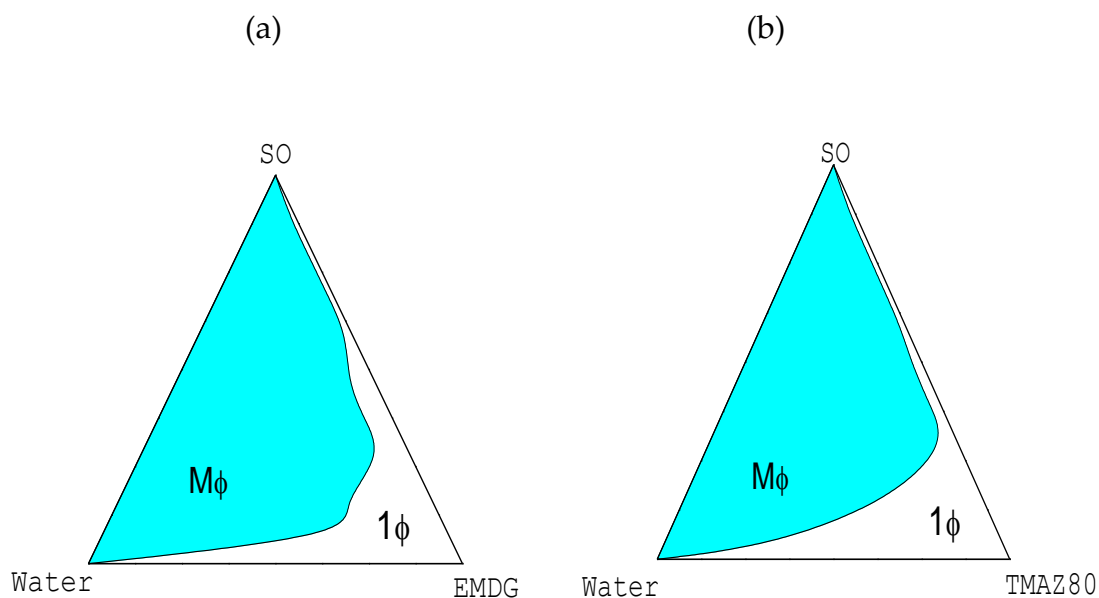


Figure 4.21: Phase diagrams of system: water/ethoxylated surfactant / sesame oil at 25 °C. Surfactants used in these diagrams were: (a) EMDG (b) TMAZ80.

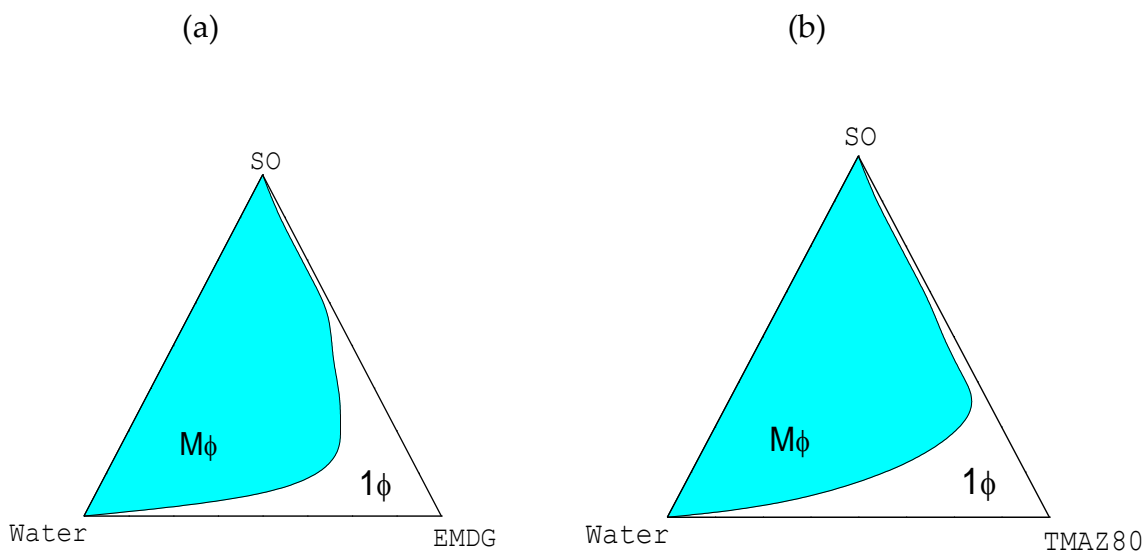


Figure 4.22: Phase diagrams of system: water/ethoxylated surfactant / sesame oil at 37 °C. Surfactants used in these diagrams were: (a) EMDG (b) TMAZ80.

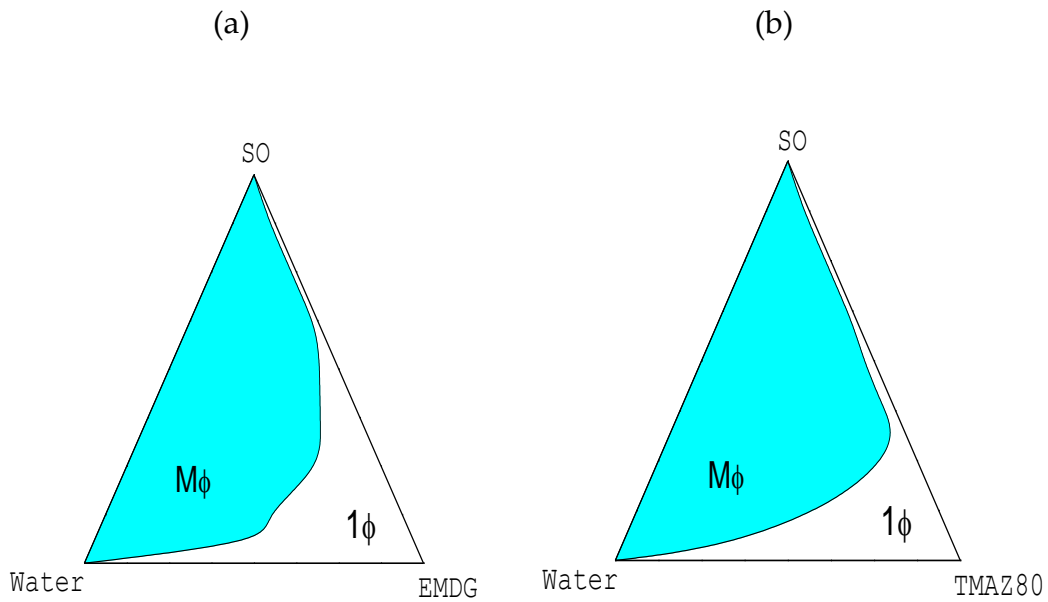


Figure 4.23: Phase diagrams of system: water/ethoxylated surfactant / sesame oil at 45 °C. Surfactants used in these diagrams were: (a) EMDG (b) TMAZ80.

Table 4.8 Total monophasic area for ethoxylated surfactants at different temperature

surfactant	A_T		
	25 °C	37 °C	45 °C
EMDG	28.3	29.2	29.95
TMAZ80	34.5	37.5	38.56

The total monophasic area (A_T) for microemulsion system based on EMDG was less than total monophasic area based on TMAZ80 in microemulsion systems based on sesame oil as shown in table 4.8 due to the same reasons which mentioned in the case of olive oil and this agree with different types of oils used in this study . The systems based on TMAZ80 and EMDG was found to be temperature-insensitive in the temperature range 25–45 °C and also for the same

reasons which were mentioned in the case of microemulsion systems based on other oils.

It was found that total monophasic area in all systems based on peppermint oil was larger than any oil used in this study. This is due to that peppermint oil has special structure which different from the structure of oils used. It composed from menthol, menthyl ester, and menthone. The menthol act as cosurfactant. It was found that all microemulsion systems based on sesame and olive oils formed less total monophasic area (Fig.4.18-23) or not formed microemulsion as in microemulsion based on SM1200, SM100, L1695 and L595 surfactants due that the two oils are triglyceride with high molecular weight and so the ability to penetrate the interfacial film is low when compared with peppermint and benzaldehyde oils which are non triglycerides oils. Formation of microemulsion depends on the oil structure and oil penetration which affected by molecular weight, triglycerides have bulky shape and high molecular weights which increase the difficulty to penetrate the interfacial film to assist the optimum curvature [23, 34, 42].

4.1.1.2 Quaternary systems

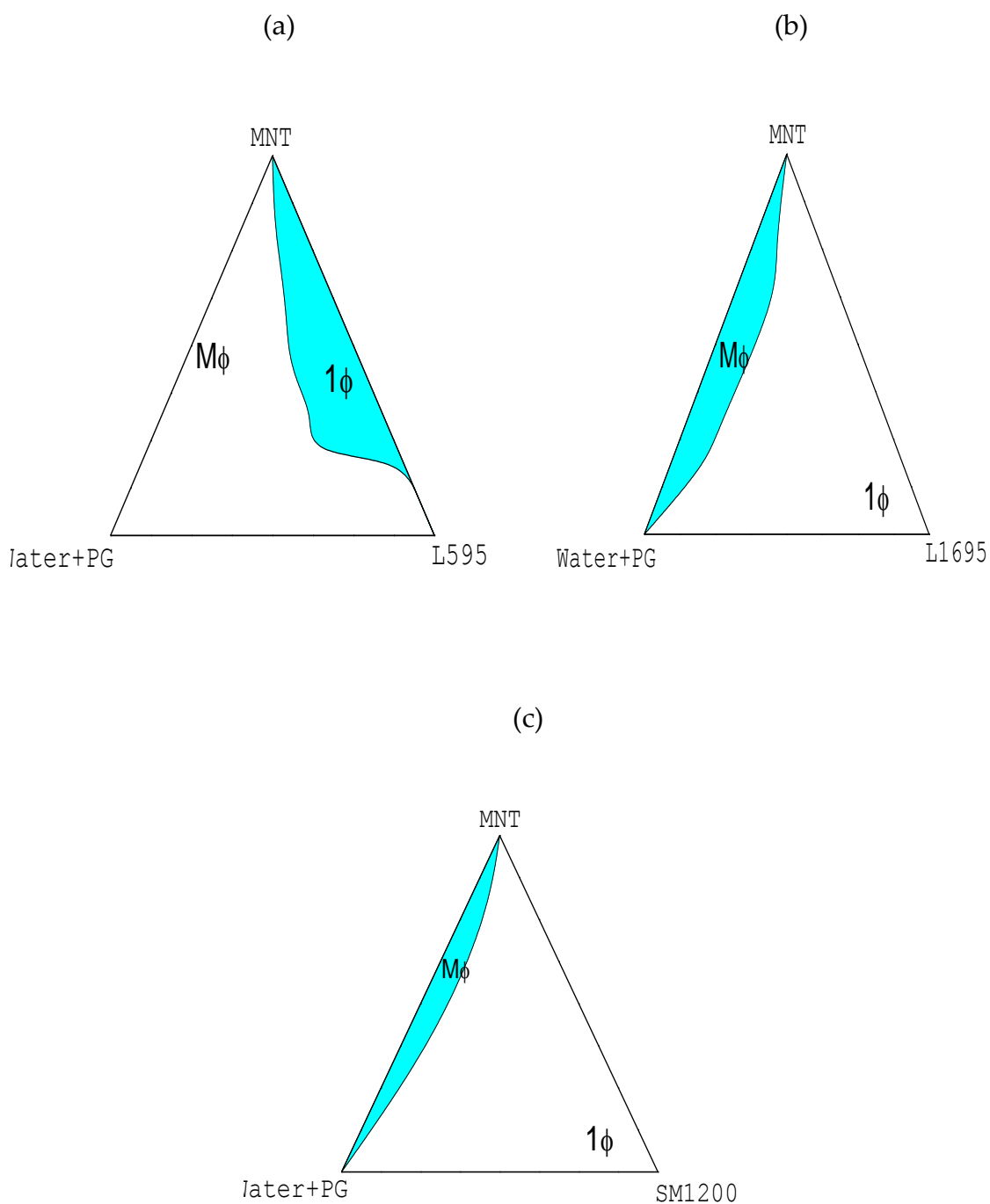


Figure 4.24: Phase diagrams of system: water +propylene glycol (2:1)/sucrose laurate / peppermint oil at 25 °C. Sucrose laurate surfactants used in these diagrams were: (a) L595 (b) L1695 (c) SM1200.

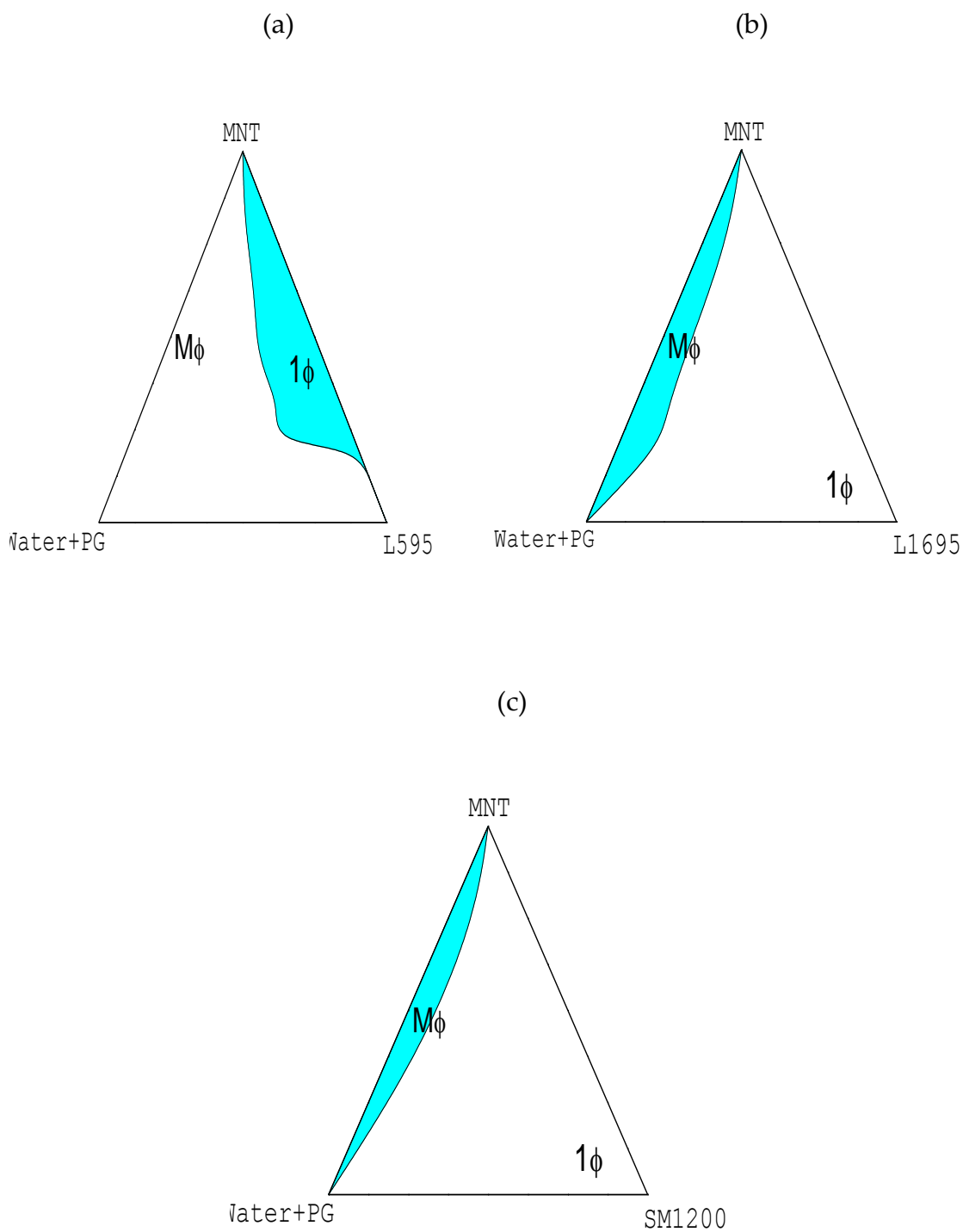


Figure 4.25: Phase diagrams of system: water +propylene glycol (2:1)/sucrose laurate / peppermint oil at 37 °C. Sucrose laurate surfactants used in these diagrams were: (a) L595 (b) L1695 (c) SM1200.

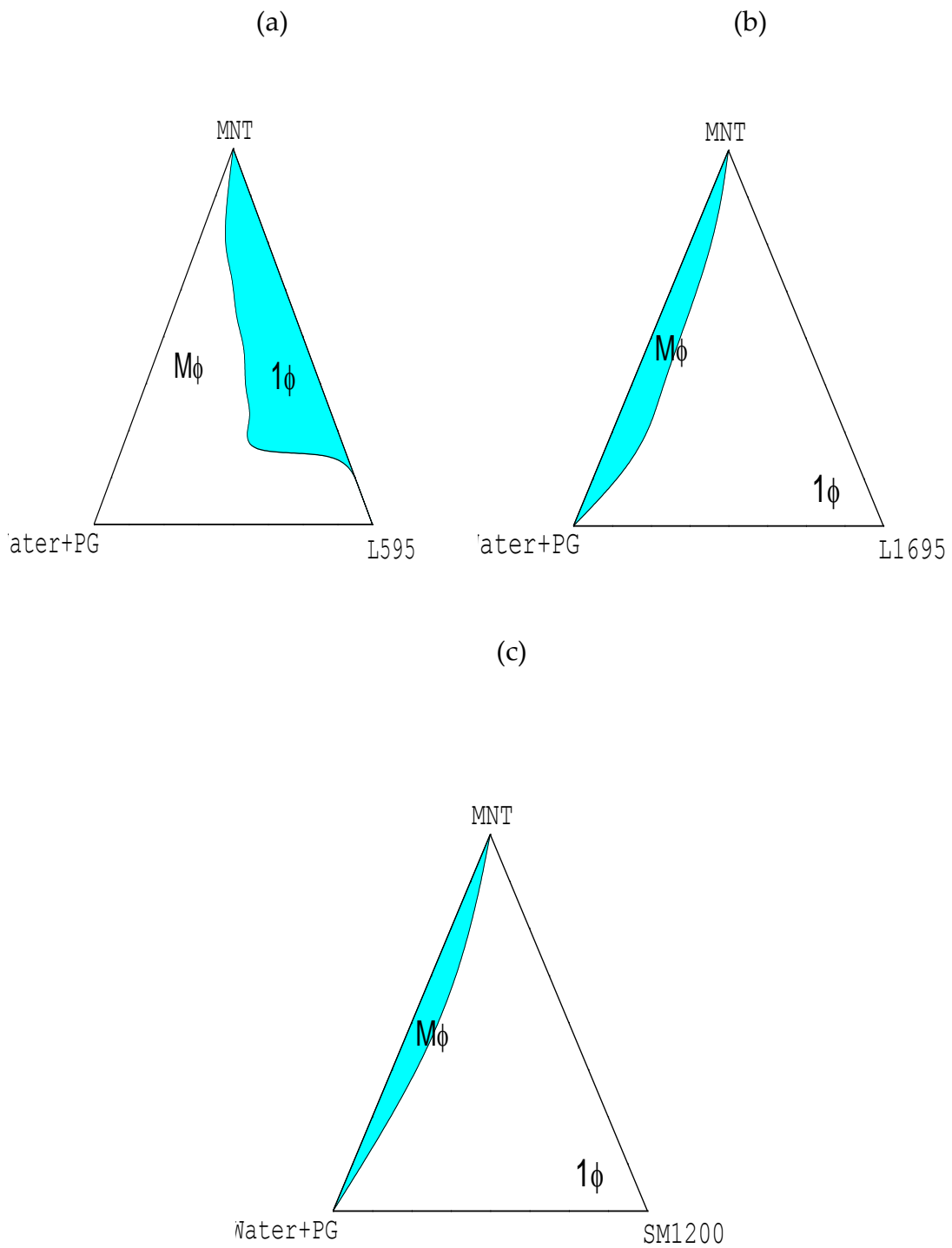


Figure 4.26: Phase diagrams of system: water +propylene glycol (2:1)/sucrose laurate / peppermint oil at 45 °C. Sucrose laurate surfactants used in these diagrams were: (a) L595 (b) L1695 (c) SM1200.

Table 4.9 Total mono phasic area for sucrose laurate at different percentage of monoester and temperatures.

surfactant	Monoester %	A_T		
		25 °C	37 °C	45 °C
L595	30	25.34	28.6	32.14
L1695	80	78.33	77.23	83.69
SM1200	95	86.28	85.89	87.22

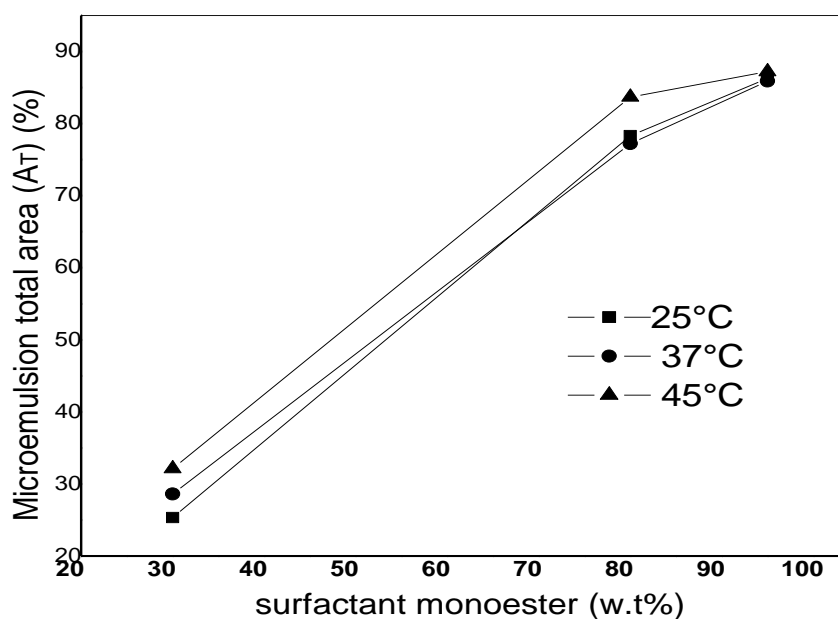
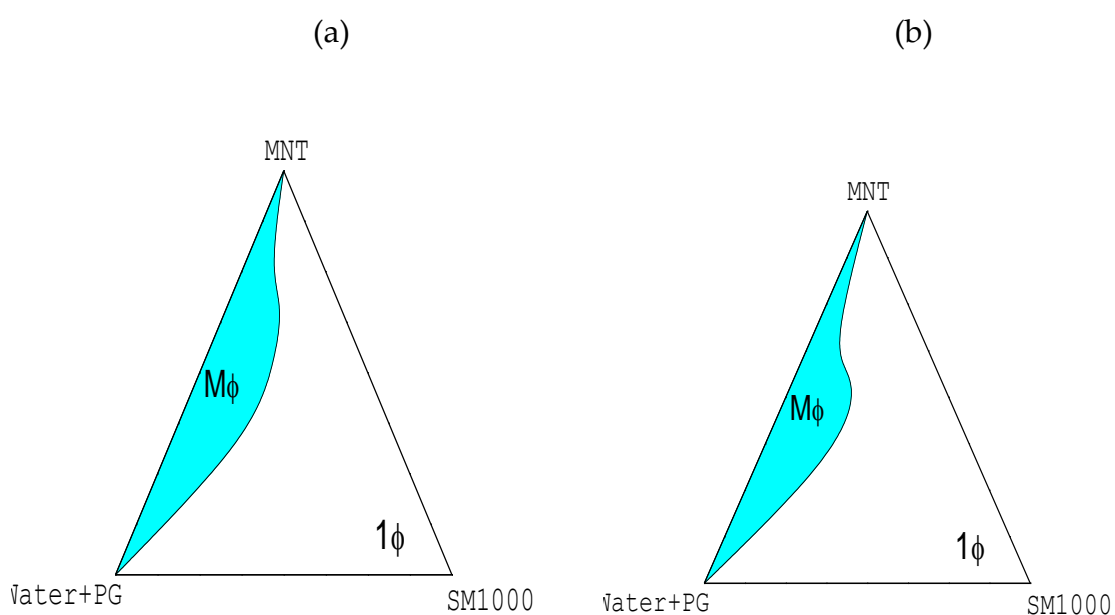


Figure 4.27: Variation of the total monophasic region (A_T) as a function of mono ester and temperature in the system water+propylene glycol (2:1)/sucrose laurate/ peppermint.

The total monophasic area (A_T) increases as the percentage of monoester increased in microemulsion system based on sucrose laurate in presence of propylene glycol as cosolvent as shown in figure 4.27. This can be due to increase of disordering in surfactant film by increasing of degree of monoester where as the total monophasic area (A_T) did not change as temperature increased for the same

surfactant at different degree of esterification with temperature in the range 25–45 °C can be due to the same reasons which were mentioned in the text for the same surfactants.

It was found that total monophasic area for sucrose laurate in presence of propylene glycol is higher than that without propylene glycol at all temperatures for the same microemulsion system which is due to that surfactant became more soluble in the aqueous phase (propylene glycol-water mixture) than it is in oil, and due to that propylene glycol destabilize the crystalline phase and the extent the isotropic region to higher surfactant concentration [32, 39].



(c)

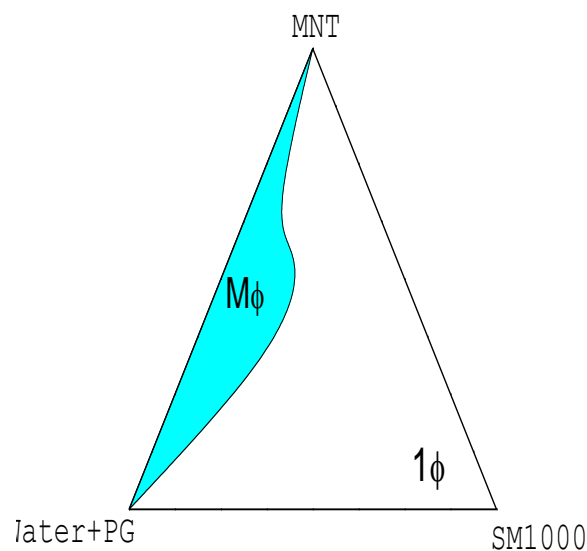


Figure 4.28: Phase diagrams of system: water +propylene glycol (2:1)/sucrose ester / peppermint oil. Sucrose laurate surfactants used in these diagrams were: (a) SM1000 at 25 °C (b) SM1000 2 at 37 °C, (c) SM1200 at 45 °C.

Table 4.10: Total monophasic area for sucrose ester at different chain length and temperature

		A_T		
surfactant	Surfactant chain length	25 °C	37 °C	45 °C
SM1000	10	86.28	85.89	87.22
SM1200	12	72.8	75.9	76.1

The total monophasic area (A_T) decreased as function of surfactants chain length of sucrose ester increased as shown table 4.10. This can be due to the increase of

chain length which causes an increase in ordering and the rigidity of surfactant film also because of increase in molecular volume and an increase in attractive forces. The systems based on SM1000 and SM1000 were temperature-insensitive in the temperature range 25–45 °C.

It found that total monophasic area for sucrose ester in presence of propylene glycol is higher than without propylene glycol at all temperatures for the same system which is due to that surfactant become more soluble in the aqueous phase (propylene glycol-water mixture) than it is in oil [27,32].

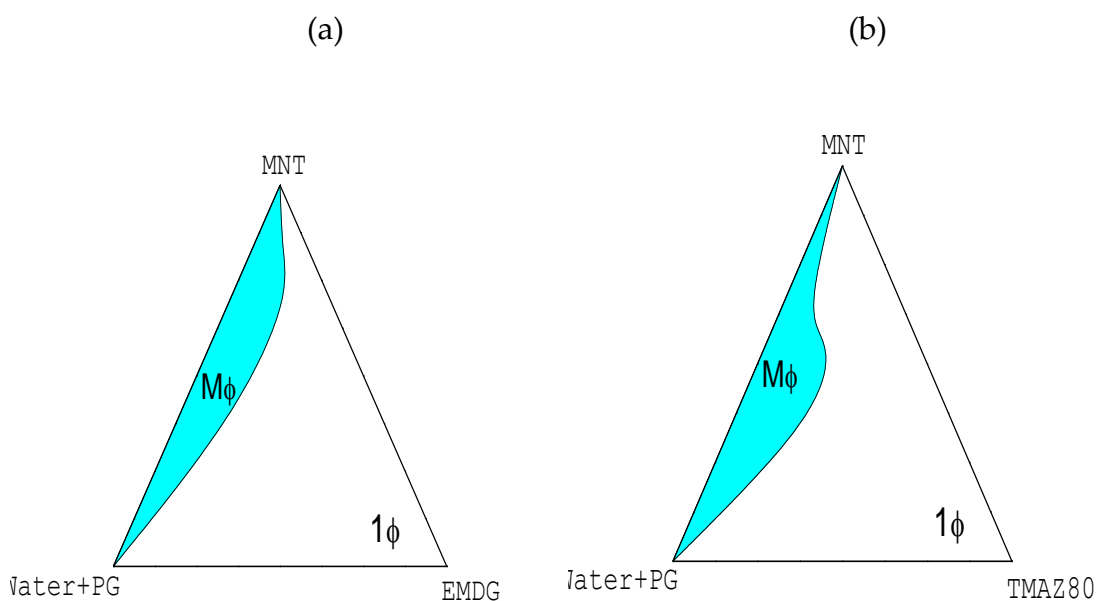


Figure 4.29: Phase diagrams of system: water +propylene glycol (2:1)/ethoxylated surfactants / peppermint oil at 25 °C. Ethoxylated surfactants used in these diagrams were: (a) EMDG (b) TMAZ 80.

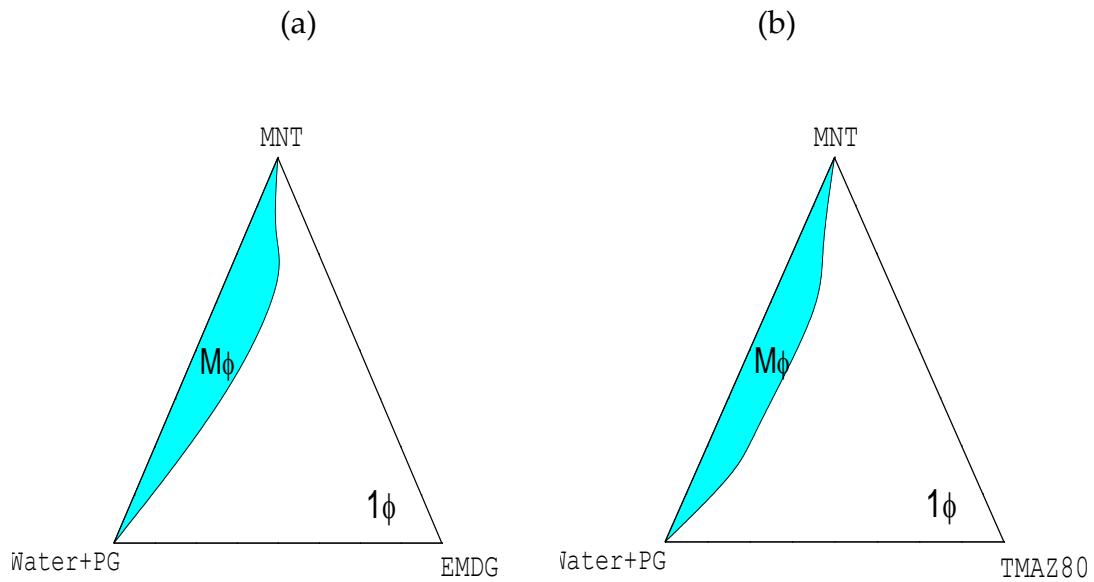


Figure 4.30: Phase diagrams of system: water +propylene glycol (2:1)/ethoxylated surfactant / peppermint oil at 37 °C. Ethoxylated surfactants used in these diagrams were: (a) EMDG (b) TMAZ 80

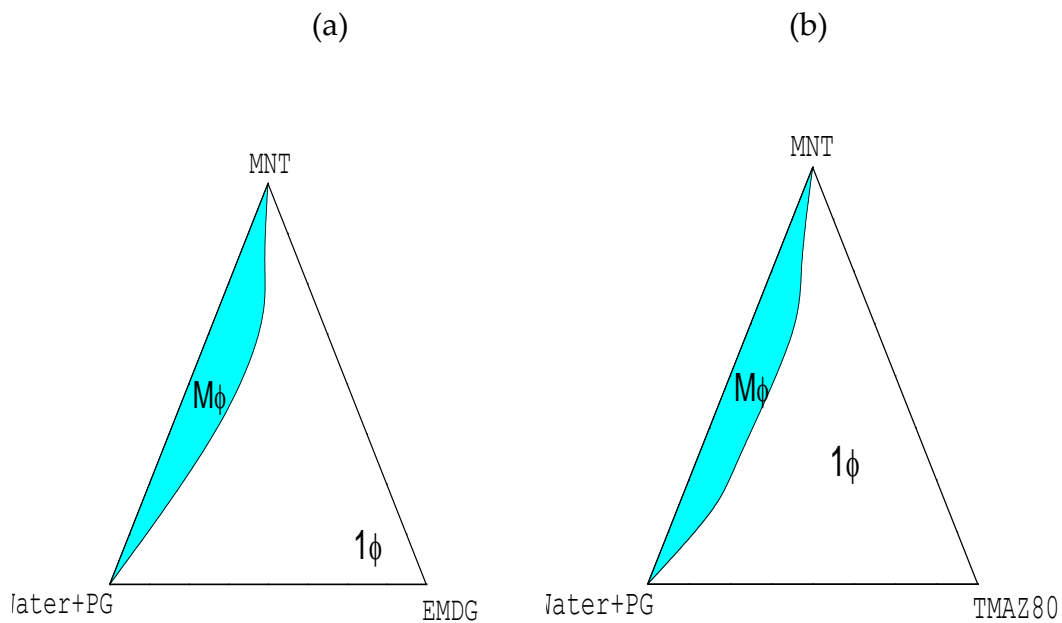


Figure 4.31: Phase diagrams of system: water +propylene glycol (2:1)/ethoxylated surfactant / peppermint oil at 45 °C. Ethoxylated surfactants used in these diagrams were: (a) EMDG (b) TMAZ 80.

Table 4.11: Total monophasic area for ethoxylated surfactant at different temperature.

surfactant	A_T		
	25 °C	37 °C	45 °C
EMDG	75.73	76.91	77.66
TMAZ80	75.81	79.37	79.43

The total monophasic area (A_T) for microemulsion system based on EMDG was found less than total monophasic area based on TMAZ80 as represent in table 4.11 due to the substitution of hydroxyl group by oxyethylene group on sorbitan ring increase the hydrophilicity of surfactant. The systems based on TMAZ80 and EMDG was temperature-insensitive in the temperature range 25–45 °C.

It was found that the total monophasic area for ethoxylated sucrose surfactant in the presence of propylene glycol is higher than without propylene glycol at all temperature for the same system which was due to that surfactant become more soluble in the aqueous phase (propylene glycol-water mixture) than it is in oil, and as a result the hydration of the hydrophilic chain of the surfactant molecules remains strong with increase of temperature [28, 32].

It was found that the total monophasic area for microemulsion systems based on peppermint oil and propylene glycol as co-solvent is larger than microemulsion systems without propylene glycol this is due to the exchange of propylene glycol between interfacial film and water phase make the film porous and so more fluid [31,35].

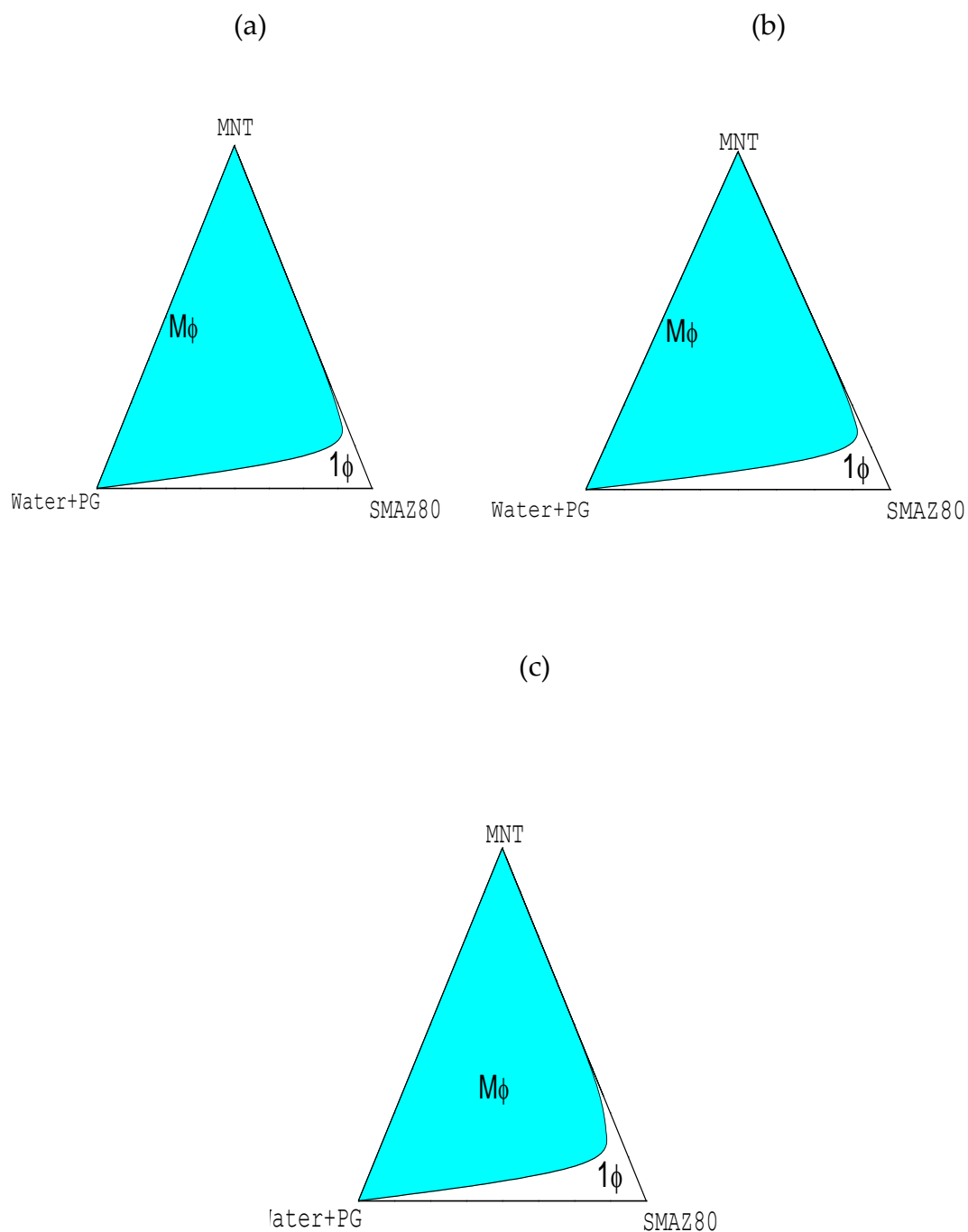


Figure 4.32: Phase diagrams of system: water +propylene glycol (2:1)/sucrose monooleate / peppermint oil where the temperature used in this system at (a) 25 °C (b) 37 °C (c) 45 °C.

Table 4.12: Total monophasic area for sorbitan monooleate at different temperatures.

surfactant	A _T		
	25 °C	37 °C	45 °C
SMAZ80	10.32	10.08	10.98

It was found that sorbitan monooleate without propylene glycol did not form microemulsion while in presence of propylene glycol microemulsions were formed due that the solubility of surfactants increases in presence of propylene glycol.

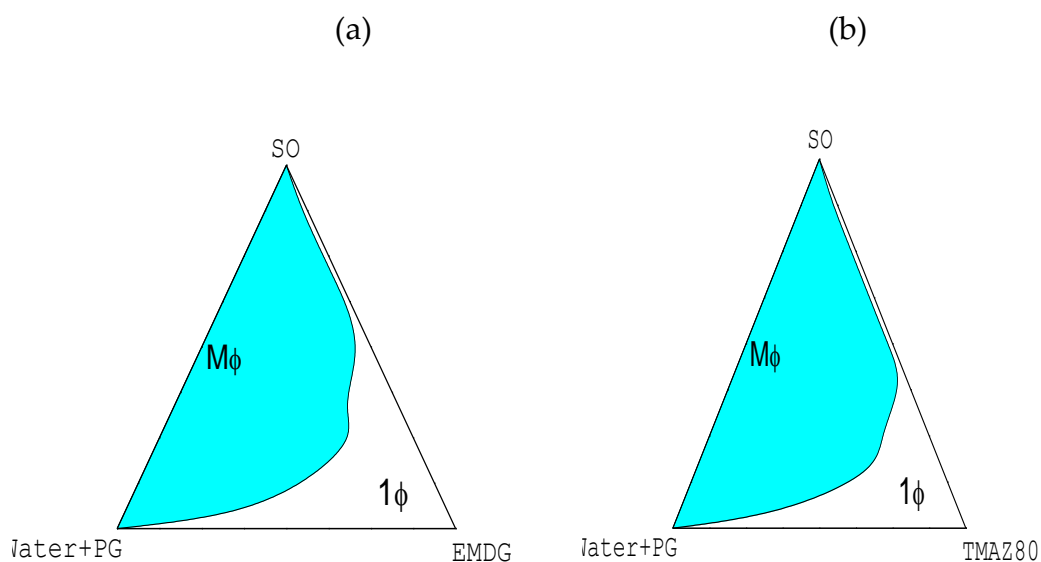


Figure 4.33: Phase diagrams of system: water +propylene glycol (2:1)/ethoxylated surfactant / sesame oil at 25 °C , ethoxylated surfactants used in these diagrams were : (a) EMDG (b) TMAZ80 .

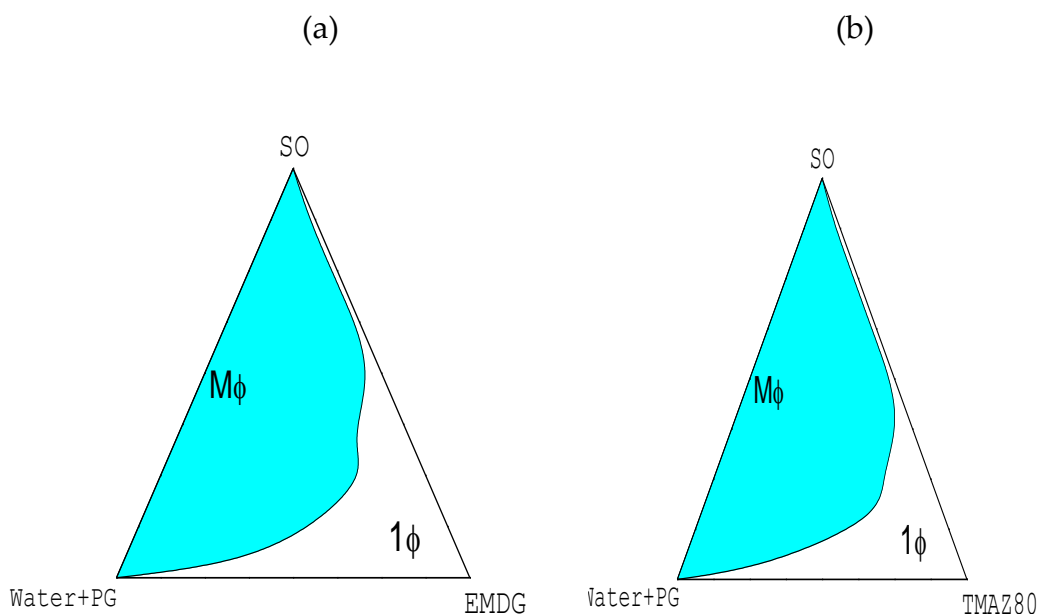


Figure 4.34: Phase diagrams of system: water +propylene glycol (2:1)/ethoxylated surfactant / sesame oil at 37 °C, ethoxylated surfactants used in these diagrams were : (a) EMDG (b) TMAZ80 .

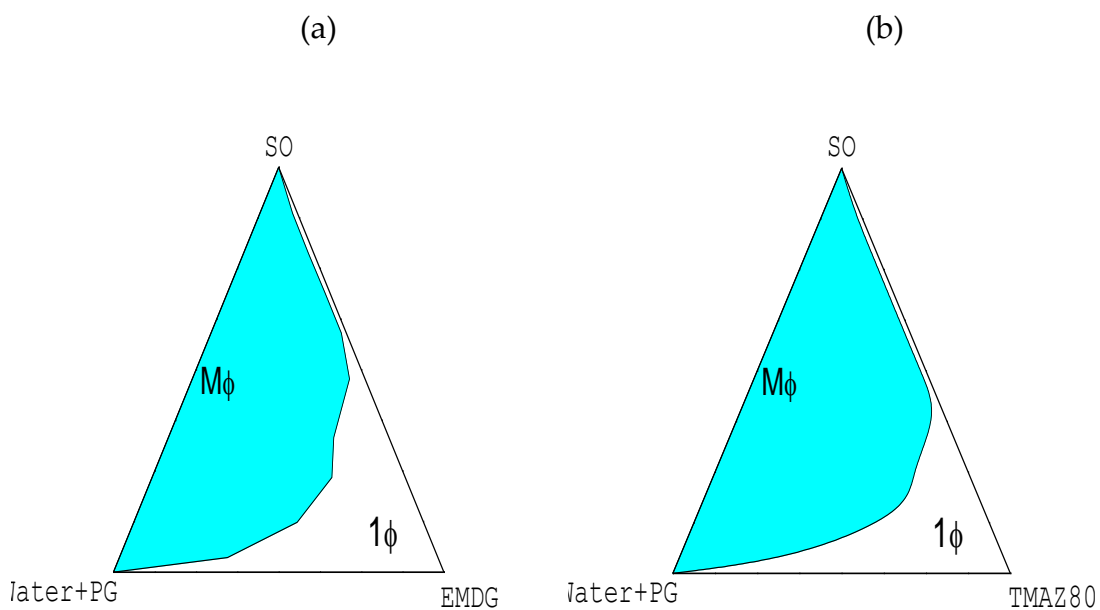


Figure 4.35: Phase diagrams of system: water +propylene glycol (2:1)/ethoxylated surfactant / sesame oil at 45 °C, ethoxylated surfactants used in these diagrams were : (a) EMDG (b) TMAZ80 .

Table 4.13: Total monophasic area for ethoxylated surfactant at different temperatures

surfactant	A_T		
	25 °C	37 °C	45 °C
EMDG	28.08	28	28
TMAZ80	22.84	25	22

The total monophasic area (A_T) for microemulsion system based on EMDG was more than total monophasic area based on TMAZ80 as represented in table 4.13. This is due to that the hydrophilicity of EMDG (more ethoxylated groups) is higher than the hydrophilicity of TMAZ80. The systems based on TMAZ80 and EMDG were temperature-insensitive in the range 25–45 °C.

4.1.1.3 Mixed surfactants

It was found that mixture of surfactant is more effective than single surfactant which was explained by synergistic phenomena. In this case synergistic phenomena caused by interaction between different head groups. Synergistic effect can be achieved by choosing surfactants that have the same head group and different tails. In general to maximize lateral molecular interaction that give stability to surfactants coated surfaces the chain length of surfactants must be the same. The difference in surfactants chain length cause interruption of monolayer film. Mixed surfactant with different chain length increases the spaces between adjacent surfactant molecules [33, 36].

Table 4.14: Total monphasic area for ethoxylated surfactant mixed with sucrose ester at 25 °C.

Surfactants (50:50)	A_T at 25 °C
O1570+EMDG	76.4
M1695+EMDG	73.87
L1695+EMDG	77.48
L595+EMDG	61.4

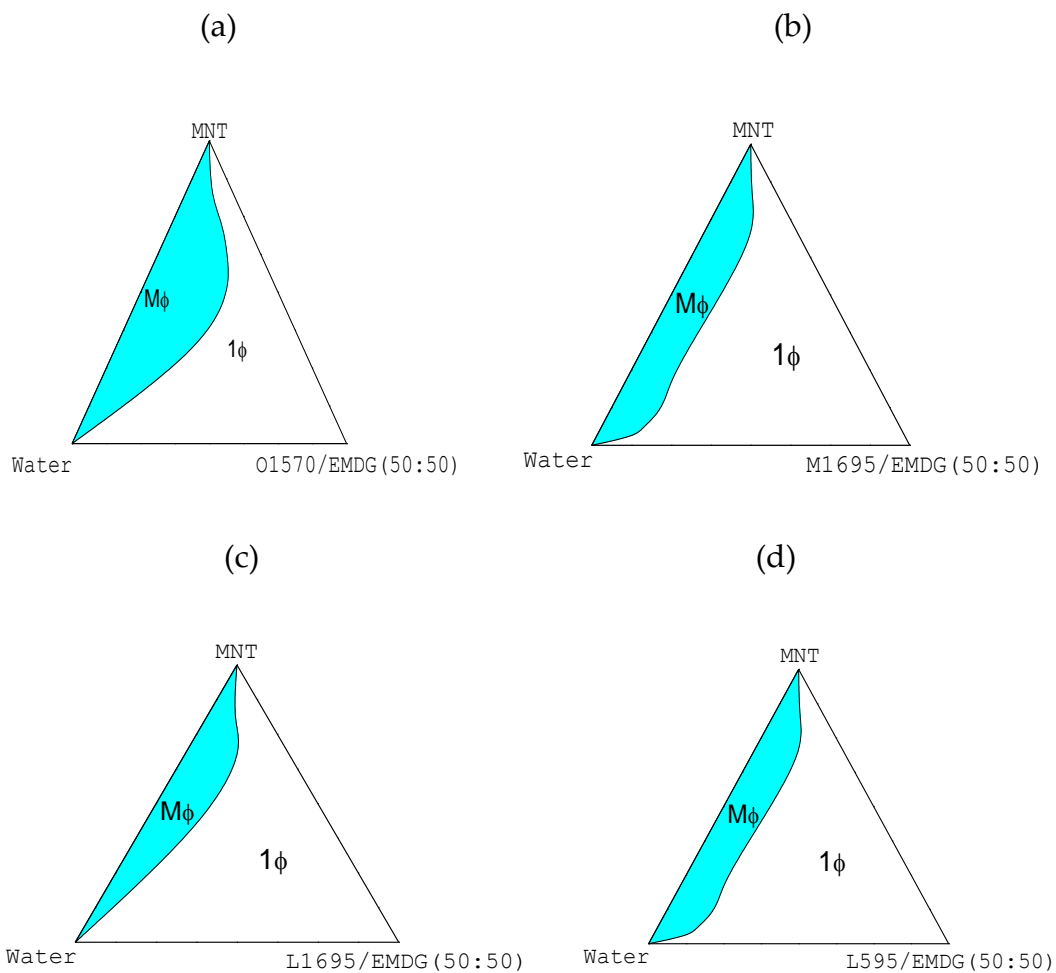


Figure 4.36: Phase diagrams of system: water /mixed surfactant / peppermint oil at 25 °C, sucrose ester surfactants mixed with ethoxylated surfactant used in these diagrams were: (a) EMDG + O1570 (b) EMDG + M1695 (c) L1695 + EMDG (d) L595 + EMDG.

It was found that when EMDG (total mono phasic area for EMDG in ternary microemulsion system based on peppermint oil at 25 °C is equal to 48%) was mixed with sucrose ester surfactants the total mono phasic area has been increased as represented in table 4.14. this was due to the increase of disordering and the fluidity of interfacial film which cause decreasing in surface tension when the two unequal surfactants chain length mixed [36, 41].

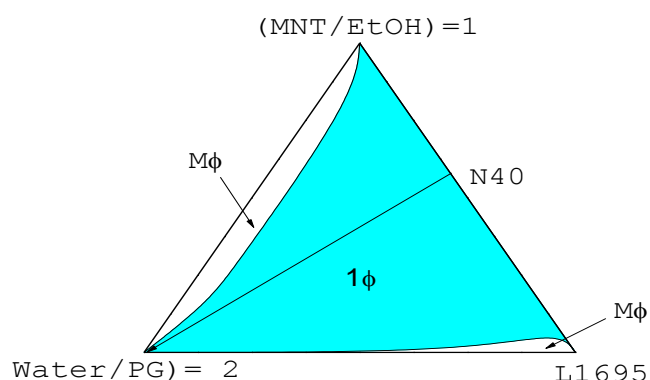


Figure 4.37: Pseudoternary phase diagram of the system (W+PG)/ L1695/ (MNT+ EtOH) at 25 °C where the weight ratios of (W/PG) = 2 and (MNT/ EtOH) = 1.

Fig 4.37 show increase in total monophasic area when ethanol introduced to the system ((W+PG)/ L1695/ (MNT+ EtOH)) due to the fact that alcohol increase the flexibility of the interfacial film by inserting itself between surfactants causing decrease the interaction between surfactants.

4.2 Dynamic Viscosity

Viscosity measurement has the potential of giving first hand information on the internal consistency and overall geometry of the material in solution. Viscosity studies have been applied to investigate the hydration and inter-particle interaction of microemulsion droplet. Viscosity of formulated microemulsion depends mainly on the micremulsion structure, type and shape of aggregation,

concentration and interaction between dispersed phases. So viscosity can be used to obtain real information about the microstructural changes in microemulsions [42].

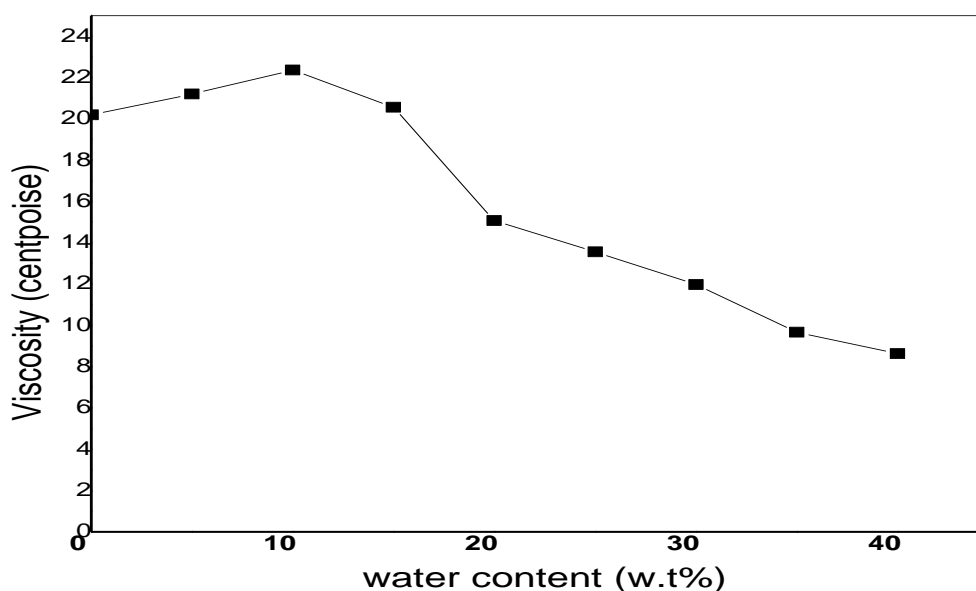


Figure 4.38: Plot of Dynamic viscosity as a function of (W+PG) content (wt %) for the system (W + PG) / L595/ (MNT+ EtOH) at 25 °C along the dilution line N40 where the weight ratio of (W /PG) = 2 and (MNT/ EtOH) = 1.

A Newtonian behavior is observed when the viscosity of the microemulsion system (W+PG)/L595/ (MNT+EtOH) was measured along the dilution line N40. Figure 4.38 presents the variation of the dynamic viscosity as function of aqueous phase (W+PG) content for the system tested. At aqueous phase contents below 10 wt% the dynamic viscosity increases slightly. For aqueous phase contents between 10 and 20 wt% sudden decrease in the viscosity was observed with increasing the aqueous phase. Then the viscosity of the microemulsion decreases slightly.

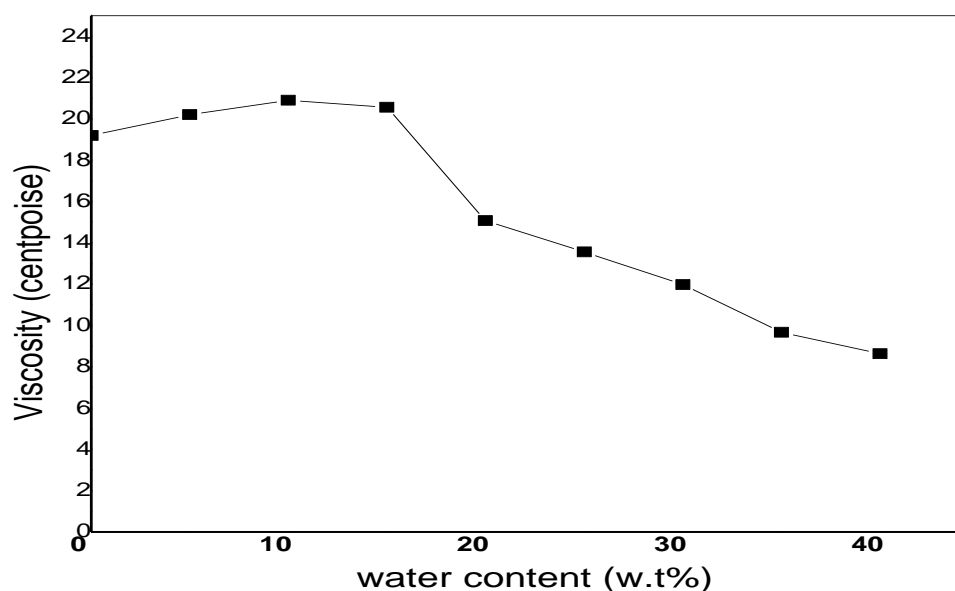


Figure 4.39: Plot of Dynamic viscosity as a function of (W+PG) content (wt %) for the system (W + PG) / L595/ (BA+ EtOH) at 25 °C along the dilution line N40 where the weight ratio of (W /PG) = 2 and (BA / EtOH) = 1.

The viscosity of the microemulsion system (W+PG)/L595/ (BA+EtOH) was measured along the dilution line N40. Figure 4.39 shows the variation of the dynamic viscosity as function of aqueous phase (W+PG) content for the system tested. At aqueous phase contents below 10 wt% the dynamic viscosity increased slightly. For aqueous phase contents between 10 and 20 wt% sudden decreases in the viscosity was observed and with increasing the aqueous phase the viscosity of the microemulsion decreased slightly.

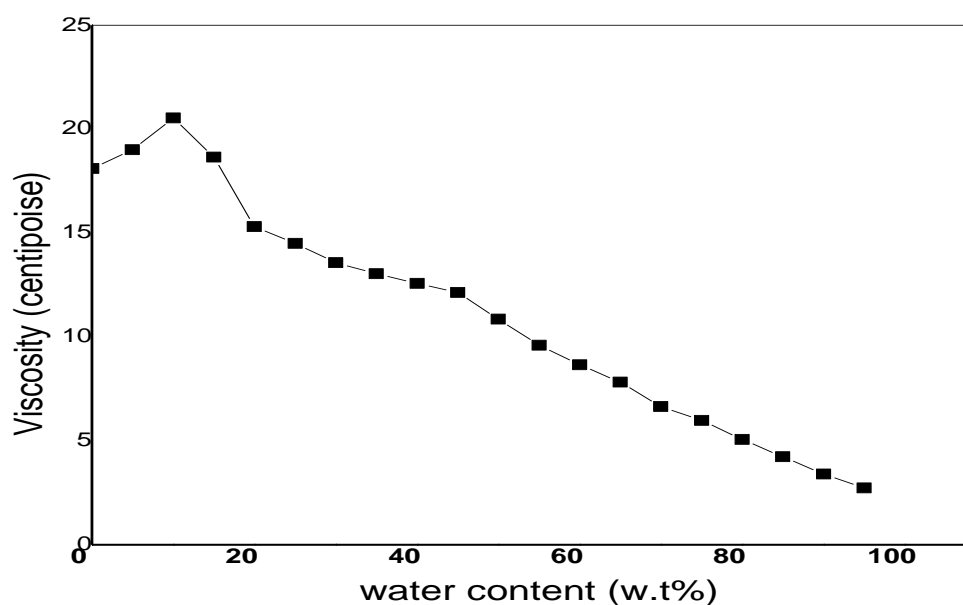


Figure 4.40: Plot of Dynamic viscosity as a function of (W+PG) content (wt %) for the system (W + PG) / L1695/ (MNT+ EtOH) at 25 °C along the dilution line N40 where the weight ratio of (W /PG) = 2 and (MNT/ EtOH) = 1.

The viscosity of the microemulsion system (W+PG)/L1695/ (MNT+EtOH) was measured along the dilution line N40. Figure 4.40 showed the variation of the dynamic viscosity as function of aqueous phase (W+PG) content for the system tested. At aqueous phase contents below 10 wt% the dynamic viscosity increased slightly. A sudden decrease in the viscosity happens at water content equals 10 wt%. For aqueous phase contents between 10 and 25 wt% the viscosity of the microemulsion decreased slightly then a sudden decrease in the viscosity observed with increasing the aqueous phase content to 30 wt%. The viscosity decreases slightly until aqueous phase content reaches 50 wt%. At 55 wt% aqueous phase content a sharp decrease in the viscosity is observed then it decreases slightly until 80 wt% aqueous phase content. Another sharp decrease in the viscosity is observed at 85 wt% aqueous phase content.

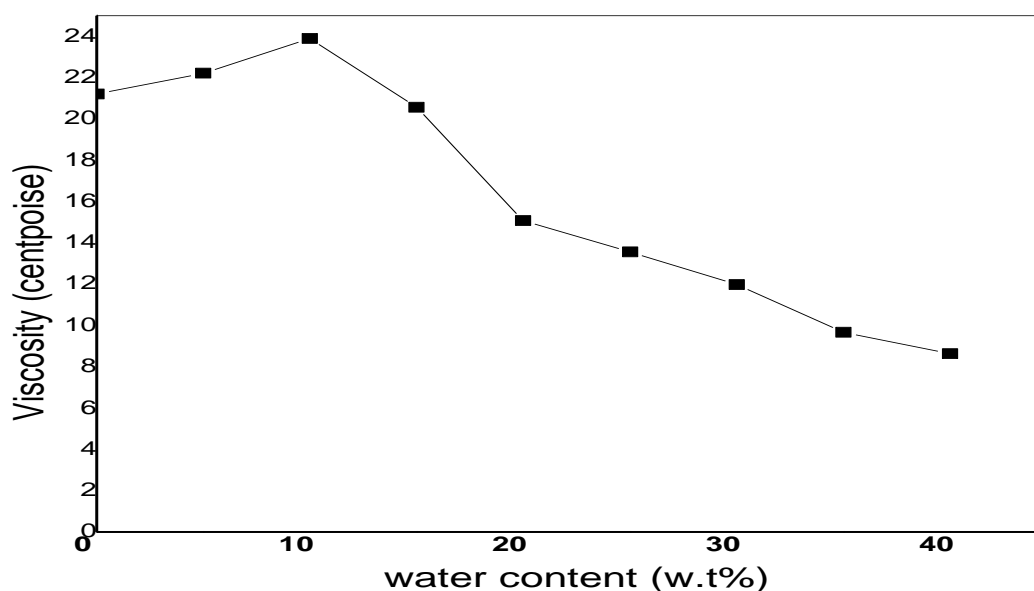


Figure 4.41: Plot of Dynamic viscosity as a function of (W+PG) content (wt %) for the system (W + PG) / L1695/ (BA+ EtOH) at 25 °C along the dilution line N40 where the weight ratio of (W /PG) = 2 and that of (BA/ EtOH) = 1.

The viscosity of the microemulsion system (W+PG)/L1695/ (BA+EtOH) was measured along the dilution line N40. Figure 4.41 presented the variation of the dynamic viscosity as function of aqueous phase (W+PG) content for the system tested. A sudden decrease in the viscosity happens at water content equals 10 wt%. Sharp decrease in the viscosity observed with increasing the aqueous phase content up to 25%. Then the viscosity of the microemulsion decreased slightly with water content increase.

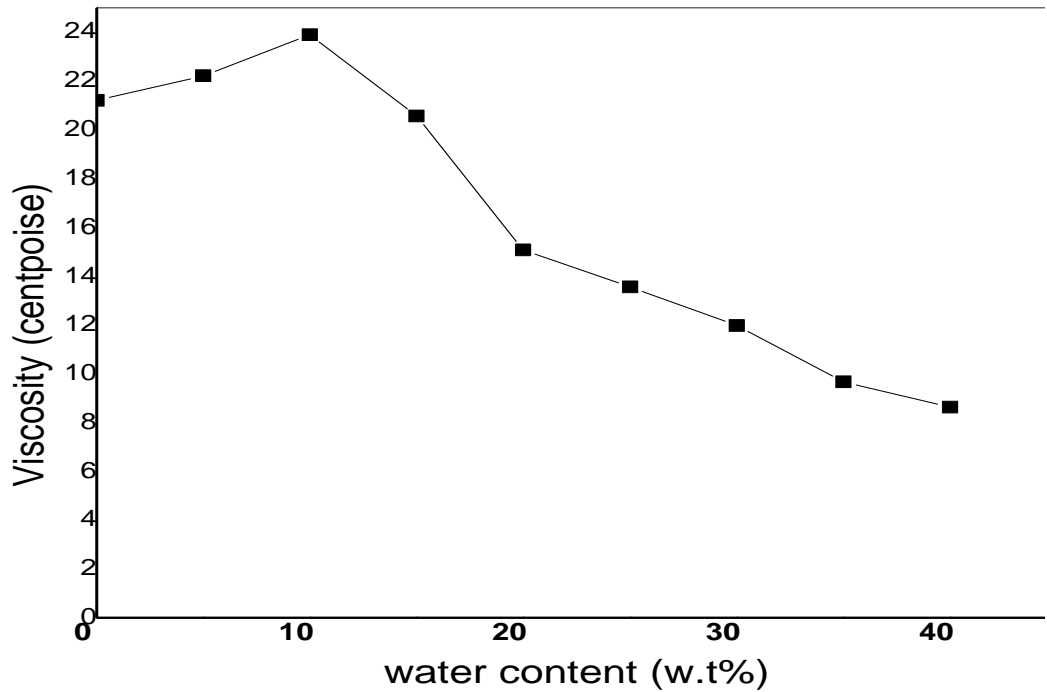


Figure 4.42: Plot of Dynamic viscosity as a function of (W+PG) content (wt %) for the system (W + PG) / L1695/ MNT at 25 °C along the dilution line N40 where the weight ratio of (W /PG) = 2.

the viscosity of the microemulsion system (W+PG)/L1695/ MNT was measured along the dilution line N40 .Figure 4.42 presented the variation of the dynamic viscosity as function of aqueous phase (W+PG) content for the system tested. A sudden decrease in the viscosity happens at water content equals 10 wt%. Then sharp decrease in the viscosity is observed up to 20 %. Then the viscosity of the microemulsion decreased slightly.

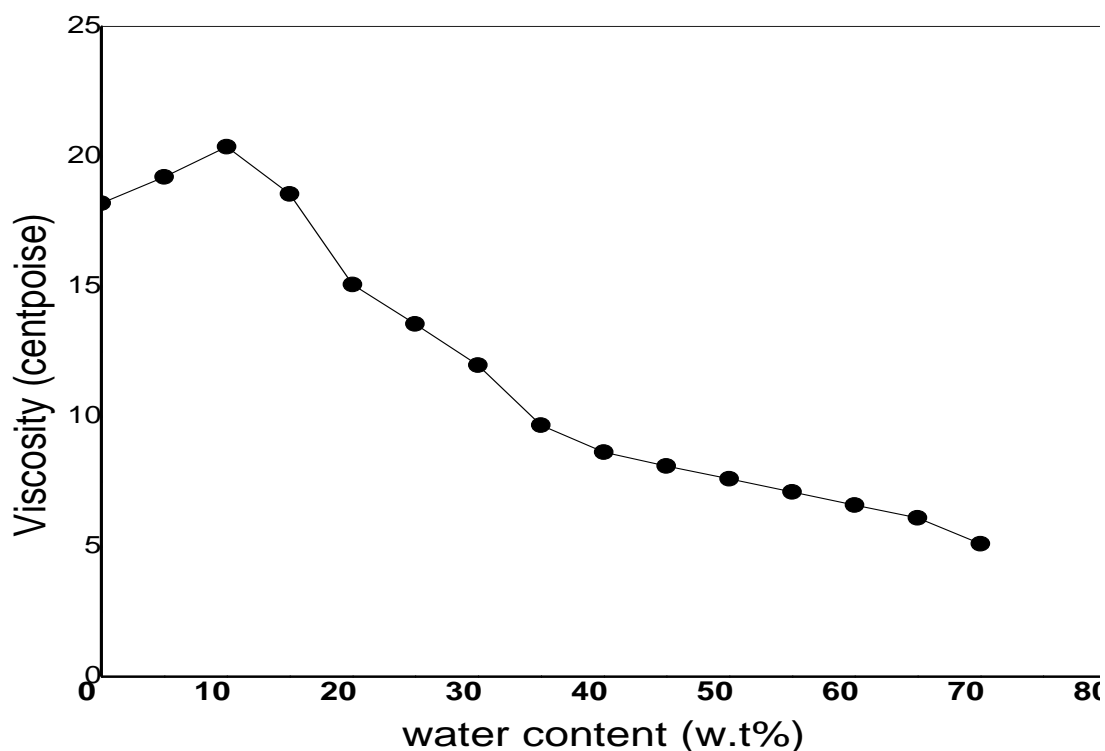


Figure 4.43: Plot of Dynamic viscosity as a function of water content (wt %) for the system W / L1695/ MNT+EtOH at 25 °C along the dilution line N40 where the weight ratio of (MNT /EtOH) = 1.

The viscosity of the microemulsion system W/L1695/ MNT+ EtOH was measured along the dilution line N40 .Figure 4.43 presents the variation of the dynamic viscosity as function of aqueous phase (W+PG) content for the system tested. A sudden decrease in the viscosity happened at water content equals 10 wt% up to 40 %. Then the viscosity of the microemulsion decreased slightly.

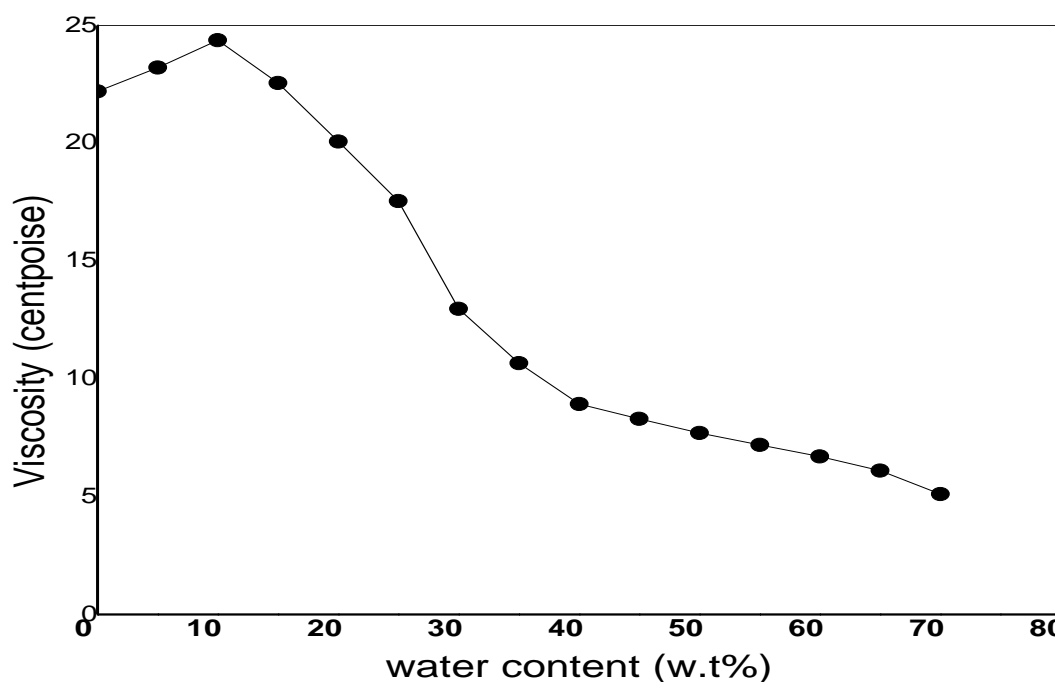


Figure 4.44: Plot of Dynamic viscosity as a function of water content (wt %) for the system W / L1695+EMDG (50:50)/ MNT+EtOH at 25 °C along the dilution line N60 where the weight ratio of (MNT /EtOH) = 1.

The viscosity of the microemulsion system W/L1695+EMDG (50:50)/ MNT+EtOH was measured along the dilution line N60. Figure 4.44 presents the variation of the dynamic viscosity as function of aqueous phase (w) content for the system tested. A sudden decrease in the viscosity happens at water content equals 10 wt%. Sharp decrease in the viscosity is observed up to 40 %. Then the viscosity of the microemulsion decreased slightly.

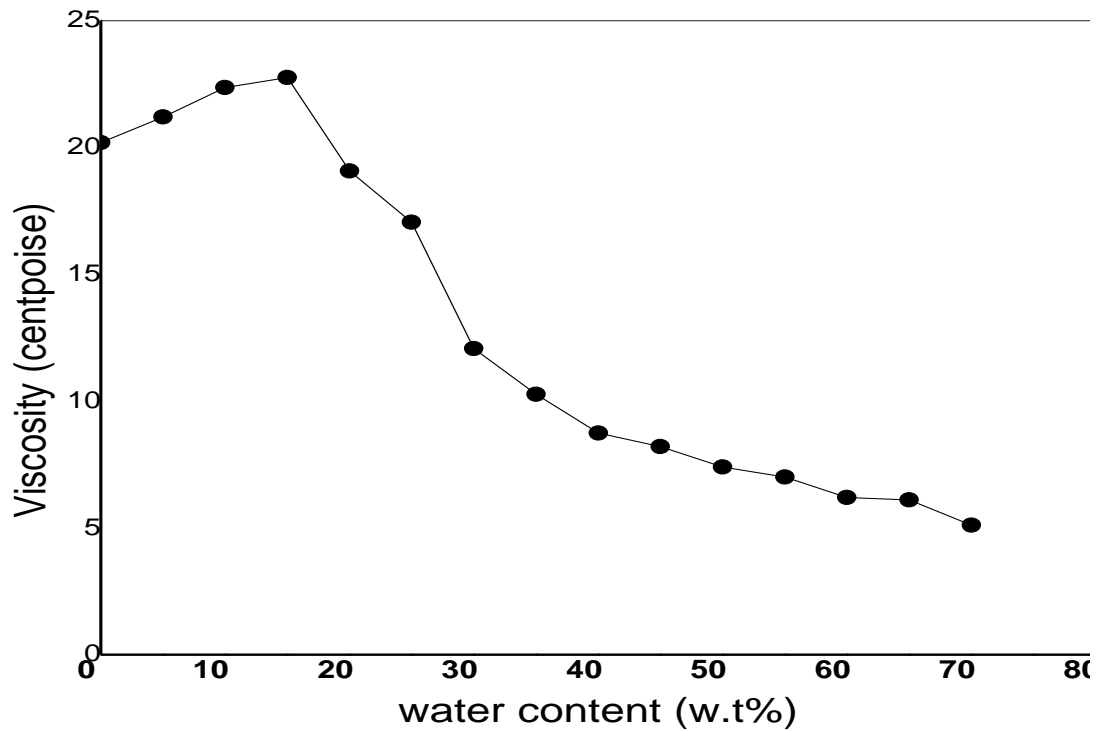


Figure 4.45: Plot of Dynamic viscosity as a function of water content (wt %) for the system W / L1695+EMDG (75:25)/ MNT+EtOH at 25 °C along the dilution line N60 where the weight ratio of (MNT /EtOH) = 1.

the viscosity of the microemulsion system W/L1695+EMDG (75:25)/ MNT+EtOH was measured along the dilution line N40 shown in Figure 4.45 presents the variation of the dynamic viscosity as function of aqueous phase (W+PG) content for the system tested. A sudden decrease in the viscosity happens at water content equals 20 wt%. Then sharp decrease in the viscosity is observed up to 35 %. Then the viscosity of the microemulsion decreases slightly.

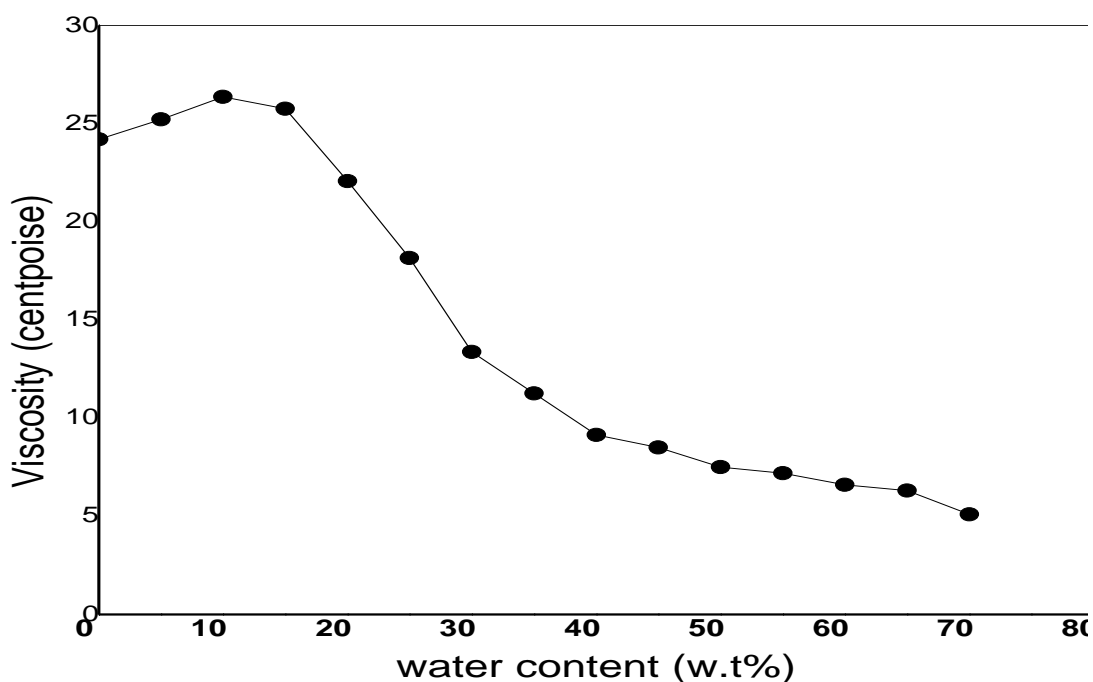


Figure 4.46: Plot of Dynamic viscosity as a function of water content (wt %) for the system W / L1695+EMDG (25:75)/ MNT+EtOH at 25 °C along the dilution line N60 where the weight ratio of (MNT /EtOH) = 1.

The viscosity of the microemulsion system W/L1695+EMDG (25:75)/ MNT+EtOH was measured along the dilution line N40. Figure 4.46 presents the variation of the dynamic viscosity as function of aqueous phase (W) content for the system tested. A sudden decrease in the viscosity happens at water content equals 20 wt%. Then sharp decrease in the viscosity is observed up to 40 %. Then the viscosity of the microemulsion decreased slightly.

All microemulsion systems which have been studied showed the same trends as follow:

At the beginning, the viscosity increase with water content increase, this is explained by the increase in diameter of water filled conduits in the bicontinuous structure and also due to the increase in the number of droplets, the peak point in

the viscosity (water) profile denotes transition point of the water –in-oil system to bicontinuous structure system [22,27,31,42].

At low weight fraction of aqueous phase, microemulsion consists of isolated water globules dispersed in the continuous oil medium and so minimal interaction between the globules happen. In the bicontinuous region of microemulsion the interconnected channels increase the molecular interactions and hence increase in the viscosity, at certain amount of aqueous phase, sudden decrease in viscosity is happened which is due to change in microstructure or transition bicontinuous phase into an oil-in-water microemulsion [31,42].

4.3 Electrical conductivity

Electrical conductivity measurements give an indication about microstructure of microemulsion. This implies that the most important factor affecting the conductivity behavior of the microemulsion is the structure characteristics. The size of micelles and the aggregation number of surfactant were controlled by the amount of water added at the beginning and the alcohol present on the interface.

In microemulsion, three kinds of water can be distinguished: free water, water hydrated to the Na⁺ counter ion, water hydrogen bonded to the surfactant polar group. Almost all water molecules will be associated with surfactant if the amount of water is low; there are few water molecules to supply a diffusion environment for charged hydrated Na⁺ ion, giving very low conductivity [20, 29, 44].

The addition of alcohol cause increase in the aggregation of surfactant molecules , thickness of interface also become larger, and water pool size become larger, as a result, firstly the amount of free water increased compared with the amount of water hydrated to the sodium ions and water hydrogen bonded to the surfactant polar groups. A rapid increase in the self-diffusion coefficient of water molecules should lead to an increase in the self-diffusion of sodium ions as well. secondly, the droplets become" softer" and it is easier for charge carriers to get through. The large rise in conductivity could be attributed to the large attractive interaction forces among the droplets leading to the permeation of the electrolyte [20, 29, 38, 43].

Electrical conductivity is affected by components exchange between existing environments: water exchange between the bound and free water, counter ions exchange between the ionic head groups of the surfactant and core water, co-surfactants exchange among the interfacial film, the continuous phase and the dispersed phase if soluble in the phase, surfactants exchange between the aqueous phase and interfacial film [28, 35].

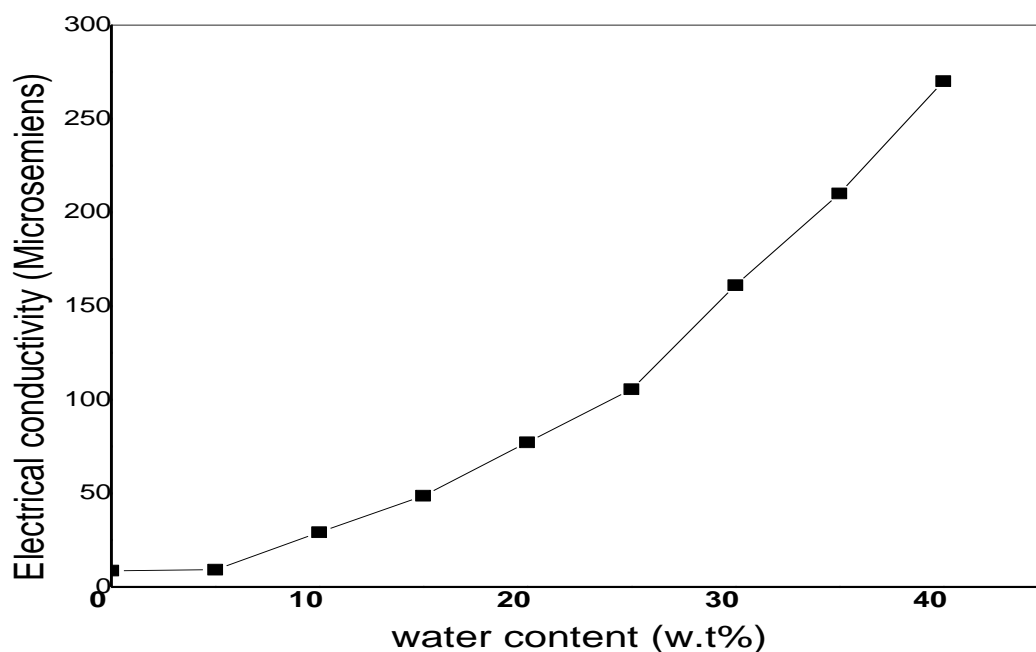


Figure 4.47: Plot of electrical conductivity as a function of (W +NaCl+ PG) content (wt %) for the system (W +NaCl + PG) / L595/ (MNT+ EtOH) at 25 °C along the dilution line N40 where the weight ratio of (W /PG) = 2 and that of (MNT/ EtOH) = 1. The concentration of NaCl in (W+PG) is 0.05 M.

The electro conductivity behavior is observed when the electrical conductivity of the microemulsion system (W+PG+NaCl)/L595/ (MNT+EtOH) was measured along the dilution line N40 shown in Figure 4.47 which presents the variation of the electrical conductivity as function of aqueous phase (W+PG) content for the system tested. At aqueous phase contents 0 wt% the electrical conductivity is very low due to the absence of electrolyte when the aqueous content increased from 0% to 20% the electrical conductivity has been slightly increased in steadily fashion. A sudden increase in the electrical conductivity happens at water content above 20 wt% until 40wt%.

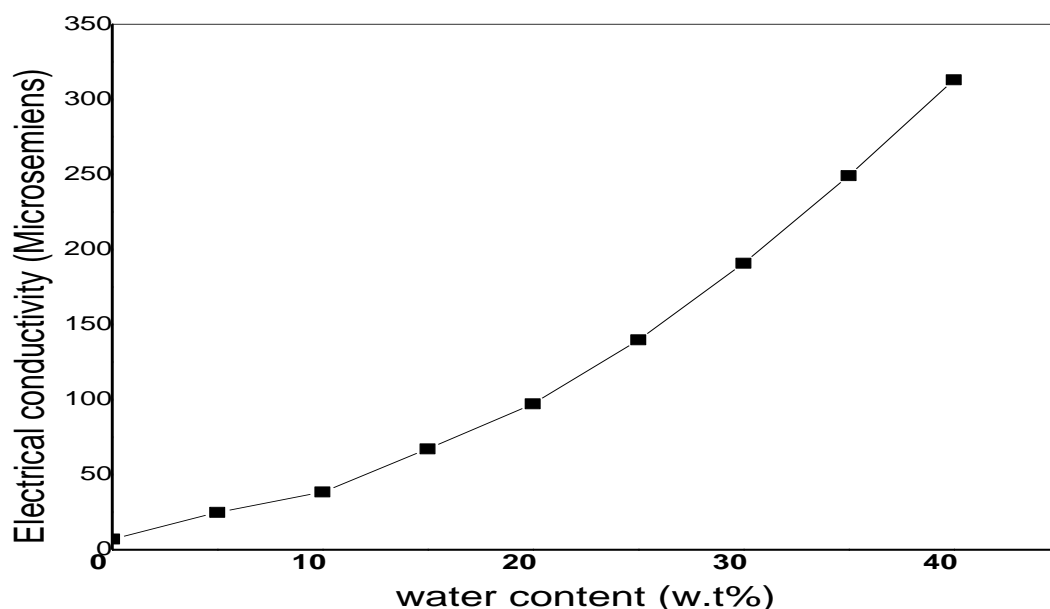


Figure 4.48: Plot of electrical conductivity as a function of (W +NaCl+ PG) content (wt %) for the system (W +NaCl + PG) / L595/ (BA+ EtOH) at 25 °C along the dilution line N40 where the weight ratio of (W /PG) = 2 and that of (BA/ EtOH) = 1. The concentration of NaCl in (W+PG) is 0.05 M.

The electroconductivity behavior is observed when the electrical conductivity of the microemulsion system (W+PG+NaCl)/L595/ (BA+EtOH) was measured along the dilution line N40 shown in Figure 4.48 which presents the variation of the electrical conductivity as function of aqueous phase (W+PG) content for the system tested. At aqueous phase contents 0 wt% the electrical conductivity is very low due to the absence of electrolyte when the aqueous content increase from 0% to 10 % the electrical conductivity has been slightly increased in steadily fashion. A sudden increase in the electrical conductivity happens at water content 15 wt% until 40wt%.

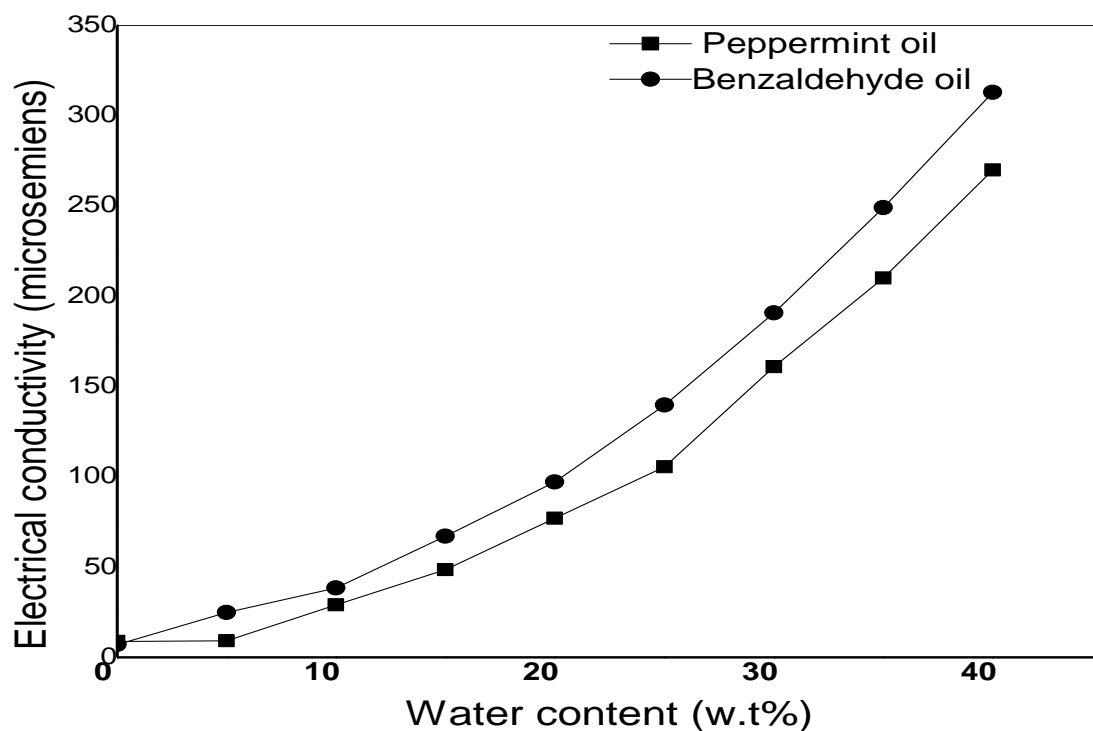


Figure 4.49: Plot of electrical conductivity as a function of (W +NaCl+ PG) content (wt %) for the systems :(\bullet) (W +NaCl + PG) / L595/ (BA+ EtOH) at 25 °C along the dilution line N40 where the weight ratio of (W /PG) = 2 and that of (BA/ EtOH) = 1. The concentration of NaCl in (W+PG) is 0.05 M (\blacksquare) (W +NaCl + PG) / L595/ (MNT+ EtOH) at 25°C along the dilution line N40 where the weight ratio of (W /PG) = 2 and that of (MNT/ EtOH) = 1.

Small decrease in electrical conductivity when benzaldehyde oil substituted by peppermint oil this is due to variation in the conductivity of these two oil as shown in figure 4.49.

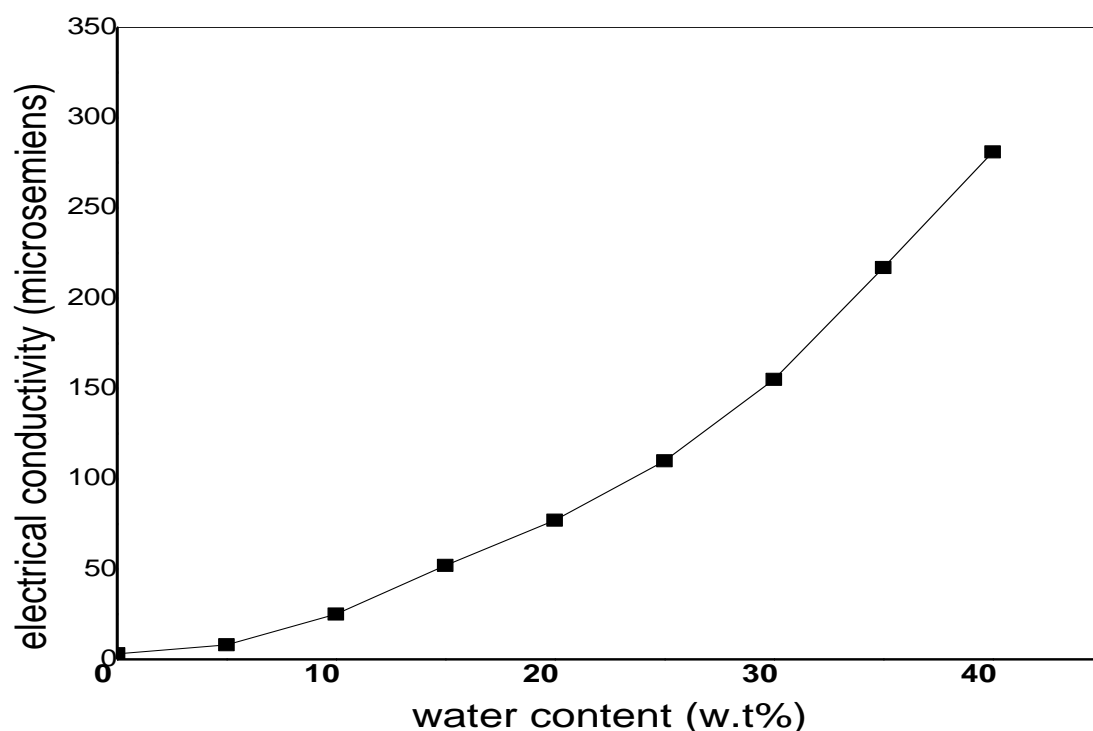


Figure 4.50: Plot of electrical conductivity as a function of (W +NaCl+ PG) content (wt %) for the system: (W +NaCl + PG) / L1695/ MNT at 25 °C along the dilution line N40. The concentration of NaCl in (W+PG) is 0.01 M.

the electrical conductivity of the microemulsion system (W+PG+NaCl)/L1695/ MNT was measured along the dilution line N40 shown in Figure 4.50 which presents the variation of the electrical conductivity as function of aqueous phase (W+PG) content for the system tested. At aqueous phase contents 0 wt% the electrical conductivity is very low due to the absence of electrolyte when the aqueous content increase from 0% to 15 % the electrical conductivity has been slightly increased in steadily fashion. A sudden increase in the electrical conductivity happens at water content 15 wt% until 40wt%.

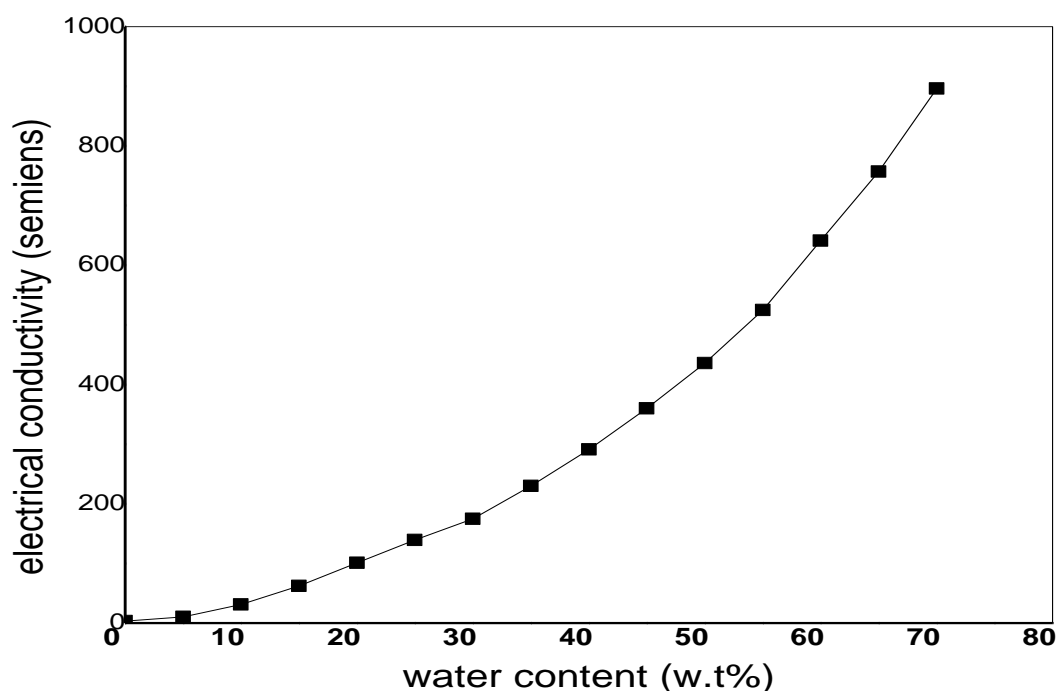


Figure 4.51: Plot of electrical conductivity as a function of (W +NaCl) content (wt %) for the system (W +NaCl) / L1695/ MNT+EtOH at 25 °C along the dilution line N40 where the weight ratio of (MNT /EtOH) = 1. The concentration of NaCl in (W+PG) is 0.01 M.

The electroconductivity behavior is observed when the electrical conductivity of the microemulsion system (W +NaCl)/L595/ MNT+EtOH was measured along the dilution line N40 shown in Figure 4.51 which presented the variation of the electrical conductivity as function of aqueous phase (W+PG) content for the system tested. At aqueous phase contents 0 wt% the electrical conductivity is very low due to the absence of electrolyte when the aqueous content increase from 0% to 25 % the electrical conductivity has been slightly increased in steadily fashion. A sudden increase in the electrical conductivity happens at water content 25 wt% until 45wt%. Another sharp decrease happened from 45% up to the end which explained by structure transition to oil-in-water microemulsion

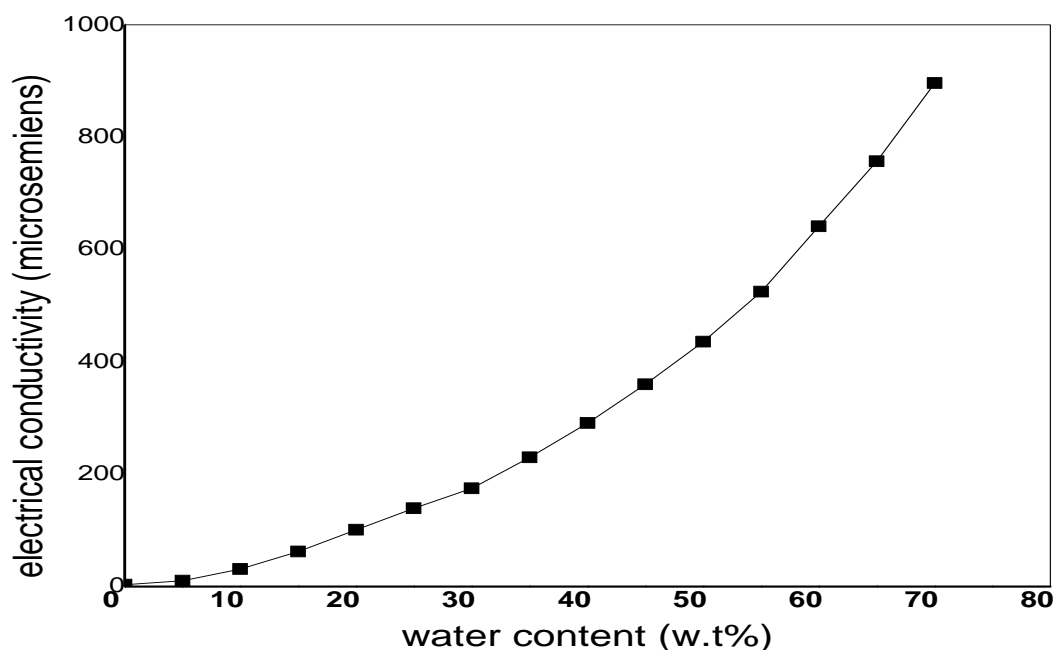


Figure 4.52: Plot of electrical conductivity as a function of (W +NaCl) content (wt %) for the system (W +NaCl) / L1695+EMDG (50:50)/ MNT+EtOH at 25 °C along the dilution line N60 where the weight ratio of (MNT /EtOH) = 1. The concentration of NaCl in (W+PG) is 0.01 M.

The electroconductivity behavior is observed when the electrical conductivity of the microemulsion system (W +NaCl)/ L1695+EMDG(50:50)/ MNT+EtOH was measured along the dilution line N60 shown in Figure 4.52 which presented the variation of the electrical conductivity as function of aqueous phase (W +NaCl) content for the system tested. At aqueous phase contents 0 wt% the electrical conductivity is very low due to the absence of electrolyte when the aqueous content increase from 0% to 25 % the electrical conductivity has been slightly increased in steadily fashion. A sudden increase in the electrical conductivity happens at water content 25 wt% until 45wt%. Another sharp decrease happened from 45% up to the end which explained by structure transition to oil-in-water microemulsion

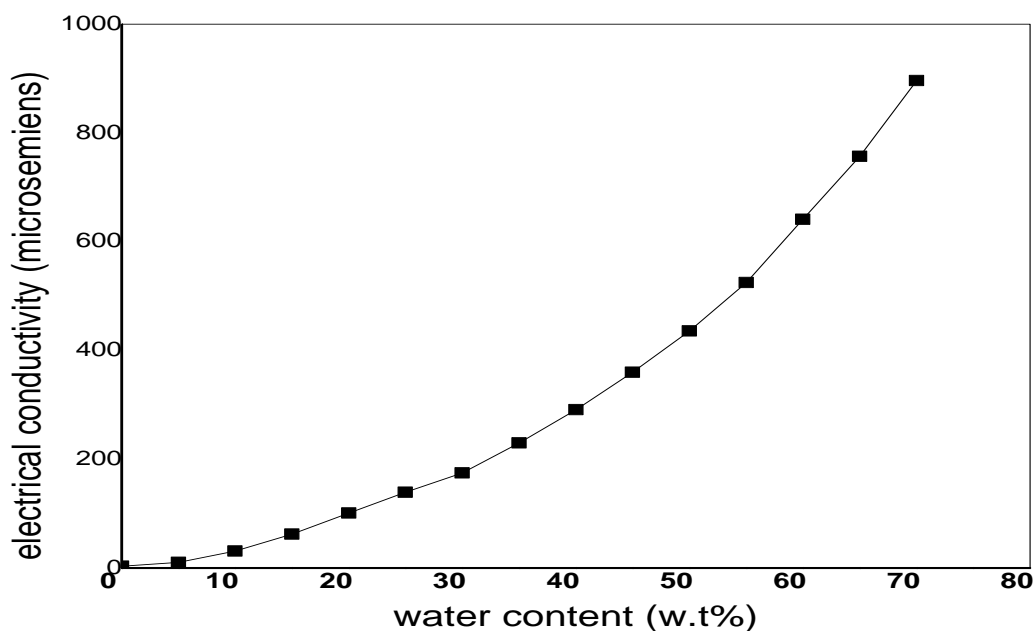


Figure 4.53: Plot of electrical conductivity as a function of (W +NaCl) content (wt %) for the system (W +NaCl) / L1695+EMDG (75:25)/ MNT+EtOH at 25 °C along the dilution line N60 where the weight ratio of (MNT /EtOH) = 1. The concentration of NaCl in (W+PG) is 0.01 M.

The electroconductivity behavior observed when the electrical conductivity of the microemulsion system (W +NaCl) /L1695+EMDG(75:25)/MNT+EtOH was measured along the dilution line N40 shown in Figure 4.53 which presents the variation of the electrical conductivity as function of aqueous phase (W +NaCl) content for the system tested. At aqueous phase contents 0 wt% the electrical conductivity is very low due to the absence of electrolyte when the aqueous content increase from 0% to 25 % the electrical conductivity has been slightly increased in steadily fashion. A sudden increase in the electrical conductivity happens at water content 25 wt% until 45wt%. Another sharp decrease happened from 45%.

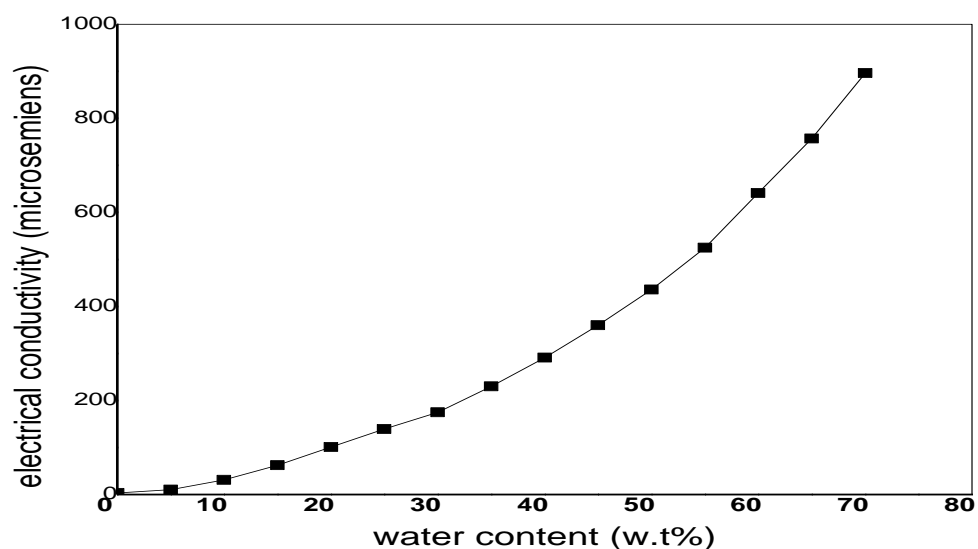


Figure 4.54: Plot of electrical conductivity as a function of (W +NaCl) content (wt %) for the system (W +NaCl) / L1695+EMDG (25:75)/ MNT+EtOH at 25 °C along the dilution line N60 where the weight ratio of (MNT /EtOH) = 1. The concentration of NaCl in (W+PG) is 0.01 M.

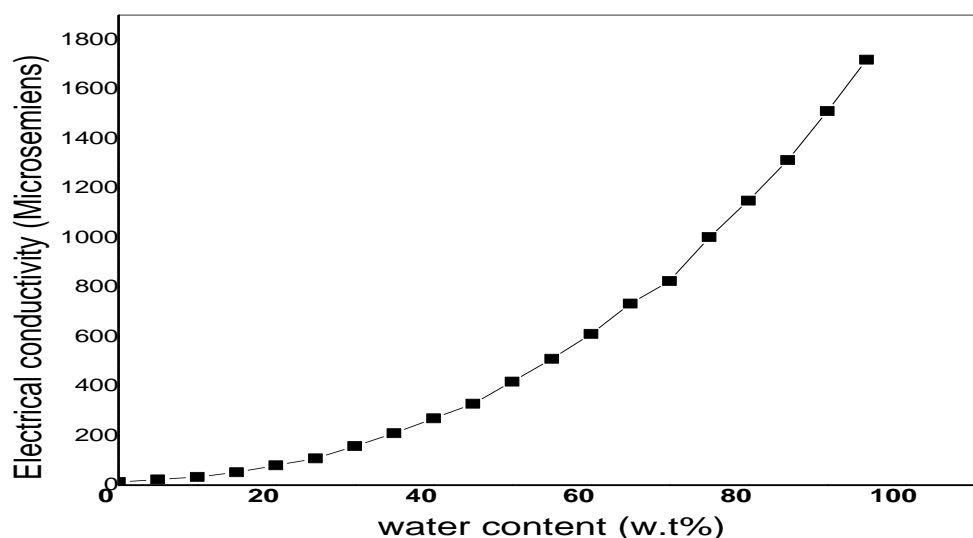


Figure 4.55: Plot of electrical conductivity as a function of (W +NaCl+ PG) content (wt %) for the system (W +NaCl + PG) / L1695/ (MNT+ EtOH) at 25 °C along the dilution line N40 where the weight ratio of (W /PG) = 2 and that of (MNT/ EtOH) = 1. The concentration of NaCl in (W+PG) is 0.05 M.

The electro conductivity behavior is observed when the electrical conductivity of the microemulsion systems: (W+PG+NaCl)/L1695/ (MNT+EtOH) and (W +NaCl) / L1695+EMDG (25:75)/ MNT+EtOH were measured along the dilution line N40 shown in Figure 4.55 and N60 shown in Figure 4.54 respectively which present the variation of the electrical conductivity as function of aqueous phase (W+PG) content for the system tested. At aqueous phase contents 0 wt% the electrical conductivity is very low due to the absence of electrolyte when the aqueous content increase from 0% to 20% the electrical conductivity has been slightly increased in steadily. A sudden increase in the electrical conductivity happens at water content 25 wt% until 40wt%. Sharply increased in the electrical conductivity happens at water content from 40 to 95% due to formation of oil in water microemulsion in which the aqueous phase become continuous forming free media for electrical current.

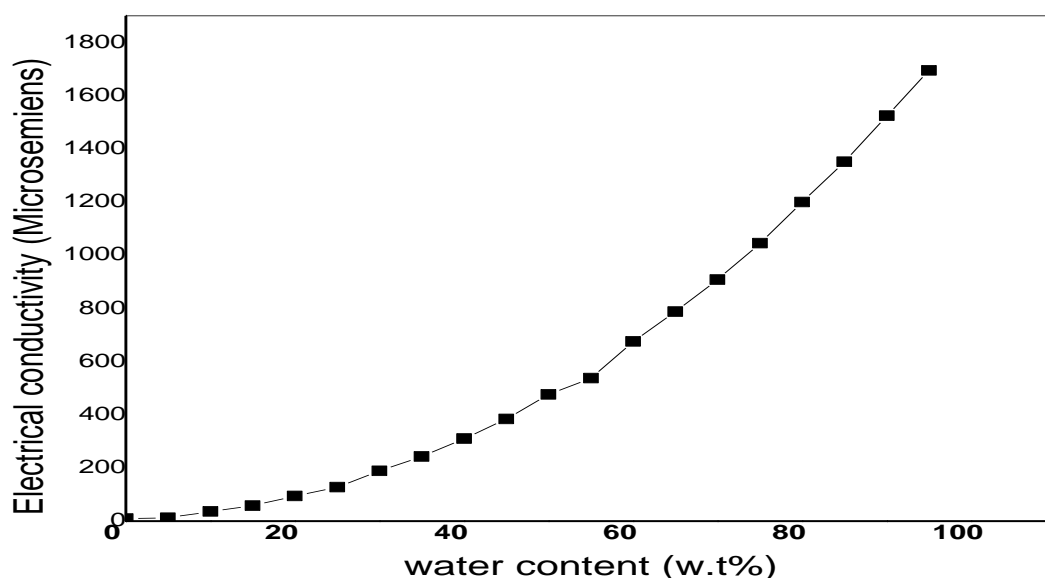


Figure 4.56: Plot of electrical conductivity as a function of (W +NaCl+ PG) content (wt %) for the system (W +NaCl + PG) / L1695/ (BA+ EtoH) at 25 °C along the dilution line N40 where the weight ratio of (W /PG) = 2 and that of (BA/ EtoH) = 1. The concentration of NaCl in (W+PG) is 0.05 M.

The system investigated is (W+PG+NaCl)/L1695/ (BA+EtOH) along the dilution line N40 shown in Figure 4.56. In principle, the substitution of a dilute aqueous solution of NaCl for aqueous phase may induce variation in the size and shape of the different regions of the phase diagram and, at the microscopic level, in the mode of aggregation of the surfactant molecules. However, if the amount of electrolyte added is small enough, these variations should not be significant [25].

At aqueous phase content smaller than 25 wt%, samples along the dilution line tested have low values of electrical conductivity suggesting that the reverse droplets are discrete and have little interaction with each other. In systems rich with water binding molecules such as ethanol, propylene glycol and sucrose esters, the water is strongly bound to one of these molecules or to all of them together [8]. At low aqueous phase contents (< 25 wt %), all of the water in the microemulsions system is confined in the vicinity of the interphasal region and no free water is found. Electrical conductivity rises as the aqueous phase content increases from 25 to 90 wt%, indicating that the interaction between the aqueous domains becomes increasingly important and a transition from W/O microemulsions to O/W microemulsions may be occurred.

The constant motion of dispersed droplet in microemulsion can cause fusion or dissociation, as well as form cluster of variable size and shape due to collide during motion. This phenomenon obviously affect on the conductance behavior of water-in-oil microemulsion. This phenomenon is called "Percolation" [34, 35].

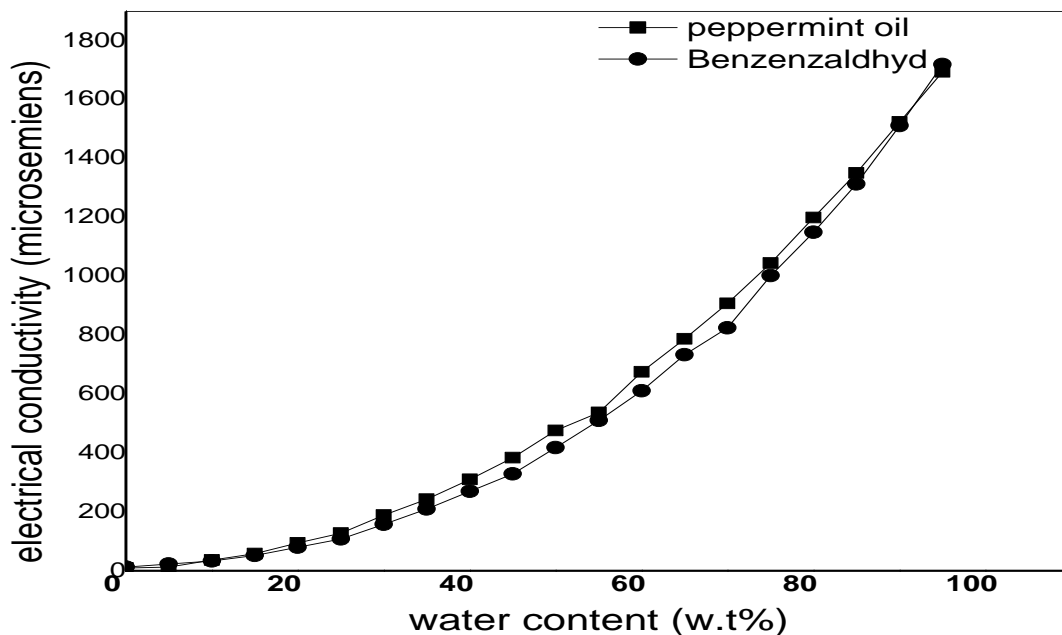


Figure 4.57: Plot of electrical conductivity as a function of (W +NaCl+ PG) content (wt %) for the systems : (■) (W +NaCl + PG) / L1695/ (BA+ EtOH) at 25 °C along the dilution line N40 where the weight ratio of (W /PG) = 2 and that of (BA/ EtOH) = 1. The concentration of NaCl in (W+PG) is 0.05 M (●) (W +NaCl + PG) / L1695/ (MNT+ EtOH) at 25°C along the dilution line N40 where the weight ratio of (W /PG) = 2 and (MNT/ EtOH) = 1.

Little difference was found in electrical conductivity profile between microemulsion systems based on peppermint oil and benzaldehyde oil when sucrose dilaurate used as surfactant on contrast to sucrose monolaurate as shown in figure 4.57.

At low water content, electrical conductivity was very low due to the fact the droplets are isolated from each other embedded in non-conducting continuous oil phase and hence contribute very little to the conductance, second stage, droplets begins to contact each other and form clusters which are sufficiently close to each other.

The number of clusters increase rapidly, giving rise to the observed changes of properties, in particular to the increase of electrical conductivity, attributed to either hopping of surfactant ions from droplet to droplet within droplet clusters, transfer of counter ions from one droplet to another through water channel opening between droplets during sticky collisions through transient merging droplet [34, 35, 39].

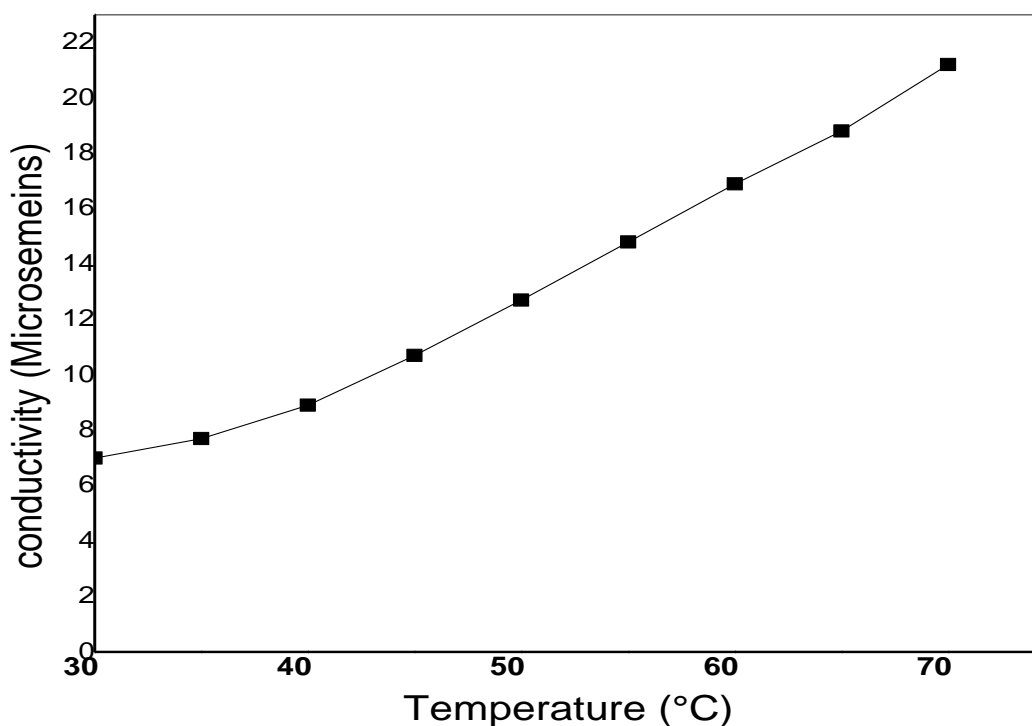


Figure 4.58: Plot of electrical conductivity as temperature at water content 10% for the system: (W +NaCl + PG) / L1695+EMDG/ MNT at 25 °C along the dilution line N40 where the weight ratio of (W /PG) = 2 and that of (MNT / EtOH) = 1. The concentration of NaCl in (W+PG) is 0.01 M.

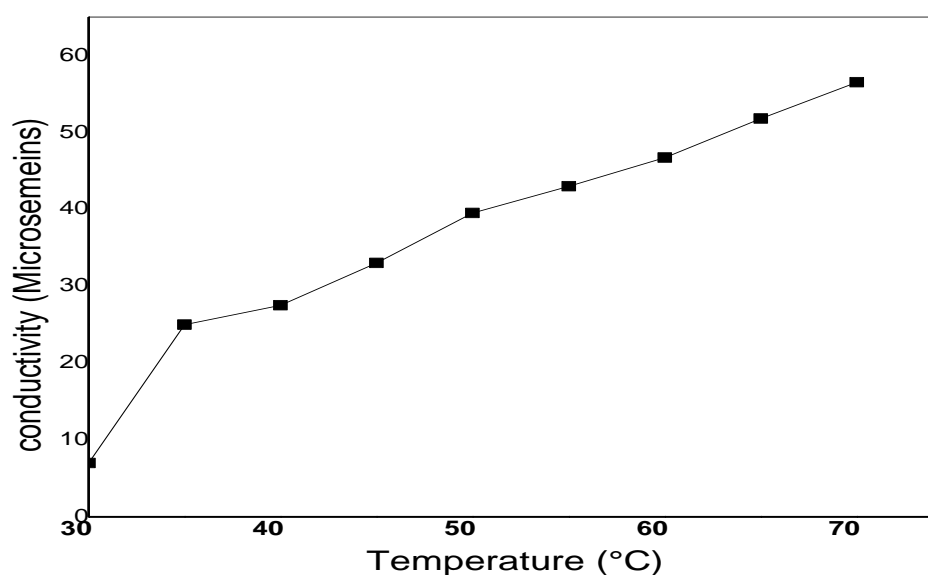


Figure 4.59: Plot of electrical conductivity as temperature at water content 20% for the system: (W +NaCl + PG) / L1695+EMDG/ MNT at 25 °C along the dilution line N40 where the weight ratio of (W /PG) = 2 and that of (MNT / EtOH) = 1. The concentration of NaCl in (W+PG) is 0.01 M.

Conductivity was increased as temperature increases in steadily fashion at water content 10% and 20% as shown in figure 4.58 and 4.59 this is due to increase in kinetic energy cause increase the collision between droplet and increase of movement of ions. Steadily fashion in conductance indicates to no structural transformation.

Conductivity curves for all systems showed three different regions. The first region at low water content showed small increase in conductivity due to formation of water-in- oil microemulsion in which water isolated in small droplet. In second region sharp increase in conductivity was occurred due to transformations in bicontinuous structure in which the ions transfer in open channels. While in the third region oil-in-water microemulsion formed, in this case the ions became completely free which cause to another sharp increase in conductance [28, 38].

Solubilization

The rate of drug release in microemulsions formulations depend mainly on the structure of microemulsions. Microemulsions can be formed in different structures which mean that they can release the solubilized drug at different rate. In o/w microemulsion hydrophobic drug solubilized mainly in the oil droplets therefore released rate is slow due to presence of drug in the core of the droplets which restrict their diffusion where as the diffusion of water soluble drug is less restrained and they released rapidly. In the bicontinuous structure, relatively fast diffusion and release occur for both water soluble and oil soluble drug [34, 35, 39].

Several microemulsions have been studied for the use as drug carriers for poorly soluble drugs and to improve bioavailability, two of these drugs which were studied are azithromycin and celecoxib. Azithromycin is one of the world's best selling antibiotic and is derived from erythromycin. Azithromycin is used to treat certain bacterial infections, most often bacteria causing middle ear infections, tonsillitis, throat infection, laryngitis, bronchitis, pneumonia, and sinusitis. Azithromycin is commonly administered in tablet or oral suspension and it is also available for intravenous injection [35, 39, 41].

Celecoxib (NSAID) is used to relieve some symptoms caused by arthritis, such as inflammation, swelling, stiffness, and joint pain. However, this medicine does not cure arthritis and will help you only as long as you continue to take it [35, 39].

Celecoxib may also be used for the following problems:

- Ankylosing spondylitis
- Familial adenomatous polyposis (polyps in the intestines);

- Moderate or severe pain, such as after dental or orthopedic procedures;
- Pain during menstruation

Celecoxib has low aqueous solubility (3-7 µg/ml at 25 °C). It is weakly acidic and hydrophobic. The content uniformity, dissolution, and bioavailability of Azithromycin and Celecoxib depend on particle size. In the case of acute pain drugs must have rapid onset to provide fast treatment for the pain. Therefore it is necessary to improve the dissolution rate and aqueous solubility for these drugs and these can be achieved by formulating drug based on microemulsion systems [35, 42].

The direct contact between the microemulsion and skin may lead to a disruption of the liquid crystalline structure of the stratum corneum layers and hence enhances penetration but increase the risk of irritation. A new step in microemulsion formulation should be reached with the use of mild surfactants of natural origin which could reduce skin injuries sucrose ester [42].

It was found that all microemulsion systems used in solubilization has the same trend, increase in solubilization capacity of antibiotic by increase of oil content.

At the first region in the curve, upon addition of water water-in-oil microemulsion is formed. The guest molecules should be localized at the interface of swollen microemulsion droplet. By continuing water addition bicontinuous structure change into oil-in-water microemulsion, the interface become convex toward the oil, the surfactant tails are more closely packed, hydrophilic guest molecules have difficulties in self assembling at convex interface curvature and are therefore, pushed away from the interface to inner oil phase of oil-in-water droplet and the solubilization capacity of microemulsion drop [42].

The excess alcohol gradually leaves the interface and partition between the oil phase and water phase the solubility in the oil phase of the most lipophilic decreases because the oil phase is enriched with alcohol lipophilic more soluble in oil/alcohol mixture [39,41,42].

Table 4.15: solubilization capacity for all compounds used in preparation of microemulsion systems.

compounds	Solubilization capacity of Azithromycin (ppm)	Solubilization capacity of Celecoxib (ppm)
Peppermint+ethanol (1:1)	74850	27100
peppermint	60531	35806.6
Water+propylene glycol (2:1)	14722	< 356.125
Water+propylene glycol(2:1)/L1695 (3.5:2.5)	49547	9384.45
Water/L1695 (8:2)	14202	< 296.862
L1695/peppermint	88000	< 3495.81
EMDG/peppermint (1:1)	43707	39306.8
Water/EMDG	<250	< 198.413
Water	<200	< 297.926
Propylene glycol	51083	35807.5
ethanol	47445	35879.1
L1695/EMDG/water (1.5:1.5:7)	74850	< 396.471

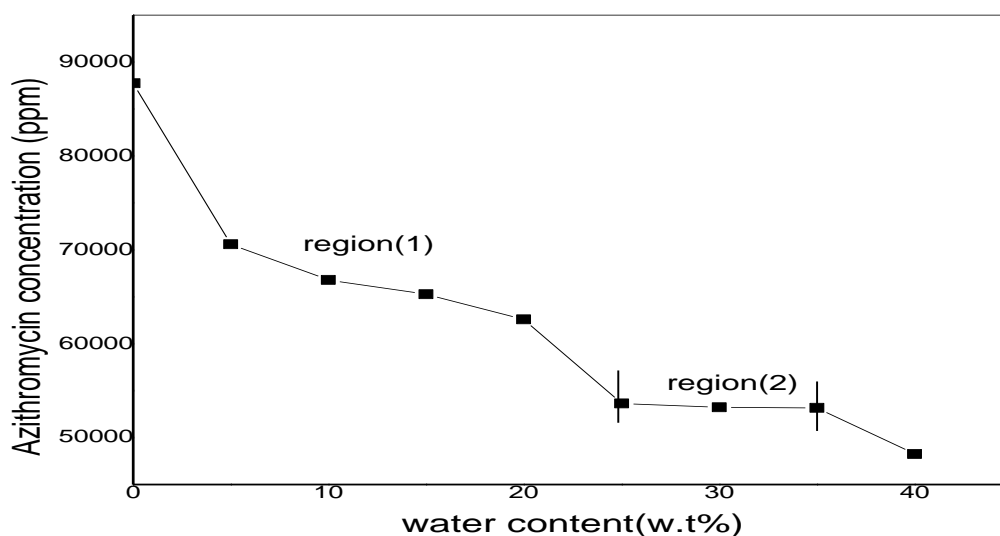


Figure 4.60: Solubilization capacity (SC) Azithromycin as function of water content in the system W/ L1695 / MNT at 25 °C along the dilution line N40.

Solubilization capacity (SC) of Azithromycin at 25°C in the micellar system W/ sucrose monolaurate / MNT as function of aqueous phase content along the dilution line N40 was presented in Figure 4.60. Two different regions can be identified along this dilution line and the third was not found because microemulsion was not formed after aqueous phase exceeded 40%. The solubilization capacity of Azithromycin decreases dramatically from 87730 to 53630 ppm for aqueous phase contents varying from 0 to 35 wt% (region I). Adding aqueous phase (W) to the mixture L1695+ MNT induce the swelling mechanism which decrease the area of droplets and more surfactant participate at the interface replacing azithromycin, and therefore decreasing its solubilization in the microemulsion droplets. In this region, the reverse micelles become less hydrophilic causing less space available to the hydrophilic Azithromycin and this also will reduce its solubilization capacity.

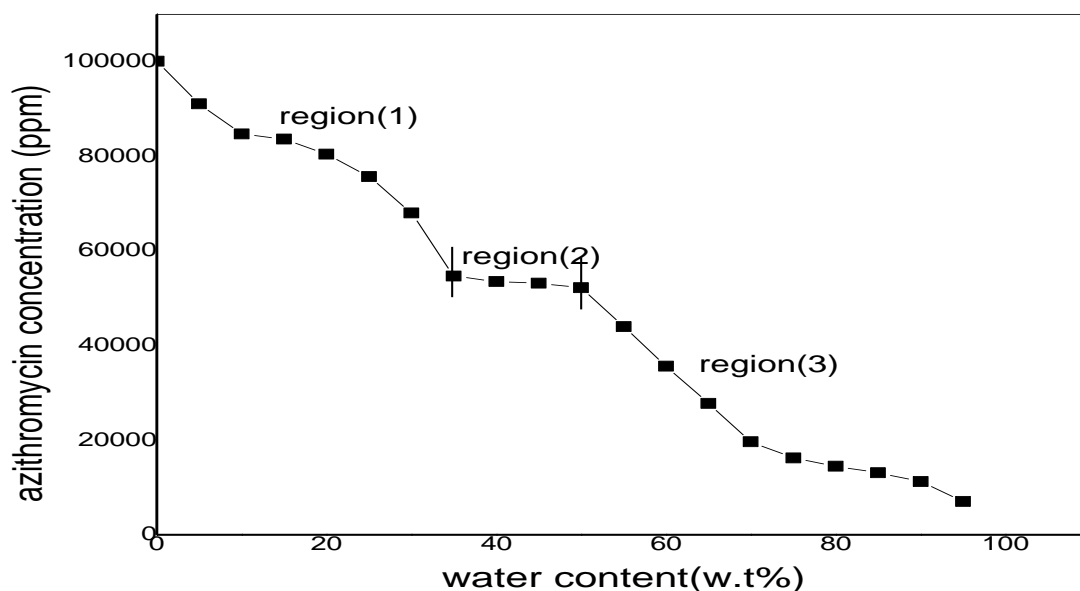


Figure 4.61: Solubilization capacity (SC) Azithromycin as function of water content in the system W+PG (2:1)/ L1695 / MNT at 25°C along the dilution line N40.

Solubilization capacity (SC) of Azithromycin at 25 °C in the micellar system in the system W+PG(2:1)/ sucrose monolaurate / MNT as function of aqueous phase content along the dilution line N40 was presented in Figure 4.61. Three different regions can be identified along this dilution line. The solubilization capacity of Azithromycin decreases dramatically from 100060 to 54640 ppm for aqueous phase contents varying from 0 to 35 wt% (region I). At 35 to 50 wt % aqueous phase content (region 2), the solubilization capacity remains almost unchanged (decreased only by additional 5%). In region 3, 50 to 95% aqueous phase contents, the solubilization capacity decreases from 52220 to 7040 ppm.

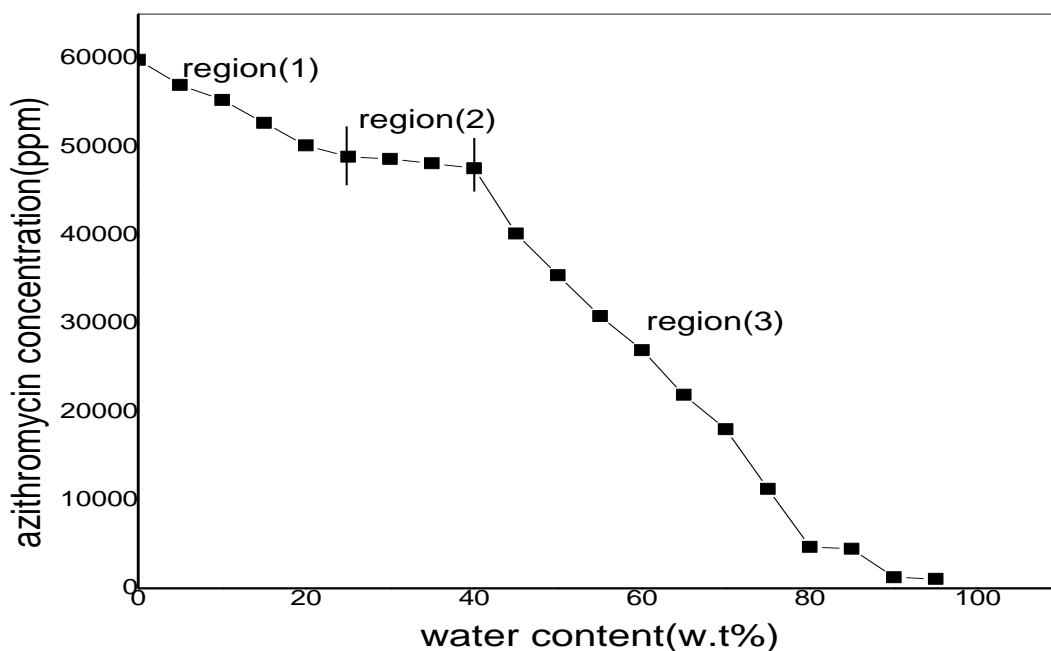


Figure 4.62: Solubilization capacity (SC) of Azithromycin as function of water content in the system W/ L1695 / MNT+EtOH (1:1) at 25 °C along the dilution line N40.

Solubilization capacity (SC) of Azithromycin at 25 °C in the micellar system in the system W/sucrose monolaurate/ MNT+EtOH as function of aqueous phase content along the dilution line N40 is presented in Figure 4.62. Three different regions can be identified along this dilution line. The solubilization capacity of Azithromycin decreases dramatically from 59800 to 48830 ppm for aqueous phase contents varying from 0 to 40 wt% (region I). At 25 to 40 wt % aqueous phase content (region 2), the solubilization capacity remains almost unchanged (decreased only by additional 5%). In region 3, 40 to 95% aqueous phase contents, the solubilization capacity decreases from 47520 to 1080 ppm.

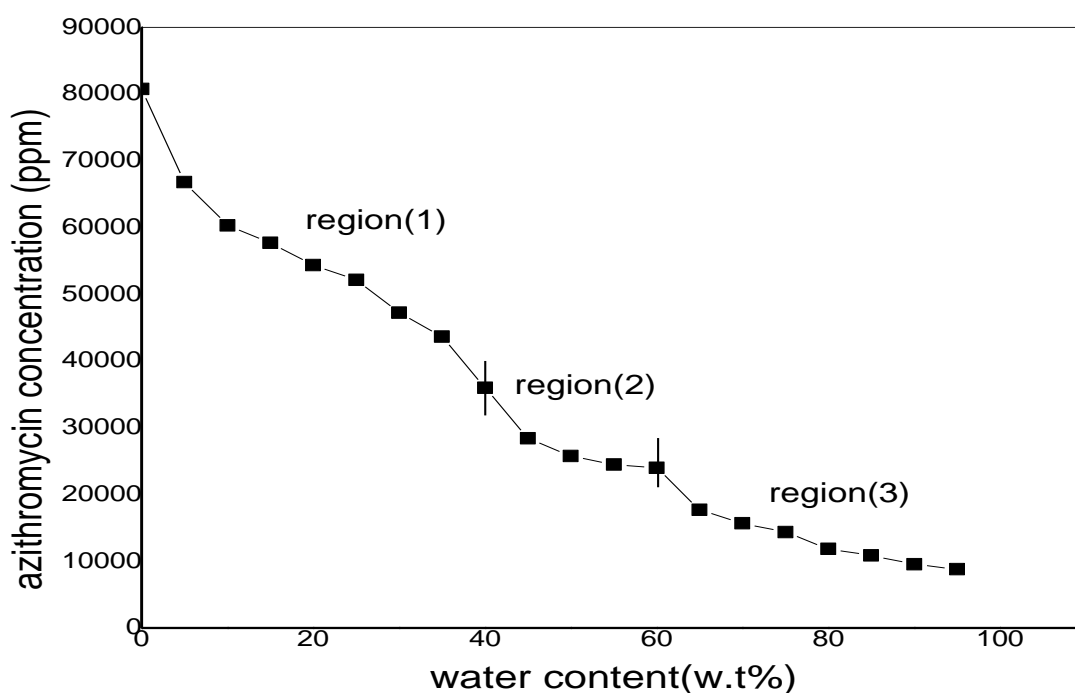


Figure 4.63: Solubilization capacity (SC) of Azithromycin as function of water content in the system W+PG (2:1)/ sucrose monolaurate+ ethoxylated mono–di glyceride (50:50) / MNT at 25 °C along the dilution line N40.

Solubilization capacity (SC) of Azithromycin at 25°C in the micellar system in the system W+PG(2:1)/ sucrose monolaurate+ ethoxylated mono–di-glyceride (50:50 / MNT as function of aqueous phase content along the dilution line N40 is presented in Figure 4.63. Three different regions can be identified along this dilution line. The solubilization capacity of Azithromycin decreases dramatically from 80700 to 36000 ppm for aqueous phase contents varying from 0 to 40 wt% (region I). At 40 to 60 wt % aqueous phase content (region 2), the solubilization capacity remains almost unchanged (decreased only by additional 5%). In region 3, 60 to 95% aqueous phase contents, the solubilization capacity decreases from 24000 to 8780 ppm.

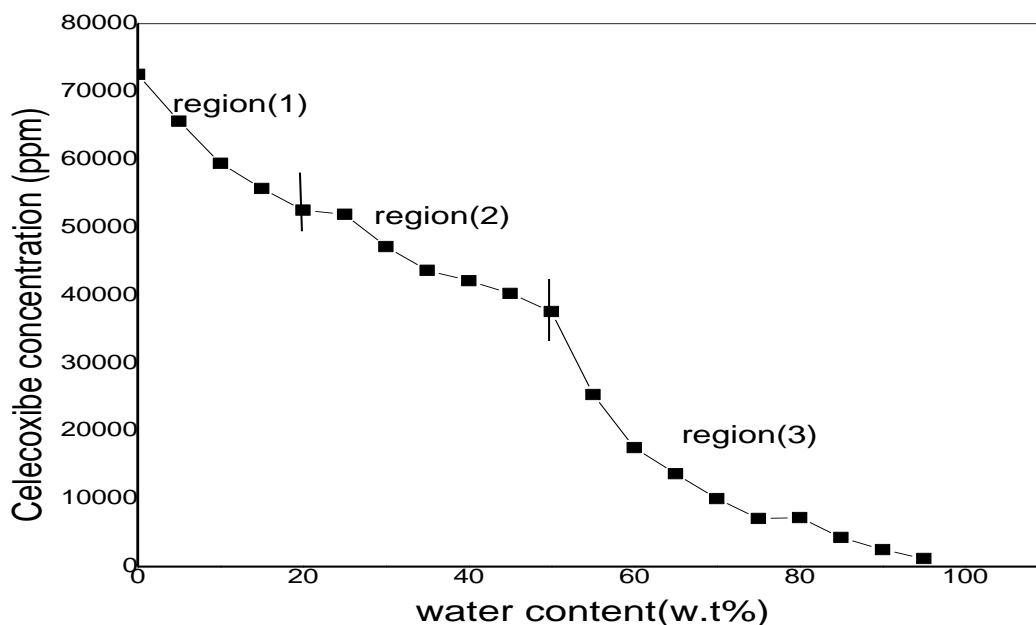


Figure 4.64: Solubilization capacity (SC) Celecoxib as function of water content in the system W+PG (2:1)/ sucrose monolaurate+ ethoxylated mono–diglyceride (50:50) / MNT+ EtOH (1:1) at 25 °C along the dilution line N40.

Solubilization capacity (SC) of Celecoxib at 25 °C in the micellar system (W+PG)/ sucrose monolaurate+ ethoxylated mono–di-glyceride (50:50) /(MNT + EtOH) as function of aqueous phase content along the dilution line N40 is presented in Figure 4.64. Three different regions can be identified along this dilution line. The solubilization capacity of Celecoxib decreases dramatically from 72530 to 52532 ppm for aqueous phase contents varying from 0 to 25 wt% (region I). At 25 to 50 wt % aqueous phase content (region 2), the solubilization capacity remains almost unchanged (decreased only by additional 5%). In region 3, 50 to 95 aqueous phase contents, the solubilization capacity decreases from 37500to 1200 ppm.

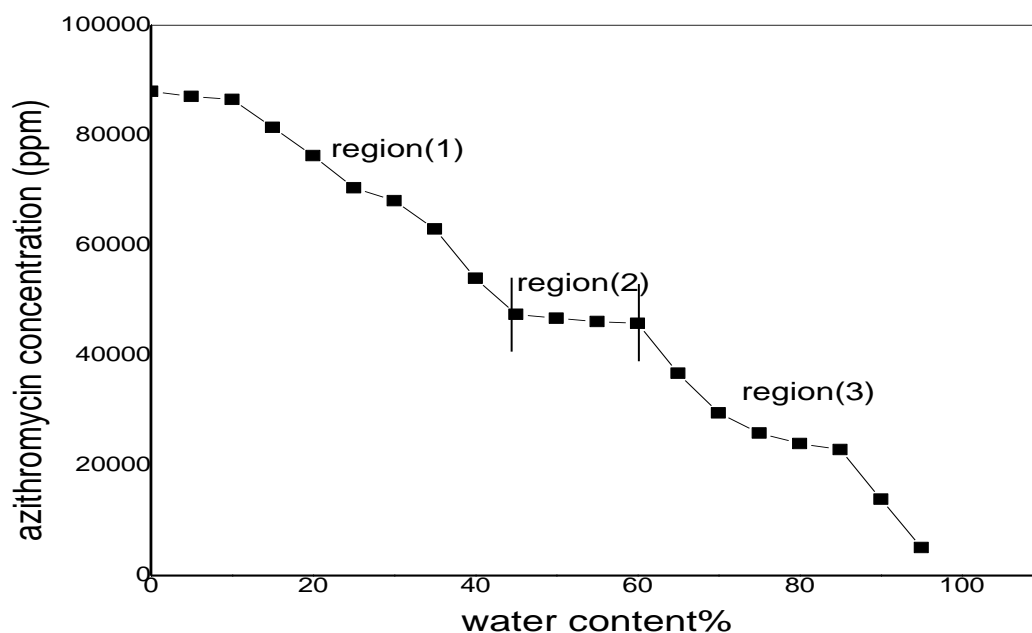


Figure 4.65: Solubilization capacity (SC) Azithromycin as function of water content in the system W+PG (2:1)/ / sucrose monolaurate/ MNT+ EtOH (1:1) at 25 °C along the dilution line N40.

Solubilization capacity (SC) of Azithromycin at 25°C in the micellar system (W+PG)/L1695/ (MNT +EtOH) as function of aqueous phase content along the dilution line N40 is presented in Figure 4.65. The SC of Azithromycin in the ternary system containing L1695, MNT and EtOH at the dilution line N40 (constant weight ratio of MNT /EtOH/L1695 equals (3:3:4) is 55000 ppm. Three different regions can be identified along this dilution line. The solubilization capacity of azithromycin decreases dramatically from 88000 to 47470 ppm for aqueous phase contents varying from 0 to 45 wt% (region 1). At 45 to 60 wt % aqueous phase content (region 2), the solubilization capacity remains almost unchanged (decreased only by additional 5%). In region 3, 60 to 95 aqueous phase contents, the solubilization capacity decreases from 45810 to 5070 ppm.

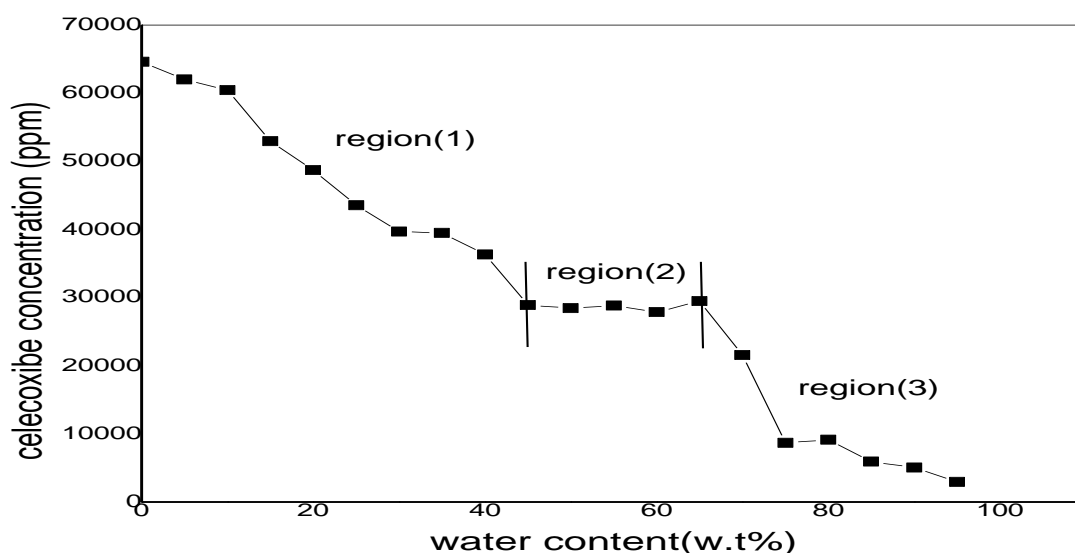


Figure 4.66: Solubilization capacity (SC) Celecoxib as function of water content in the system W+PG (2:1)/ / sucrose monolaurate / MNT+ EtOH (1:1) at 25 °C along the dilution line N40.

Solubilization capacity (SC) of Celecoxib at 25°C in the micellar system (W+PG)/L1695/ (MNT +EtOH) as function of aqueous phase content along the dilution line N40 is presented in Figure 4.66. Three different regions can be identified along this dilution line. The solubilization capacity of Celecoxib decreases dramatically from 64300 to 28900 ppm for aqueous phase contents varying from 0 to 45 wt% (region I). The decrease of the solubilization capacity (SC) in region 1 can be attributed to the increasing interactions between the surfactant and water molecules. Adding aqueous phase (W+PG) to the mixture L1695+ MNT +EtOH induce the swelling mechanism which decrease the area of droplets. At 45 to 65 wt % aqueous phase content (region 2), the solubilization capacity remains almost unchanged (decreased only by additional 5%). In region 3, 65 to 95% aqueous phase contents, the solubilization capacity decreases from 29500to 2670 ppm.

Table 4.16 show the solubilization capacity of azithromycin and celecoxib in different microemulsion regions.

drug	oil	surfactant	aqueous	Region1	Conc. (ppm)	Region3	Conc. (ppm)
azithr	MNT	L1695	water	0-35%	87730-53630	no	
azithr	MNT	L1695	Water+PG	0-35%	100060-54640	50-95%	52220-7040
azithr	MNT+EtoH	L1695	water	0-40	59800-48830	40-95%	47520-1080
azithr	MNT+EtoH	L1695	Water+PG	0-45	88000-47470	60-95%	45810-5070
azithr	MNT	L1695+EM DG	Water+PG	0-40	80700-36000	60-95	24000-8780
celec	MNT+EtoH	L1695+EM DG	Water+PG	0-25	72530-52532	50-95	37500-1200
celec	MNT+EtoH	L1695	Water+PG	0-45	64300-28900	65-95	29500-2670

Three region of solubilization within phase diagram has been revealed in the solubilization profiles explained by the structural transformation through water dilution lines. In the first region water in oil microemulsion will be formed and in the second region bicontinuous structure will be formed while in the third region oil in water will be formed. The solubilization capacity has been the highest in the first region due to the high concentration of surfactants and the small aggregation number forming the micelles in which increase their number and decrease their size leading to high surface area for drug solubilization. Up on the water content increase the hydrophilic surfactant packs to flat surface (bicontinuous region) the second region in which the solubilization capacity of the drug become nearly constant while as dilution proceeds the micelle will be swollen the surface area for drug to solubilize on it will be decrease forming oil in water microemulsion.

It was found that solubilization of Azithromycin in microemulsion based on alcohol is less than in microemulsion free from alcohol as presented in table 4.15. In the case of oil-in-water microemulsion alcohol molecules migrates to the interface and competes with Azithromycin molecules on the free interfacial locus

which affect significantly on solubilization capacity. When alcohol molecules depart from interface the surfactants in the droplet become tightly packed. Solubilization capacity for Azithromycin has been improved when propylene glycol introduced to microemulsion formulation while when sucrose monolaurate mixed with ethoxylated mono-diglycerides surfactants the solubilization capacity of Azithromycin has been decreased. This due to the packing parameter for the mixed surfactant increased leaving less free spaces for Azithromycin molecules [32, 36].

The three distinguished regions that appeared in previous curves for all microemulsion systems can be explained as follow:

Region1

At the beginning, by water adding it was found that solubilization capacity decreased this is due to two factors. the first water dilution effect where the oil content decreased and so it is contribution to the total solubilization decreased, resulting in drastic solubilization decrease, and also cause a change in the micelle curvature and elasticity as water is incorporated into the micelle. the curvature is reduced and fewer guest molecules are accommodated. The second factor was the increasing interactions between the surfactant and water molecules. By adding aqueous phase to the mixture of surfactants and oils induce the swelling mechanism which decrease the area of droplets and more surfactant participate at the interface replacing guest molecules (drugs), and therefore decreasing its solubilization in the microemulsion droplets. In this region, the reverse micelles become less hydrophilic causing less space available to the hydrophilic drugs (Azithromycin and Celecoxib) and this also will reduce its solubilization capacity [40,42].

An increased solubility of lipophilic drugs in the microemulsion regime was observed and explained by the penetration of these drugs into the interfacial film [38, 42].

Region 2

The solubilization capacity in region 2 unchanged or decreased slightly due to the fact that the system transforms gradually into a bicontinuous phase, and the interfacial area remains almost unchanged when the aqueous-phase concentration increases. So the solubilization capacity of Azithromycin and Celecoxib did not change.

Region 3

In this region solubilization capacity of Azithromycin and Celecoxib sharply decreased due to that small amount of oil exist in the core of microdroplet the interface became convex toward the oil, resulting in very low solubility in the core and poor accommodation of the drugs at the hydrophilic interface. As an aqueous phase is introduced, water-in-oil (W/O) swollen micelles are formed, and the hydrophilic groups of drugs are oriented toward the aqueous phase, thus causing the molecules to insert themselves between the surfactant hydrophobic chains. The decrease in solubilization capacity as the aqueous phase concentration increases may be also attributed to microstructure transformations.

4.5 Conclusions

Peppermint oil was the best oil used in this study for preparation of microemulsion with different non ionic surfactants. Total monophasic area decreased as surfactant chain length increased while total monophasic area increased as degree of monoester in the surfactant increased. It was found that the introducing propylene glycol and ethanol to microemulsion formulations increase the area of one phase region and using mixed surfactants caused tuning in one phase region to the positive direction. The increase in temperature has no effect on microemulsion formation when sucrose esters used as surfactants. Conductivity and viscosity measurements showed three different regions where the first region represented water-in-oil microemulsion, and the second region represented bicontinuous structure while the third region represented oil-in-water microemulsion. On another hand, solubilization capacity of Celecoxib and Azithromycin in microemulsion was higher than any single component that formed the microemulsion. It was found that the solubilization curves for Azithromycin and Celecoxib showed three different regions, the first at low water content where the solubilization capacity was the highest due to high surface area and high oil content. The second region occurred at 35-65% water content in which the solubilization capacity almost remains constant due to the fact that surface area remains constant at this stage while at the third region solubilization capacity was sharply decreased due to that small amount of oil exist in the core of microdroplet and the interface became convex toward the oil resulting in very low solubility in the core and poor accommodation of the drugs at the hydrophilic interface. Introducing ethanol to microemulsion formulation caused to decrease the solubilization capacity of Azithromycin and Celecoxib due to the competition between drugs molecules and ethanol molecules at the interface. The difficulty in the solubility of ethoxylated surfactant and some sucrose ester like sucrose stearate were the main limitation in our study.

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