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"Biocompatible Microemulsion : phase behavior, Formulation, Characterization and some applications"

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"Biocompatible Microemulsion : phase behavior, Formulation, Characterization and some applications"

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Dedication

I would like to dedicate this work to the spirit of my grandfather Nassar Al Jundi and to the spirit of my grandmother Numan Al Jundi and my grandmother Sara Al Jundi, to all my family, my mother Montaha, my sister Diana and Biain, and my brothers Moutaz and Mountser and my aunt Nissrine and Ibtesam in recognition of their efforts for encourage me to complete master thesis.

Assala Al Jundi

Declaration:

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

Signed: ……

Assala Nassri Nasar Al Jundi

Date: .....

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First of all I thank God, the merciful and the passionate, who gave me strength and patience in order to fight the first degree of science .

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Abstract

Isotretinoin is 13-cis-retinoic acid and is related to both retinoic acid and Retinol (Vitamin A). Isotretinoin has some deficiencies, such as poor solubility in water and in most organic solvents. Isotretinoin can be solubilized and formulated in nanoemulsions.

Recently, Tetronic surfactants have been studied as possible vehicles for drug delivery; hence, studies on their behavior under a variety of conditions will be an important part of the formulation in delivery agents.

Tetronic1107 is a tetrafunctional block copolymer surfactant terminating in primary hydroxyl groups. A nonionic surfactant that is 100% active and nontoxic .

This study aims to investigate the phase behavior of Tetronics 1107 with Propylene Glycol as a model oil and cationic surfactant tetra butyl ammonium bromide at different temperature (25C,37C,and 45 C), and then investigate the phase behavior of Tetronics1107 with R (+)-Limonene oil at three pH (9.0 , 6.7,4.15) by using buffer solution, water with or without propylene glycol, at different temperature (25C , 37 C).

Also, we will be tried to formulate biocompatible microemulsion systems to enhance solubility of Isotretinoin by using Tetronics1107 as Surfactant, biologically compatible limonene oils, Peppermint oil, Isopropylmyristate ,single or mix, and aqueous phase with addition of cosurfactant at room temperature .

Visual inspection, cross polarizers and polarized microscopy were used to detect anisotropy. A cubic phase and microemulsion phase were detected in the corresponding ternary phase diagram.

Each of them will be used to formulate of Isotretinoin in a second stage. The amount of drug solublized in microemulsion region is approximately 17.9 mg /1gm microemulsion. The amount of drug solublized in liquid crystal region is approximately 10 mg/1 gm liquid crystal.

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Abbreviations, Symbols & Terminology:

HLB : Hydrophilic Lipophlic Balance

L1 : Normal Micelle

I : Cubic Structure

PG :Propylene Glycol

LC : Liquid Crystal

L2 :Inverse Micelle

T : Temperature

Φ : Phase

TBAB: Tetra Butyl Ammonium Bromide

LIM : R (+)-Limonene

MNT : Peppermint Oil

IPM : Isopropylmyristate

PAI : Pharmaceutical Active Ingredients

T1107 : Tetronics1107

O/W : Oil in Water

W/O : Water in Oil

P : Packing Parameter

V : Hydrocarbon volume

a : Cross sectional area of head groups

L : Tail length

pH : Activity of hydrogen ion H^+

GI : Gastrointestinal

ME : Microemulsion

EO : Ethylene Oxide

PO : Propylene Oxide

PPO : Poly Propylene Oxide

PEO : Poly Ethylene Oxide

Met-T1107 : Methylation Terronic1107

β : The ratio between the flory radius of PPO blocks , and that of the PEO blocks

NPO and NEO : Numbers of EO and PO units , respectively

IPO and IEO : Corresponding lengths of the PO(5.1A) ,and EO (2.4A) unites respectively.

CMT : Critical Micelle Temperature

CP : Cloud Point

CMC : Critical Micelle Concentration

GLY : Glycerol

EG : Ethylene Glycol

H-bond : Hydrogen Bond

CTAB : Cetyltrimethyl Ammonium Bromide

SDS : Sodium Dodecyl Sulfate

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Chapter one
Introduction

Introduction

Oil and water separate into two phases when mixed, each saturated with traces of the other component. An attempt to combine the oil and water requires energy input to establish water-oil contacts that would replace the water-water and oil-oil contacts.

The interfacial tension between bulk oil and water can be as high as 30-50 dynes/cm. To overcome this, surfactants are used[Carrie L. Zachar, 2010][1].

1.1 Surfactant

Surfactant (or surface active agent) are organic compounds with at least one lypophlic (solvent loving) group and one lyopholic (solvent fearing) group in the molecule . Surfactants are amphiphilic, meaning they contain both hydrophobic groups (their tails) and hydrophilic groups (their heads) and is represented in a somewhat stylised form shown in figure 1.1.

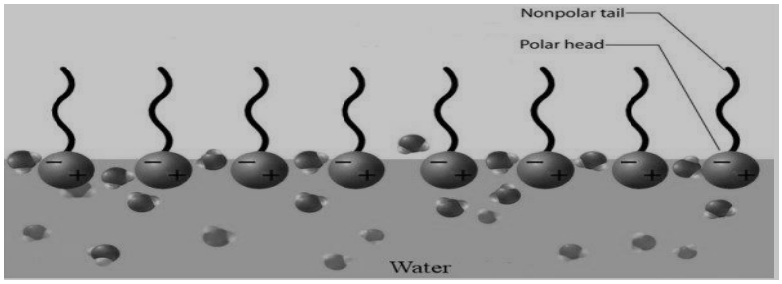


Figure 1.1:Schematic illustration of surfactant molecule

Adsorption and aggregation are two phenomena result from these opposing forces within the same molecule .For example , in aqueous media , surfactant molecule will migrate to air /water and solid/water interface and orientate in such a fashion as to minimize , as much as possible , the contact between hydrophobic groups and the water . this process is referred to as adsorption , and result in a change in the properties at the interface .

Many surfactants can also assemble in the bulk solution into aggregates with the hydrophilic head group oriented toward the aqueous phase ,these aggregate of surfactant molecule vary in shape depending on concentration and range in shape from spherical to cylindrical to lamellar (sheets/layers). Example of such aggregates is micelles. The concentration at which surfactants begin to form micelles is known as the critical micelle concentration (CMC) [Richard J. Farn . , 2008][2].

The sizes of micelles can vary from tens to thousands of monomers. With the increase of size, micelle shape can grow from spherical to rod-like one dimensional, or into two dimensional disc-like aggregates. The structure change of micelle with size is illustrated in Figure 1.2.

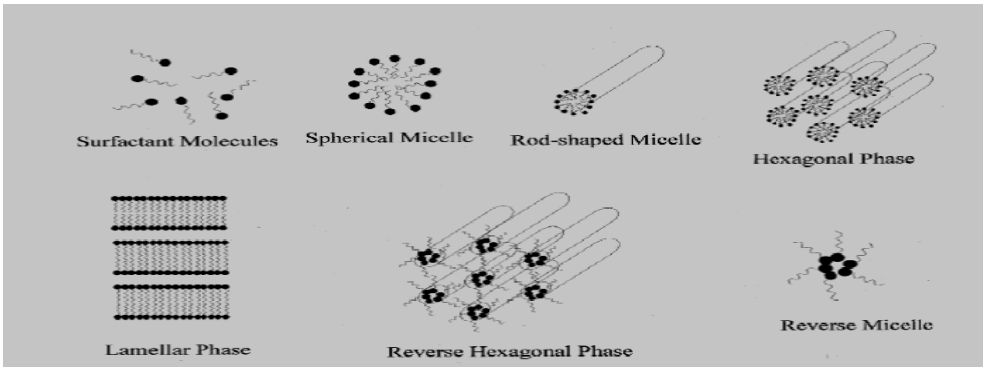


Figure 1.2 : Schematic Presentation of Most Occurred Surfactant Associates

Surfactant can be classified in number of ways , but the most useful classification methods based on the nature of their hydrophilic head groups .So, what type of surfactant based on hydrophilic head groups nature ?

1.2 General classification of surfactant

The most common surfactant classification is based on the nature of the head group : anionic, cationic, zwitterionic , nonionic [Tharwat F. Tadros ., 2006][3] .

1. Cationic surfactant : surfactant that posses positive electrical charge in their head groups when ionized in solution ,for example long chain quaternary ammonium salts .
2. Anionic surfactant : surfactant that have functional groups generate negative charge when ionized in solution such as sulfonate a, sulfate and carboxylate group attached to them . sodium salt of fatty acids (soaps) and sodium alkylsulphates are the common examples of this type of surfactant .
3. Nonionic surfactant : in aqueous solution these surfactant don't provide electrical charge .fatty alcohols , ethoxylated nonylphenols ,and polypropylene glycol are common examples of these surfactant .

4. Amphoteric (zwitterionic) surfactant : group of surfactant which have both acidic and basic in their structure , they may exhibit anionic or cationic features in aqueous solution , depending on pH of the solution .phospholipids is the best example of natural zwitterionic surfactant [Alexander Gurgel .,2004][4] .

When a small amount of an appropriate surfactant is mechanically agitated with the oil and water , emulsion is formed . emulsions are milky or turbid in appearance , due to the fact that the droplet sizes range from 0.1 to 1 micron in diameter .

Emulsions are kinetically stable, but are ultimately thermodynamically unstable. Over time, they will begin to separate back into their two phases. The droplets will merge together, and the dispersed phase will sediment (cream) . At this point, they degrade back into bulk phases of pure oil and pure water with some of the surfactant dissolved in preferentially in one of the two.

A different oil and water system will be produced , If a surfactant that possesses balanced hydrophilic and lipophilic properties is used in the right concentration .The system is still an emulsion, but exhibits some characteristics that are different from the milky emulsions discussed previously. These new systems are called “microemulsions” [Carrie L. Zachar, 2010][1] . So what is microemulsion ?

1.3 Microemulsions

In 1943, microemulsion was first reported by Hoar and Schulman. However the term "microemulsion" was only coined till 1958 by Schulman and coworkers to describe the single phase transparent solution of small droplet size formed after addition of alcohol. For the purpose of this work, the microemulsion is defined as 'a system of water, oil and amphiphile which is optically isotropic and thermodynamically stable liquid solution", same definition as provided by Danielsson and Lindman in 1981 [M. J. Lawrence, et .al .,2000][5] .

The presence of large quantities of surfactant provides microemulsions with unique physical and chemical properties, including thermodynamic stability, low kinetic barriers to formation, low viscosity and interfacial tension. Given these special properties, microemulsions have attained increasing significance both in research and in industry.[M.-J. Schwuger , et .al ,.1995][6]

Microemulsion can assume various microstructures depending on the temperature, composition, molecular structure, and hydrophilicity and hydrophobicity of these components. Typically, microemulsions can be classified as oil-in-water (O/W) microemulsion, water-in-oil (W/O) microemulsion, and bicontinuous microemulsion in terms of the internal microstructure. As increase of the oil-to-water ratio, the microstructure of microemulsion progresses from oil-swollen droplets dispersed in water, to bicontinuous structures, and finally to water-swollen micelles dispersed in oil [R. De Vries,et.al.,2001][7].

In the intermediate region, equivalent amounts of water and oil are presented and no droplets are formed. The bicontinuous microemulsions have macroscopic domains of both water and oil which sometimes are described sponge-like [C. M. Paleos., 1992][8] .

Based on the phase equilibrium of microemulsions, they can be also classified into four different types. Winsor has developed a classification scheme as illustrated in Figure 1.3.

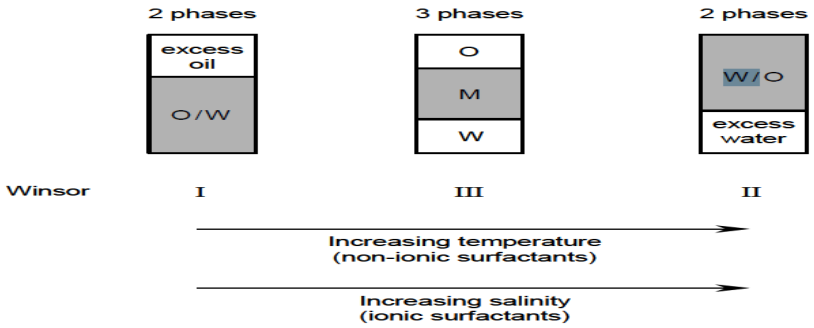


Figure 1.3: Winsor Classification of Microemulsion and phase sequence of microemulsions encountered as temperature or salinity is scanned for non-ionic and ionic surfactant respectively

- Winsor I : the surfactant is preferentially soluble in water and oil-in-water (o/w) microemulsions form it . The surfactant-rich water phase coexists with the oil phase where surfactant is only present as monomers at small concentration.
- Winsor II : the surfactant is mainly in the oil phase and water-in-oil (w/o) microemulsions form. The surfactant-rich oil phase coexists with the surfactant-poor aqueous phase .
- Winsor III or middle-phase microemulsion : a three-phase system where a surfactant-rich middle-phase coexists with both excess water and oil surfactant-poor phases.
- Winsor IV : a single-phase (isotropic) micellar solution, that forms upon addition of a sufficient quantity of amphiphile (surfactant plus alcohol).

The formation of various types of Winsor I, II, III or IV , as illustrated in Figure 1.3, Depending on surfactant type and sample environment , phase transitions are brought about by increasing either electrolyte concentration (in the case of ionic surfactants) or temperature (for non-ionics) [Terence Cosgrove .,2010][9].

1.4 Hydrophilic-Lipophilic Balance (HLB) :

The hydrophilic-lipophilic balance (HLB) of the surfactant can be considered as starting point in the selection of components that will form a microemulsion.

The hydrophilic-lipophilic balance (HLB) of the surfactant can be taken into account to try to rationalize the surfactant's behavior. It is generally accepted that a surfactant with HLB from 3-6 will favor the formation of water-in-oil (w/o) microemulsions, whereas surfactants with HLB from 8-18 are preferred for oil-in-water (o/w) microemulsions [Griffin, W. C. ,1949][10] .

The hydrophilic-lipophilic balance (HLB) , can be calculated by Griffin equation [Tharwat F. Tadros , 2011][11] .eq (1.1) :

$$HLB = 7 + \sum (\text{hydrophilic group Nos}) - \sum (\text{lipohilic group Nos}) \quad \text{.....(1.1)}$$

1.5 Micelle

A salient feature of surfactant is the self-association to form micelles to avoid the contact of hydrophobic moieties at the concentration beyond the critical micelle concentration [S.K. Mehta .et.al,2011][12].

The increase size of micelle shape can grow from spherical to rod-like one dimensional, or into two dimensional disc-like aggregates . The sizes of micelles can vary from tens to thousands of monomers. [S. Puvvada,et.al.,1990][13] .

A useful concept for characterizing micelle geometry is the packing parameter (P) which was shown by Israelachvilli et al [Israelachvilli ,et .al ,.1976][14] .
They considered that surfactant molecules can be regarded as two piece structure , polar head and hydrophobic tail . Represented by eq .1.2 that for surfactant cross sectional area of head groups (a) , hydrocarbon volume (v) and tail length (L) the value of ($P \approx 0.33$) spherical micelle will be formed , and ($0.33 < P < 0.5$) cylindrical micelle formed , and ($P \approx 1$)

bilayer is formed , and (P>1) inverse micelle is formed figure 1-4 [Audrey Renoncourt,2005][15] .

P=V/a L ……. ……(eq.1.2)

Where ,
P : packing parameter or shape factor
V: hydrocarbon volume
a : cross sectional area of head groups
L : tail length

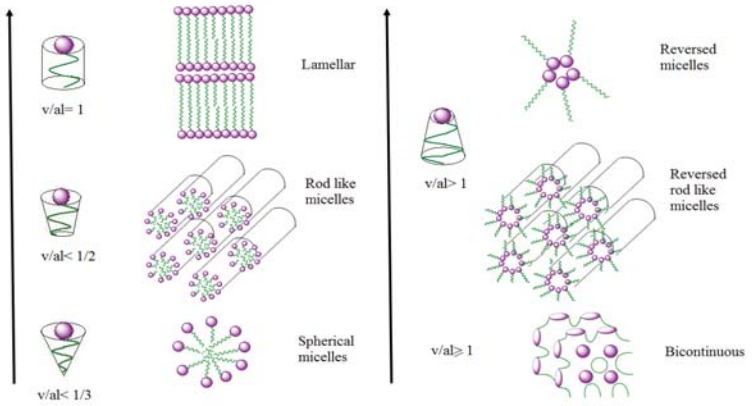


Fig.1. 4 : The surfactant aggregate structure for critical packing parameters from <1 3 (lower left) to >1 (upper right) .

Surfactant play a key role in many of novel drug delivery system developed , and a wide range of surfactant containing systems, including emulsion , liposomes , liquid crystalline phases (e.g., lamellar , hexagonal , or cubic) , and microemulsions , are being extensively investigated in relation to drug delivery [Attwood, 1994][16] . So what types and properties of colloidal drug delivery system used in pharmacy ?

1.6 Types and properties of colloidal drug delivery system :-

The design and development of a new drug delivery systems with the intention of enhancing the efficiency of exciting drugs of an ongoing process in pharmaceutical research .

It is necessary for pharmaceutical solution to contain a therapeutic dose of the drug in a volume convenient for administration . colloidal drug delivery system has great potential for achieving the goal in drug targeting , so many types of drug delivery systems that have been

developed . A few of the most widely examined colloidal drug delivery systems are micelles , microemulsions , macroemulsions , nisosoms , liposomes , and nanoparticels [Jörg Kreuter, 1994][17] .

Emulsion are metastable colloids and optically turbid desperation and can only be obtained by mechanical mixing of the components because of their thermodynamic instability. However , a large amount of hydrophobic drug can be dissolved in the dispersed phase , because exists large amount of oil solublized in an oil in water (o/w) emulsion .

The oil droplets in an emulsion can be made small enough that they don't refract light , hence forming a transparent dispersion .This dispersion is called a microemulsion , where I will discuss on later [R.P.Bagwe et .al,2001][18] .

Niosomes are formed on the admixture of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media , which are microscopic lamellar structures. [M. Malhotra.et.al , 1994][19].

Liposomes are microscopic spheres with an aqueous core surrounded by one or more outer shell(s) consisting of lipids arranged in a bilayer configuration [Arcadio Chonn.et.al,1995][20] .

A final colloidal system to consider is composed of nanoparticles that are solid , colloidal particles consisting of macromolecular substance that vary in size from 10nm to 100nm .

Table 1.1 show a comparison of physical properties of these colloidal drug delivery system [R.P.Bagwe et .al,2001][18].

Delivery system	Advantages'	Disadvantages
Microemulsion	high solubility of drug small droplet size easy preparation long shelf life	Large amount of surfactant Drug solubility influenced by environmental conditions Potential toxicity of surfactant
Emulsion	Small amount of surfactant High solubility of drug into carrier	High viscosity Instability Larger droplets Short shelf life
Nanoparticles	Long storage life In vaccination , slow degradation on body	Limited solubility of drug Difficult to prepare Difficult to control size Polymers which represent constituents are usually not bioacceptable

Table 1.1 : A comparison of physical properties of these colloidal drug delivery system .

1.7 Microemulsion in pharmaceuticals :

The ever increasing demands on the performance of pharmaceutical formulations with respect to , e.g., storage stability , increased dosage levels , greater bioavailability , fewer side effects , controlled release , and biological response (e.g., tissue distribution) constitute the main motivation for drug delivery research . In the last few decades , this research has resulted in the development of , e.g., parenteral emulsion , liposomes with improved circulation in the bloodstream , cyclodextrins , and lipoprotein mimics for cancer therapeutics . Surfactant play a key role in many of novel drug delivery system developed , and a wide range of surfactant containing systems, including microemulsions which have shown great potential in the area of pharmaceuticals. They can be applied to a wide variety of dosage forms including oral, topical, ocular, parenteral, periodontal, buccal, and nasal formulations. [Attwood, 1994][16][Carrie L. Zachar, 2010][1] .

The successful formulation of poorly water soluble drugs is one of the major problems in pharmaceutical manufacturing . Drugs can be solubilized and formulated in microemulsions .

What makes microemulsions fundamental in the pharmaceutical field, apart from their high Stability and ease of preparation, is their ability to increase considerably the bioavailability of sparingly water-soluble drugs. These aggregates allow slow release of drugs, providing prolonged effects and avoiding overly high concentration in the Blood [Suria Ramli , et .al .,2009][21].

Isotretinoin is 13-cis-retinoic acid and is related to both retinoic acid and Retinol (vitamin A). It is a yellow to orange crystalline powder with a molecular weight of 300.44. The structural formula is [N.L. Sykes, et.al,1994][22] :

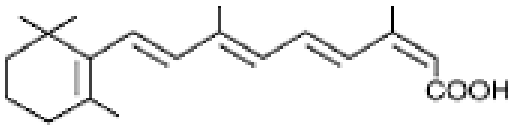


Figure 1.5 : structure of Isotretinoin

It has been commonly used for the treatment of serve acne and the other dermatological disease , Isotretinoin has some deficiencies, such as poor

solubility in water and in most organic solvents and poor stability, being easily oxidized when heated or exposed to light [P.A. Lehman , et.al,1988][23].

Because water insoluble drugs often show low absorption and weak bioavailability, improvement in dissolution rate and/or solubility are important for development of drug preparations [*Lobenberg, R.*et.al,200][24]

The successful formulation of poorly water soluble drugs such as Isotretinoin is one of the major problems in pharmaceutical manufacturing. Isotretinoin is administered via the oral route, which has the disadvantage of low bioavailability [P.C. Adamson,et.al,1993][25],and is unacceptable for patients who cannot swallow capsules.

Also in the oral route , drugs can be degraded by the low pH found in the stomach (stomach acid) or by digestive enzymes, however these problems can be overcome in some cases by coating the active compound.

Isotretinoin is poorly absorbed across the gastrointestinal (GI) lumen, it may be too rapidly cleared from the blood or rapidly inactivated by the body on its first pass through the GI tract wall and the liver.

Retaining Isotretinoin in the body would require a very short interval between doses causing the risk of overdose and ultimately a highly patient-unfriendly dosing regimen or taking the full day's dose in conventional tablet form [N. Garti.et.al,2006][26].

Intravenous delivery may be seen as a good alternative, but may require a high volume of drug to be injected each time or require frequent administration. The disadvantages of these Measures are expense, poor patient compliance and the risk of adverse effects [R.H. Muller,et.al,2004][27] .

Alternatively, Isotretinoin can be solubilized and formulated in microemulsions .Several attempt to incorporating Isotretinoin in microemulsion .

Suria Ramli , et al , have found that the Isotretinoin, is soluble about 0.025 wt. % in a microemulsion formulation using tween80 as surfactant , tetraglycol as cosurfactant , isopropyl myristate (IPM) as oil , and water as aqueous phase [Suria Ramli , et .al .,2009][21] .

Also , Kashyap Nagariya et al , have found that the Isotretinoin , poorly soluble drug , displayed high solubility about 1 wt % in microemulsion formulation using Captex - 355, Cremophor EL, Ethanol , and water .

The in vitro diffusion study revealed an increase of bioavailability (38.56 times) after in vitro drug diffusion analysis of the microemulsion formulation as compared with the commercially available soft gelatin capsules [Kashyap Nagariya ,et al.,2010][28].

Finally, Mrunali R. Patel et al , have studied the photostability of Isotretinoin when loaded about 0.5% w/w in microemulsion , they studied the photodegradation of Isotretinoin, in methanol and microemulsion formulation was studied under direct sun light . They found that the Isotretinoin inclusion in microemulsion results in a good photostability of The drug, whereas in methanol Isotretinoin degraded almost completely after about 240 min under a direct sun light, while in the microemulsion matrix still 75% of residual Isotretinoin concentration could be measured.

Results obtained from this photostability study lead us to suppose that the better photoprotection of Isotretinoin in ME matrix is the consequence of the inclusion of this drug in ME matrix. Further, studied kinetics of the Photodegradation processes for isotretinoin loaded ME formulation demonstrated to increase Isotretinoin half-life about five-times in comparison with methanol solution, under a direct sun light [Mrunali R. Patel , et al .,2011][29].

These previous study, are used conventional surfactant as try to incorporating Isotretinoin in microemulsion.

In our lab , we will be tried incorporated Isotretinoin in microemulsion , using polymer surfactant called Tetronics1107 , compatible oil such as Peppermint oil , Limonene oil , and Isopropylmyristate .

1.8 Block copolymer

Block copolymers made of polyethylene oxide (PEO) and polypropylene oxide (PPO) are commercially available as star-blocks (Tetronic) and linear triblocks of the type ABA and BAB (Pluronics) with varying hydrophilic-lipophilic balance (HLB).

These polymeric amphiphiles self-assemble to form nanosize aggregates (micelles) in aqueous solutions and display a unique core-shell structure with spherical/rod-like morphology and a fairly low polydispersity that is strongly dependent on temperature/concentration [K. Nakasima , et al.,2006][30],[G. Riess , et al ., 1985][31].

The Tetronics is a family of surfactants based on X-shaped copolymers ,formed by four polypropylene oxide (PPO) and Polyethylene oxide (PEO) block chains bonded to an ethylene diamine central group. These surfactants, also known as Poloxamines or Synperonics and first introduced in the 1950's by BASF (New Jersey, USA) .

There are three types of Polxamine , the first is regular Polxamines , which are synthesized by the sequential reaction of acceptor ethylene diamine molecule , first with Propylene oxide (PO) , and then with ethylene oxide (EO) , resulting in a four arm (PEO) terminated molecular structure (figure 1.6).

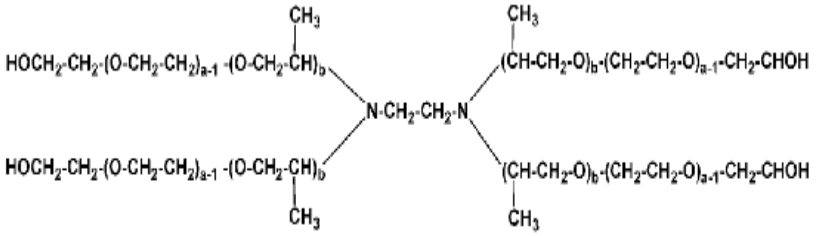
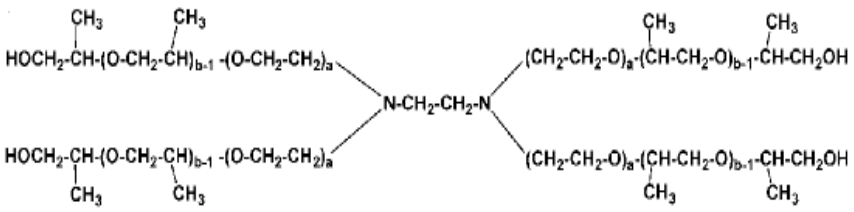


Figure (1.6) :-structure of sequential poloxamine

The second type of Poloxamine , is called reverse sequential Poloxamines , which acceptor is first reacted with (EO) , and then with (PO) leading to tetra functional block copolymers displaying (PPO) terminal sequential .figure (1.7).



Figure(1.7):- structure of reverse sequential poloxamine

In order to a attain additional abilities , the Poloxamines have a unique structure , which provides them , with multistimulus responsiveness , which the two tertiary amine central groups , play an essential role in conferring thermodynamically stability , and pH sensitivity , and enabling further modification .(methylation of amine group , figure1.8)

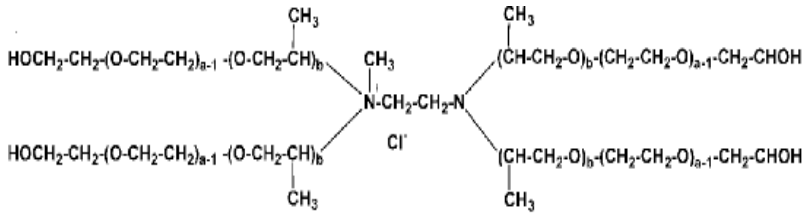


Figure (1.8):- structure of methylated sequential poloxamine

The unique structure of Poloxamines provides them with multistimulus responsiveness.

In this context, the two tertiary amine central groups play an essential role in conferring thermodynamical stability and pH sensitivity and enabling further chemical modifications in order to attain additional abilities [Sosnik, A , et al ,.2006][32] .

The most commonly used Poloxamines , are the sequential surfactant ;among these seven varieties of different molecular weight ,(PO/EO) and consistency (liquid , paste , solid) in table (1.2).

Poloxamine	Physical state at room temperature	Molecular weight	HLB	β value
T304	Liquid	1650	12-18	2.32
T901	liquid	4700	1-7	6.68
T904	paste	6700	12-18	2.29
T908	Cast solid	25000	>24	0.77
T1107	Cast solid	15000	18-23	1.10
Met-T1107	powder	15030	-	1.10
T1301	Liquid	6800	1-7	6.53

Table (1.2):-structural properties of different Poloxamine derivatives

Tetronics are commercially available in wide range of HLB values .the Hydrophobicity of PEO-PPO –based amphiphile can be characterized Through both the hydrophilic –lipophlic balance (HLB) and β value .
β value represents the ratio between the flory radius of PPO blocks , and that of the PEO blocks .equation (1.3).

$$\beta = \frac{I_{PO}(N_{PO})^{3/5}}{I_{EO}(N_{EO})^{3/5}} \qquad \text{.....(eq1.3)}$$

Where ;

NPO and NEO : Numbers of EO and PO units , respectively

IPO and IEO : Corresponding lengths of the PO(5.1A) ,and EO (2.4A) unites .

Poloxamines can be classified according to the value of both HLB and β value in three main groups in table (1.3) .

Classification of poloxamines	HLB	β value	Examples of tetronics
Highly hydrophilic	HLB>18	β ~1	T908,T1107, T1307
Highly hydrophobic	HLB ranging between 1 and 7	β above 6	T901, T1301,andT150R1
Intermediate polarity			T304andT904

Table (1.3) :-classification of poloxamine according HLB and β value

The presence of the amine group in Tetronics , provides some acidic and basic character , and thermodynamically stability to the amphaphiles [Jaime Gonzalez-Lopez , et al.,2008][33].

Tetronics are used in a verity of application ranging from cleaning to Personal care products (eg. hard surface cleaner , dishwashing liquid , rinse aids , and laundry detergent) , and industrial processing fluids (metal working fluids , lubricant , emulsion polymerization , and water treatment).

Recently , Tetronics surfactants have been studied as possible vehicles for drug delivery , hence studies on their micellular and solution behavior under a variety of conditions will be an important part of the formulation in delivery agent.

Solublization of poorly soluble drugs in amphaphilic polymeric micelles and their subsequent release studies have gained much interest in resent years .

The solublizing power of micelles depends on numerous factors , such as chemical structure of amphaphilic and drug molecule , temperature , pH, and ionic strength [P. Parekh , et al.,2011][34] .

Jaime Gonzalez –lopez et al , have investigated the aggregation phenomena under acid pH of three types of four arm PEO-PPO block copolymers , displaying a wide spectrum of molecular weights and hydrophilic –hydrophobic balances. The finding demonstrate that both parameters play an important role in the behavior pattern of Poloxamine based systems .

The longer the PEO block , the greater the area occupied per molecule at the air water interface at low pressures. In contrast, the longer PPO block, the larger the area occupied in the condensed state, and the more intense the surface activity. In addition, it was found that Poloxamines with relatively high PO/EO ratios and molecular weights (T1301 and T150R1) also lead to the generation of micelles with larger and more hydrophobic cores. This feature has been shown to be critical for hosting hydrophobic molecules and stabilizing drugs displaying labile functional groups, such as the Lactonic form of Simvastatine.

In contrast, the findings suggest that the hydroxyl acid form of Simvastatin interacts electrostatically with the central ethylenediamine group of T304 at the alkaline pH that this variety communicates to the medium. A similar phenomenon was apparent when a quaternary ammonium moiety was produced by methylation, although, in this specific case, the positive charge was permanent. Any of these factors also contribute to enhance the ability of the Poloxamine systems to solubilize anionic drugs regarding demicellization upon dilution, the most stable micelles are those constituted by long Poloxamine molecules containing large PPO blocks (with 23-29 units, i.e., T1301, T1307, and T150R1), particularly T1307, which also has long PEO blocks [Jaime Gonzalez-Lopez , et al.,2008][33].

P.Bahadur et al, have investigated the effects of temperature , added salt , pH, and concentration of the X-shaped triblock copolymer Tetronic , T904 on its aggregation behavior in aqueous solution. In the presence of added salt 5%shows a significant decrease in critical micelle temperature (CMT) value in the absence of salt (CMT ≈28.8C) .

T904 forms spherical micelles with an aggregation number increases with increasing temperature and in the presence of Na_2SO_4 . An increase in temperature or the presence of salt dehydrates the PEO shell , particularly the EO units close to the PO core . The micelle shape however changes at high salt concentration and at high temperatures in alkaline medium (pH=8.5) . T904 remains unaggregated in acidic pH .The added salts (NaCl, Na_2SO_4,and Na_3PO_4) induce micellization and favor the micellar transition at

lower temperatures due to the salting out effect ;the effect of anions follows the Hofmeister series ($PO_4^{3-} > SO_4^{2-} > Cl^-$) [Y.Kadam ,et al ,2010][35] .

P.Bahadur et al, have investigated the aggregation behavior of T904 in presence of NaCl and solubilization of a model drug nimesulide. T904 shows a cloud Point (CP) ranging from 74–65 C in the concentration range of 1–10% and forms aggregates (micelles) with a hydrodynamic diameter around 10–12nm in the temperature range 30–40 "C. Stable, bluish solutions containing aggregates of variable Size (several hundred nm in some cases) were observed even at temperatures much less than the critical micellization temperature (CMT = 30 C for a 2% solution in water).

The CP and the CMT markedly decrease in the presence of NaCl due to the dehydration of the polyethylene oxide shell. The size of the micelles in water or salt solutions increases at temperatures close to the CP as inferred from viscosity measurements. A model drug compound (nimesulide, NIM) was solubilized in T904 micelles which showed a remarkable increase in solubilization at higher temperature; however, a decrease in solubilization was observed in salt solutions. So , the solubilization of drug in micelle is not favored in the presence of NaCl. At low pH the solubilization of drug is not favored because at acidic pH, micellization is hindered and NIM also shows poor solubility in acidic medium [P. Parekh , et al.,2011] [34].

Teng Liu et al , have investigated the effects of cosolvents such as ethanol, n-propanol, ethylene glycol (EG) , and glycerol (GLY) on the aggregation behaviors of branched block polyether T1107 at air/liquid surface as a function of the cosolvent content in the mixed solvent. They found that the addition of ethanol or n-propanol to water disfavors the micellization ,and the CMC shifts to higher concentration. Ethanol and n-propanol are more hydrophobic than the PEO blocks, and they have a higher affinity for the hydrophobic PPO blocks than for water. The addition of ethanol or n-propanol to water results in better solvent conditions for T1107, decreases the hydrophobic interaction, and leads to an increase in the CMC. GLY and EG affect the micellization in opposite ways compared with the cases of ethanol and n-propanol. GLY and EG are more hydrophilic than the PEO blocks, and GLY_water and EG_water mixed solvents become poor solvents for T1107 compared to pure water. T1107 molecules tend to self-assemble at lower concentrations. Furthermore, GLY and EG interact favorably with water and strengthen the H-bond network of the mixed solvent. They produce an increase in hydrophobic interactions; consequently, the CMC decreases [Teng Liu, et al .,2011][36] .

Regardless of the impact that these structural parameters have on their performance, the information currently available is limited to a few varieties under some specific conditions, and a comprehensive and comparative investigation of behavior of the Poloxamines is still lacking [Dong, J , et al ,.2004][37] .

Poluronic block copolymer (also known poloxamers) consist of hydrophilic poly ethylene oxide (PEO) , and hydrophobic poly propylene oxide (PPO) blocks arranged in A-B-A , tri block structure : PEO-PPO-PEO .

The block copolymer with different numbers of hydrophilic ethylene oxide and hydrophobic propylene oxide units are characterized by different hydrophilic –lipophlic balance (HLB) .

Due to their amphaphlic character these copolymers display surfactant properties including ability to interact with hydrophobic surfaces and biological membranes [Kabanoy A , et al .,1995][38] .

Rouja Ivanova et al , have studied the Ternary isothermal (25°C) systems of Pluronic F127 (Poloxamer 407) in the presence of water and polar water-miscible solvents (glycerol, propylene glycol or ethanol), a partially water-miscible solvent (glycerol triacetate), a nonionic surfactant (tetraethylene glycol monooctyl ether, ($C_8(EO)_4$), an anionic surfactant (sodium dodecyl sulfate, SDS), and a cationic surfactant (cetyltrimethyl ammonium bromide, CTAB) to investigate the potential Offered by cosolvents and surfactants for the modification of the lyotropic liquid crystalline microstructures formed by Pluronic F127 (Poloxamer 407) . The cosolvent/surfactant effects in the phase behavior are related to the preference of the cosolvents/surfactants, depending on their polarity , to locate in different domains of the self-assembled microstructures formed by the block copolymer . Phase behavior studies indicate that polar water miscible solvents are able to maintain the ternary composition range of stability of a given structure up to high solvent/water ratios. Polar water-miscible solvents may have some preference to locate in the PPO-rich domains but cannot induce the formation of water-in-oil structures (with negative curvature).

Partially water-miscible solvents such as triacetin form a larger variety of lyotropic liquid crystalline structures but within smaller composition regions than the Polar water miscible solvents. Compared with a polar solvents (which have a strong preference for the PPO domains), partially water-miscible solvents exhibit fewer types of structures but over larger composition regions. and they found that with increasing the a polarity of the solvent increases the solvent preference to locate in the relatively a polar PPO-

rich domains, and hence increases the variety of the microstructures that are attained by the block copolymer but decreases their stability concentration range.

They found that ionic surfactants such as SDS and CTAB are known to interact much stronger than nonionic surfactants with Poloxamer block copolymers. Several orders of magnitude larger amounts of non-ionic surfactants are necessary to achieve the same effect as that of ionic surfactants. Starting with a block copolymer micellar solution, the addition of ionic surfactants leads to association of the surfactant with the block copolymer. Although there is no direct evidence at which part of the macromolecule the binding with the surfactant takes place, it is mostly accepted that the surfactant hydrophobic tail binds to the relatively hydrophobic PPO block of the copolymer with increasing the surfactant concentration, the complexes become less amphiphilic and more hydrophilic. Finally ,they found that Ionic surfactants such as SDS and CTAB are much smaller extent of the liquid crystalline structures in comparison to $C_8(EO)_4$ [Rouja Ivanova , et al ., 2001][39].

Chapter Two
Objective

2.2 objective

In this study , the effect of the addition of cationic surfactant tetra butyl ammonium bromide to copolymer Tetronics1107 at different concentration and temperatures (25C,37C,45C) will be investigated.

Furthermore , the phase behavior of Tetronics1107 with limonene oil at three pH (9.0 , 6.43, 4.14) will be investigated by using buffer solution, water with or without propylene glycol , at different temperature (25C , 37 C).

Also, we will be tried to formulate biocompatible microemulsion systems using Tetronics 1107 as Surfactant, biologically compatible limonene oils, Peppermint oil, Isopropylmyristate, single or mix, and aqueous phase with Addition of co-surfactant at room temperature.

Investigate the effect of addition of 1-pentanol on phase behavior of Tetronics1107 with Peppermint oil and water at room temperature.

Finally, we will be tried to evaluate the maximum solubilization capacity of the pharmaceutical active ingredients (Isotretinoin) in microemulsion and liquid crystal regions.

Chapter Three
Materials And Methods

3.1 Surfactants (surface active agent)

- Tetronics 1107

Tetronic1107 is a tetrafunctional block copolymer surfactant terminating in primary hydroxyl groups figure 3.1. It Regular poloxamine which is synthesized by the sequential reaction of the acceptor ethylenediamine molecule first with propylene oxide (PO)and then with ethylene oxide (EO) precursors, resulting in a four-arm PEO-terminated molecular structure.

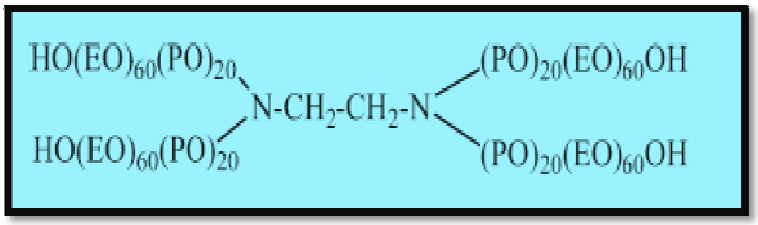


Figure 3.1 : Chemical structure of Tetronics1107

A nonionic surfactant that is 100% active and relatively nontoxic obtained from Baden Aniline and Soda Factory (BASF).Table 2.1 shows the physical properties of Tetronics1107 (BASF specification sheet ,2004) .

Physical properties	**Description**
Form	Cast solid
pH	8-10
Average molecular weight	15000
Melting point	51 C
Surface tension	43 dynes /cm
HLB	18-23

Table 3.1 : physical properties of Tetronics1107

- Tetra butyl ammonium bromide

Tetra butyl ammonium bromide is type of cationic surfactant , table 2.2 shows the physical properties of Tetra butyl ammonium bromide obtained from sigma Chemicals Co . (St . Louis , USA) .

Physical properties	Description
Form	Crystalline powder
Odor	weak odor - amine-like
pH	Not available
Solubility	600 g/L
Density	1.15 g/cm3

Table 3.2 : physical properties of Tetra butyl ammonium bromide

3.2 Oils

Cyclic oils : Peppermint oil and R (+)-limonene .

❖ R (+)-limonene (LIM)

R (+)-limonene (LIM), (98%) was purchased from Sigma Chemicals Co. (St. Louis, USA).

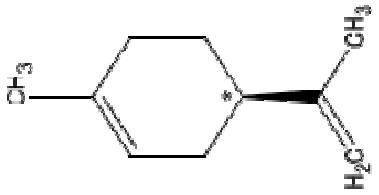


Figure 3.2 : (R)-limonene structure

❖ Peppermint oil (MNT)

Peppermint oil (MNT) , (98%) was purchased from Sigma Chemicals Co. (St. Louis, USA).

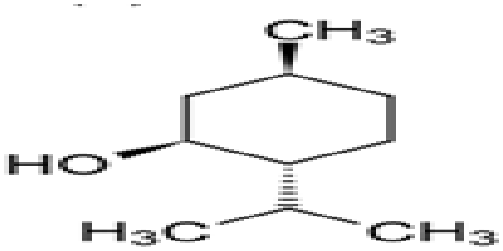


Figure 3.3 : structure of Peppermint oil

Linear oil : Isopropylmyristate (IPM)

❖ Isopropylmyristate (IPM) :

Isopropylmyristate (IPM) , tetradecanoic acid , 1-methyethyl ester (99%) was purchased from Sigma Chemicals Co . (St . Louis , USA) .

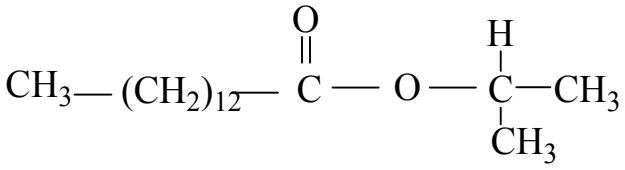


Figure 3.4**:** The chemical structure of Isopropylmyristate oil

3.3 Co-surfactant

- Propylene glycol, PG

The co-surfactant used is 1,2-Propandiol (Propylene glycol, PG) (99.5%) obtained from Sigma Chemicals Co . (St . Louis , USA).

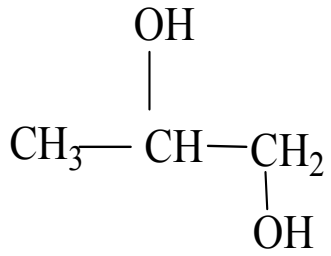


Figure3.5: The chemical structure of 1, 2-Propandiol (propylene glycol, PG).

- 1-Pentanol

99% obtained from Sigma Chemicals Co . (St . Louis , USA) .

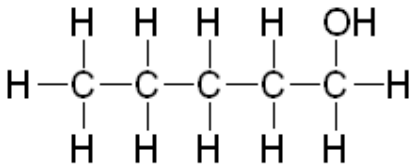


Figure 3.6 :chemical structure of 1-pentanol

3.4 Aqueous phase (water)

Water was double distilled , and it is gifts from the Colloids and Surfaces Research Laboratory Faculty of Science and Technology AL-Quds University.

3.5 Buffer solution pH=9

To prepare buffer solution at pH=9 , Dissolve 12.37g of anhydrous boric acid, H_3BO_3, and 10.51g of citric acid, $H_3C_6H_5O_7.H_2O$ in distilled water and dilute to 1L in a volumetric flask denoted by solution (1) . Then Dissolve 38.01g of $Na_3PO_4.12H_2O$ in distilled water and dilute to 1L in volumetric flask denoted by solution (2) .

345 ml from solution (1) mixing with 655ml from solution (2) to get pH=9 [Shugar, R, et al ,1981][40] .

3.6 Pharmaceutical Active Ingredients (PAI)

Isotretinoin is 13-cis-retinoic acid and is related to both retinoic acid and Retinol (vitamin A). It is a yellow to orange crystalline powder with a Molecular weight of 300.44 obtained from Jerusalem company for medical products . The structural formula is :-

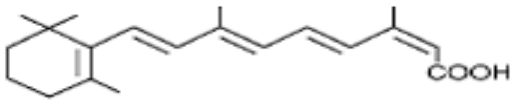


Figure 3.7 : Isotretinoin structure

3.7 Instruments and equipment

five digits analytical balance , vortex , cross polarizer , centrifuge . rotary shaker , glass test tube with screw caps , transistor from department of physical chemistry , polarized microscope , water bath (Selecta) , pH meter , thermometer, origin program to draw phase diagram.

3.8 Procedure :

3.8.1. Construction of ternary and pseudoternary phase diagrams

The phase behaviour of the systems consisting of water (with or without co-surfactant), oil, surfactant (or mixed surfactants) may be described on a phase tetrahedron whose Apexes respectively represent the pure components.

1g of a mixture consisting of oil, surfactant (or mixed surfactants) at different weight ratios were prepared in culture tubes sealed with viton lined screw caps and stirred at high temperature (40-50°C) by vortex until clear solution was obtained. Then titrating these samples with water which was added drop wise until its solubilization limit was reached. Vigorous stirring followed all of the aqueous phase additions on a vortex mixer. The time for equilibration between each addition was typically, from a few minutes up to 24 h. Phase transitions were detected visually by the appearance of cloudiness or sharply defined separated phases; the completion of this process was hastened by centrifuging the samples. The phase diagrams were investigated at three

temperatures (25°C, 37°C and 45°C) or only at room temperature . Polarized light will be used to detect birefringence phases if it appears .

3.8.2.Formulated biocompatible microemulsion systems.

The phase behavior of the systems consisting of water (with or without co-surfactant), oil, surfactant T1107 may be described on a phase diagram whose give 1 phase. the weight of all tube equal 1g .

3.8.3. Evaluation the maximum solubilization capacity of the Isotetronoin in microemulsion and liquid crystal by adding .01g of drug to these structure and mixing in vortex mixer at room temperature until all amount of drug dissolve , and then adding new amount of drug .the addition of drug was stopped when two phase were appeared .

Chapter Four
Result And Discussion

4.1 Ternary phase diagram of Tetronics1107 with propylene glycol at different temperatures (25C ,37C, 45C) .

The phase behavior of Tetronics block copolymers is primarily affected by the PEO/PPO block ratio. However, the addition of solvents selective for the copolymer blocks introduces an additional degree of freedom and can modify the structure initially set by the block ratio. The resulting phase behavior depends on the relative volumes of the polar PEO rich domains, consisting of the PEO blocks of the copolymer and their selective solvent, and of the relatively a polar PPO-rich domains, consisting of the PPO block of the copolymer and its selective solvent. For example, water, a solvent selective for PEO, swells the PEO blocks and induces formation of structures with higher (positive) curvature (oil in-water morphology). This tendency can be seen in Fig.4.1 by following the progression of the self-assembly structure along the Tetronics1107-water axis at different temperatures.

At (T=45C), with increasing the water content (and decreasing the block copolymer content) the cubic phase stable from 55 to 87 wt% Tetronics 1107, and this eventually melts into a micellar water rich solution stable less than 25 wt % Tetronics1107.

At (T= 37C), with decreasing the block copolymer content (and increasing the water content) the cubic phase stable from 47 to 83 wt% Tetronics 1107, and this reverts to micellar water rich solution stable less than 26 wt % Tetronics1107.

At (T=25C), the cubic phase stable from 48 to 81 wt% Tetronics1107, and this reverts to micellar water rich solution stable less than 27 wt % Tetronics1107.

The cubic phase to micelle phase sequence is a result of an increase in the preferred curvature: it changes from positive in the cubic phase to highly positive in the micelle phase.

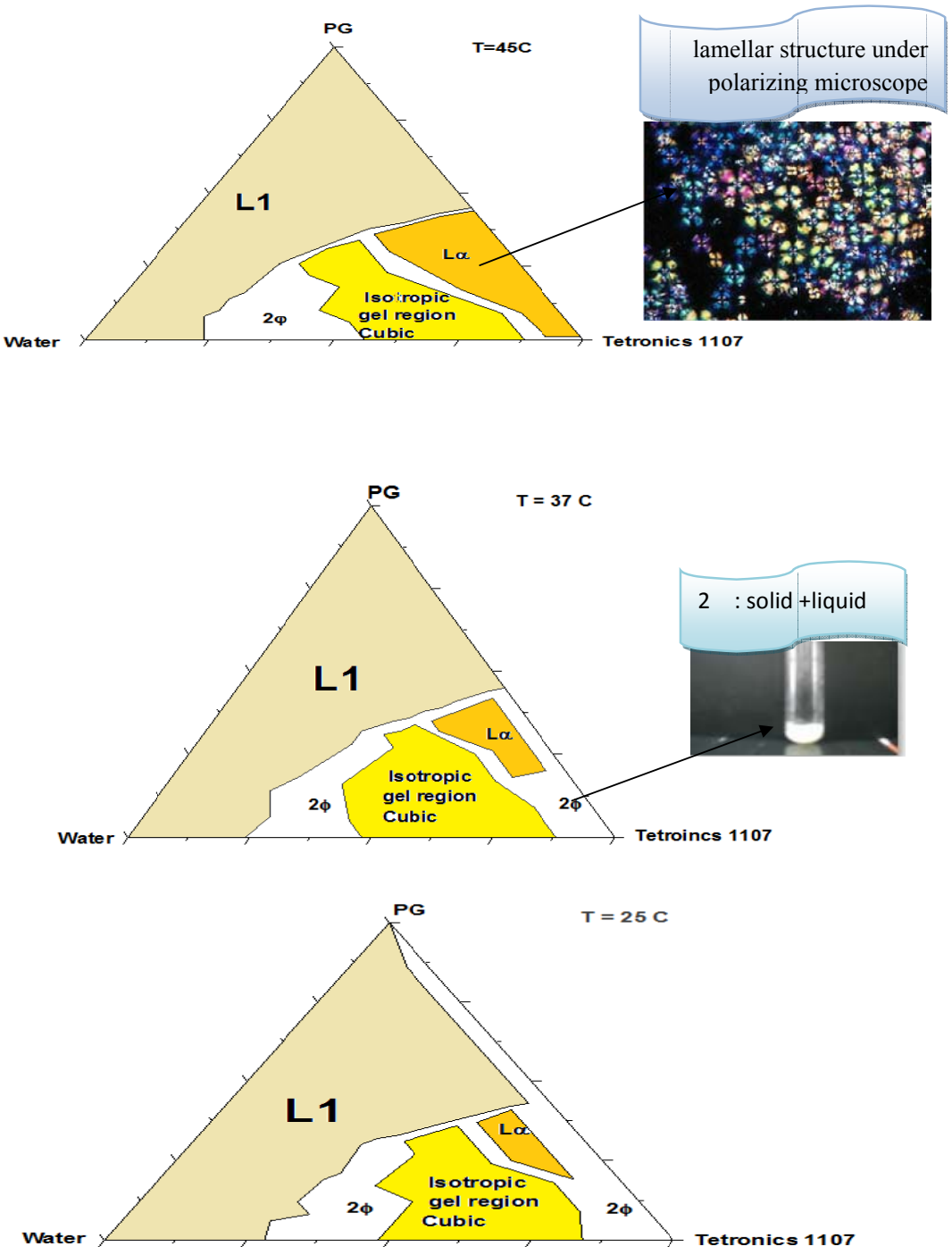


Figure 4.1 : the isothermal phase diagram of three component system Tetronic1107 / Propylene glycol (PG) / water at (45C,37C ,25C) . Lα represent Lamellar area and L1 represent normal micelle .

Propylene glycol is a polar solvent, where octanol / water partition coefficients are negative (log *P*=−1.41), it show a common behavior with respect to the self-assembled structures attained by the block copolymer.

In each of the above ternary system only the structures formed in the binary Tetronics1107 –water system, cubic I1, and L1, were obtained.
Polar water-miscible solvents are able to maintain the stability of a given microstructure up to high solvent/water ratios.

Ternary phase diagram of Tetronics1107 with propylene glycol at (25C), reveled that forming lamellar structure which is stable to 46 wt.% Tetronics1107, and cubic structure which is stable to 37 wt.% Tetronics 1107, the region between cubic phase and lamellar phase is biphasic region denoted by 2Φ.

Also, this phase diagram forming normal micelle denoted by L1, the region between cubic phase and L1 region is biphasic liquid and gel.

The region before lamellar structure is biphasic solid and liquid .

At (37C), Ternary phase diagram of Tetronics1107 with propylene glycol forming the same regions . lamellar structure which is stable to 45 wt.% tetronics1107, and cubic structure which is stable to 37 wt.% tetronics1107, the region between cubic phase and lamellar phase is biphasic region . forming normal micelle L1, the region between cubic phase and L1 region is biphasic liquid and gel.

The region before lamellar structure is biphasic solid and liquid .

At (45C), lamellar structure which is stable to 40 wt.% Tetronics1107, and cubic structure which is stable to 31 wt.% Tetronics1107, the region between cubic phase and lamellar phase is biphasic region. Forming normal micelle L1, the region between cubic phase and L1, region is biphasic liquid and gel .
The region before lamellar structure is biphasic solid and liquid .

Propylene glycol is a polar solvent cannot induce the formation of structures with negative curvature (water-in-oil morphology) in block copolymer systems with highly positive initial preferred curvature, i.e. polxamine block copolymers with large PEO/PPO volume ratio such as tetronics1107.
Depending on previous study on liner counterpart of polxamine Poluronic F127, reveled that propylene glycol is preferably located in the relatively a polar PPO rich domains and at the interface, and keep the curvature constant.

In our lab, we will be noted that the ternary phase diagrams of Tetronics1107 with propylene glycol and binary system Tetronics1107 with water are slightly different at different temperatures due to the temperature increase the solubility increase, so at (25C,37C,45C) temperatures, the phase diagram of Tetronics1107 with propylene glycol and binary system Tetronics1107-water axis at different temperatures are the same, and insensitive to change temperatures due to have large number of terminal hydroxyl group ,which forming strong hydrogen bond with water so insensitive to change temperatures from (25C-45C).

4.2 Effect of cationic surfactant tetra butyl ammonium bromide (TBAB) at different ratio and different temperature on the phase diagram of Tetronics1107 with propylene glycol .

Surfactant mixtures are common place in a wide range of consumer products such as detergents, shampoos, and conditioners. The mixing of different types of surfactants gives rise to synergies that provide the opportunity to optimize product performance .[I. Tucke,et .al , 2008][43]

Studies of liner counterpart of Tetronics Poloxamer block copolymer micellization in the presence of Cetyltrimethyl ammonium bromide (CTAB) reveal that with increasing the CTAB concentration, the micelle association number decreases until pure CTAB micelles and individual Poloxamer macromolecules saturated with CTAB are present.

Surfactants are believed to bind to the PPO block of the block copolymer and progressively decrease the block copolymer amphiphilicity. At saturation of the Poloxamer with surfactant, the block copolymer micellization is completely suppressed and this also leads to the destruction of the liquid crystalline phases formed by the block copolymer.

The interaction of Tetronics1107 , with cationic surfactant tetra butyl ammonium bromide (TBAB) at different ratio and at different temperature has been explored by studying the ternary phase diagrams of the three systems.

In the beginning, will be studied the phase behavior of tetra butyl ammonium bromide (TBAB)which is a quaternary ammonium salt with propylene glycol at different temperatures (25C,37C,45C), the result revealed that all phase diagrams have two region, the first region is

biphasic solid and liquid and this region become very small when increase temperature because increase solubility of component. The second region is normal micelle L1.figure 4.2.

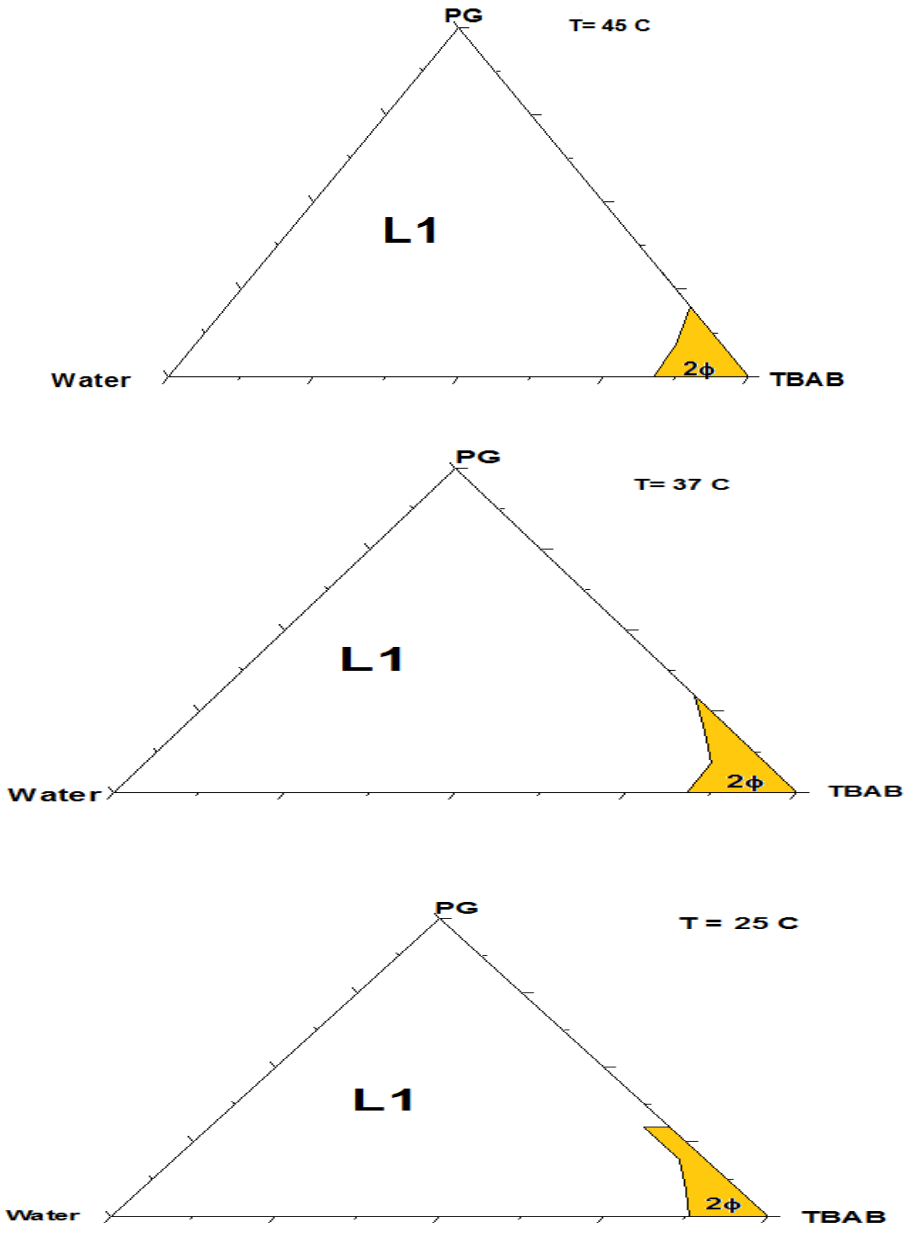


Figure 4.2 : the isothermal phase diagram of three component system tetra butyl ammonium bromide / Propylene glycol (PG) / water at (45C,37C ,25C) . 2Φ represent solid +liquid region and L1represent normal micelle

Fig 4.3 . presents the pseudoternary phase diagram of the water/Tetronics 1107 /TBAB/Propylene glycol determined at different temperatures (25C , 37C,45C) . The mixing ratios (w/w) of Tetronics1107 /TBAB equal (75% Tetronics1107 : 25% TBAB) .

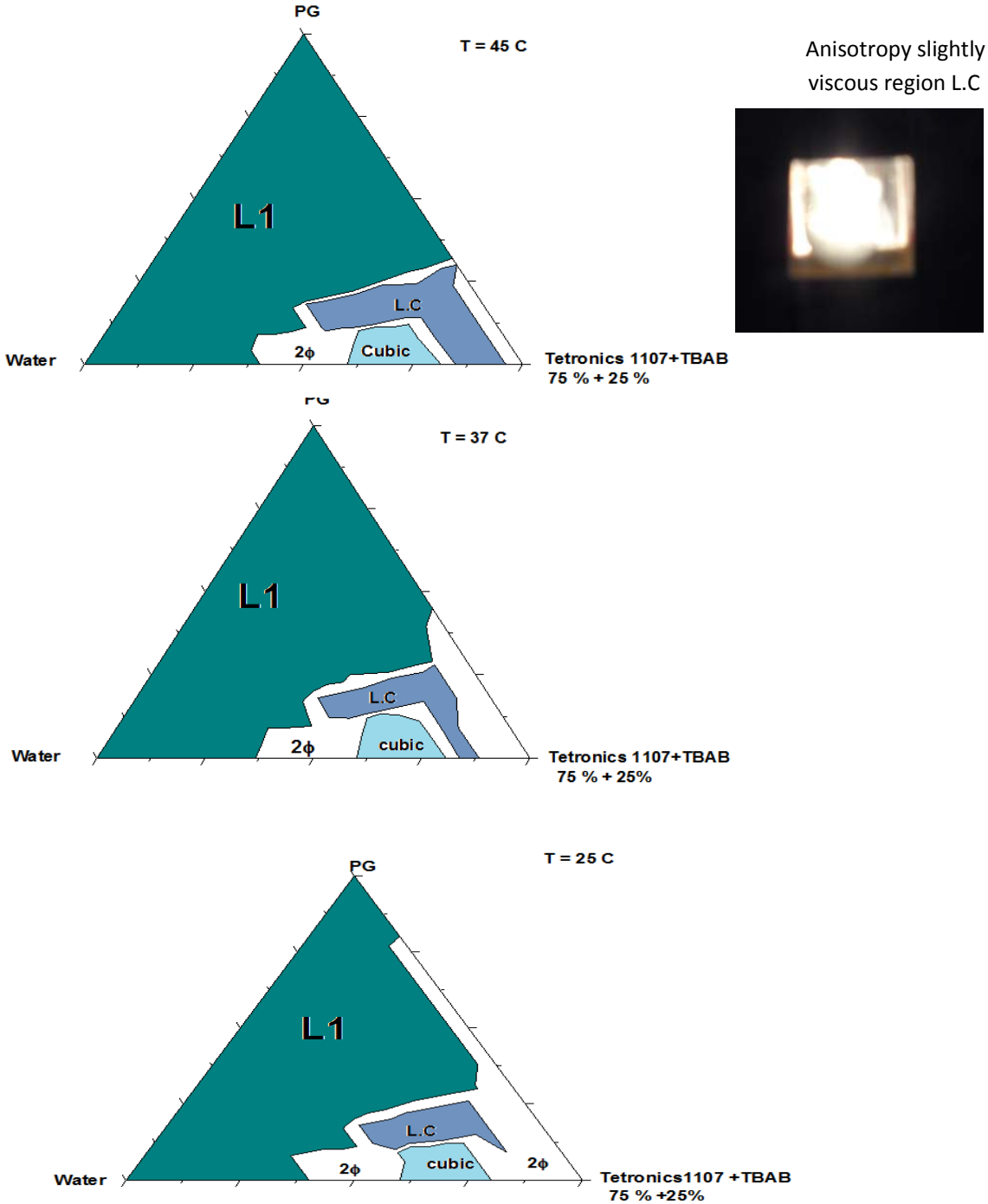


Figure4.3 : the isothermal phase diagram of four component system tetra butyl ammonium bromide +Tetronic1107 at ratio 75% :25% respectively / Propylene glycol (PG) / water at (45C,37C ,25C) . LC slightly viscous anisotropic region and L1represent normal micelle, finally cubic isotropic gel region .

At (25C , 37C,45C), the cubic structure can accommodate more than 57wt.% surfactant. and anisotropic slightly viscous region can accommodate more than 42 wt.% surfactant. The area before slightly viscous region and between this region and cubic region and after of them is biphasic region denoted by 2Φ. The remainder of the phase diagram represents a normal micelle L1.

At 25C the self-assembly structure along the Tetronics1107/TBAB -water axis show that, with increasing the water content (and decreasing Tetronics1107/TBAB), the cubic phase stable from 61 to 86 wt% Tetronics1107/TBAB, and this reverts to micellar water rich solution stable less than 41 wt % Tetronics1107/TBAB .

Then at (37C,45C), the self-assembly structure along the Tetronics1107/TBAB -water axis show that the slightly viscous region stable from 87 to 93 wt% Tetronics1107/TBAB.

With increasing the water content (and decreasing Tetronics1107/TBAB) the cubic phase stable from 61 to 86 wt% Tetronics1107/TBAB, and this reverts to micellar water rich solution stable less than 39 wt % Tetronics1107/TBAB .

When decreasing, the amount of Tetronics1107, and increasing the amount of cationic surfactant TBAB, where the mixing ratio (50% Tetronics 1107 :50%TBAB) and (25% Tetronics1107:75% TBAB), the liquid crystalline region slightly viscous and cubic phase are destructive . and replacement by normal micelle L1 region at (25 C,37C,45C) figure 4.4 and 4.5.

Starting with a block copolymer micellar solution, the addition of cationic surfactant TBAB leads to association of the TBAB with the block copolymer. Although there is no direct evidence at which part of the macromolecule the binding with the surfactant takes place, it is mostly accepted that the surfactant hydrophobic tail binds to the relatively hydrophobic PPO block of the copolymer.

With increasing the surfactant concentration, the complexes become less amphiphilic and more hydrophilic. This process continues until all the copolymer molecules are saturated with surfactants and the block copolymer assembly is suppressed . At this point, two types

of aggregates are present: pure surfactant micelles and aggregates consisting of one Tetronics1107 macromolecule and bound surfactant molecules.

This clarification depending on the previous study on liner counterpart poloxamer, when studying the interaction poloxamer with cationic surfactant, and cosurfactant. The result on this study deal with this previous study . [Rouja Ivanova , et al ., 2001][39]

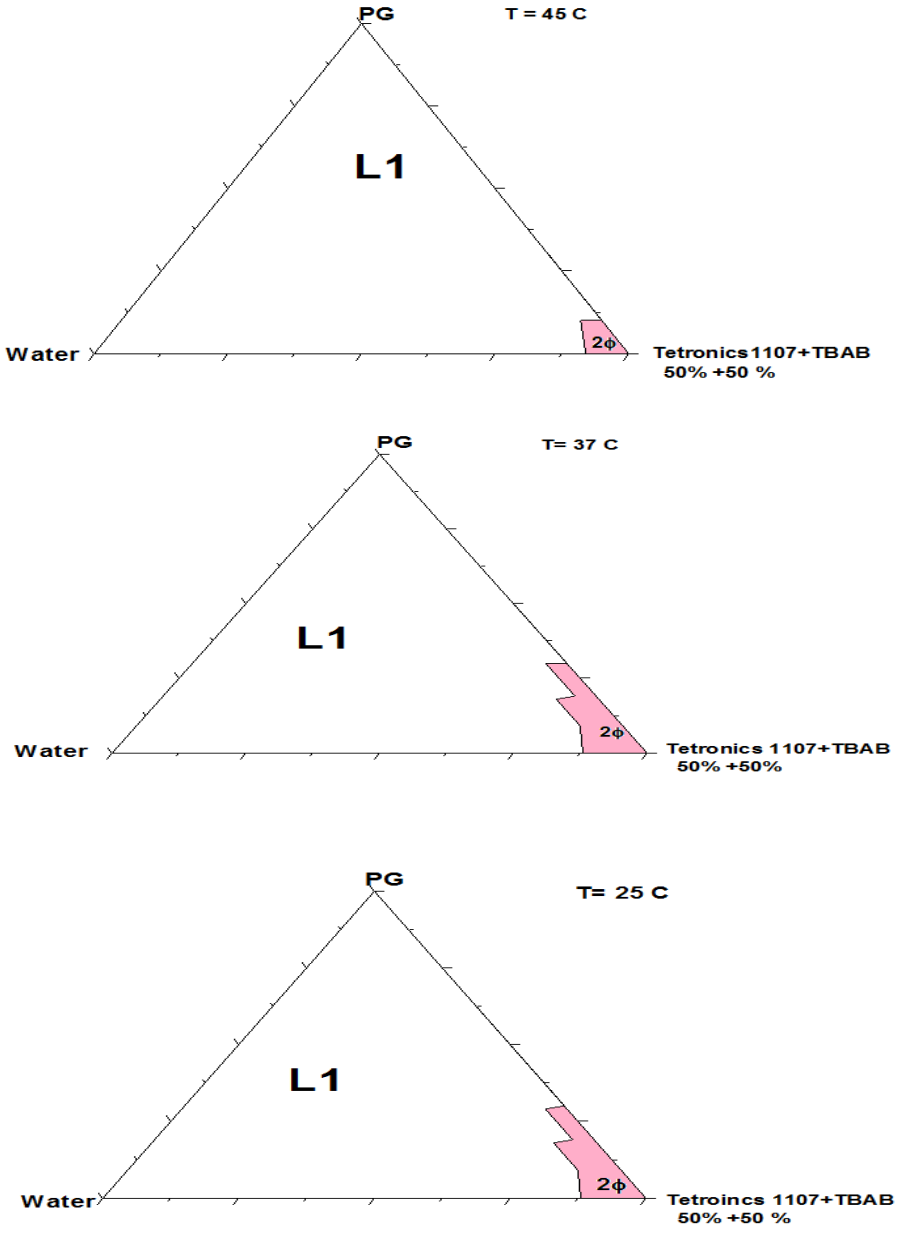


Figure 4.4 : the isothermal phase diagram of four component system tetra butyl ammonium bromide +Tetronic1107 at ratio 50% :50% respectively / Propylene glycol (PG) / water at (45C,37C ,25C).2Φ represent liquid +solid phase and L1 represent normal micelle .

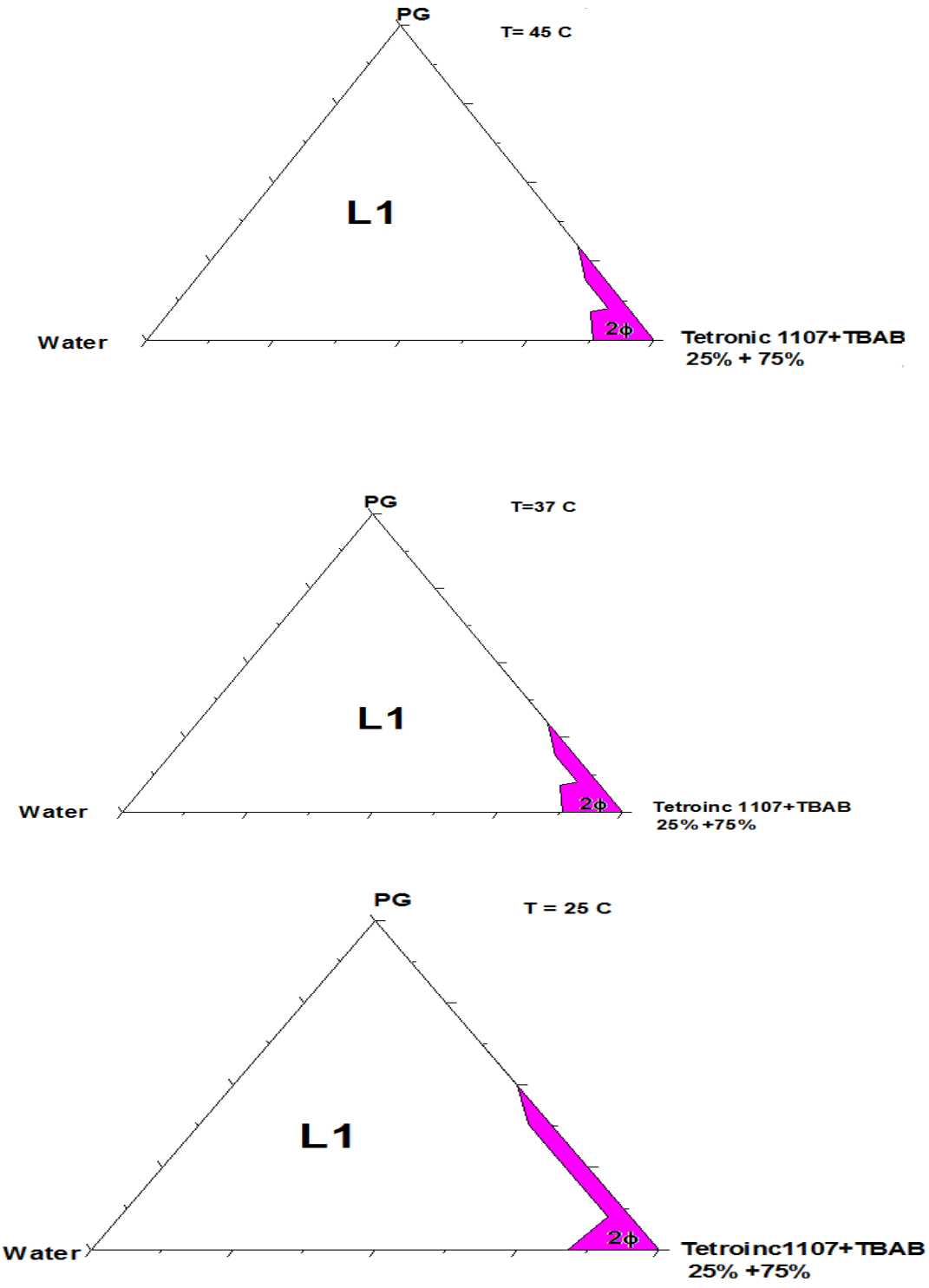


Figure 4.5 : the isothermal phase diagram of four component system tetra butyl ammonium bromide +Tetronic1107 at ratio 75% :25% respectively / Propylene glycol (PG) / water at (45C,37C ,25C). 2Φ represent liquid +solid phase and L1 represent normal micelle .

4.3 The effect of different pH at ternary phase diagram of Tetronics1107:

We will be studied the ternary and pesudoternary phase diagram of Tetronics 1107/Limonene oil system at different pH, by using buffer solution (pH= 9.0), water with Propylene glycol at ratio (2:1) (pH=4.14), and water (pH=6.43) at 25C.

The result by using water with Propylene glycol at ratio (2:1) (PH=4.14) was small isotropic liquid crystal phase region, figure 4.6 obtained until addition of 0.43g Tetronics1107, 0.05g Limonene oil and 0.52g water, at this point upon further addition of water the mixture turned rapidly to biphasic region gel and liquid then to single turbid phase.

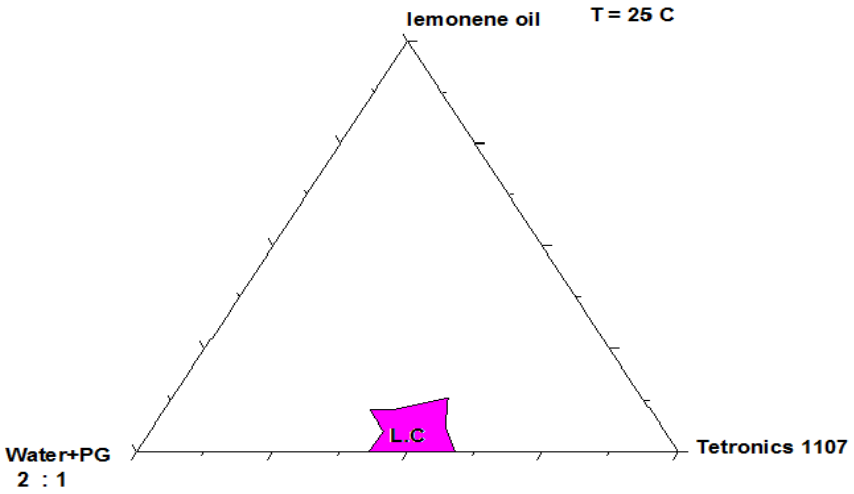


Figure 4.6 : the isothermal phase diagram of three component system Teronic 1107 / limonene oil /PG+ water at 25C . LC represent liquid crystal region .

The result when we used water (pH=6.43) was isotropic liquid crystal phase region and nanoemulsion region, figure 4.7 obtained until addition of 0.40g Tetronics1107, 0.04g Limonene oil and 0.56g water for liquid crystal and 0.11g Tetronics1107, 0.01 Limonene oil and 0.88 g water for nanoemulsion region, at this two point upon further addition of the water mixture turned rapidly to biphasic region gel and liquid or a single turbid phase respectively.

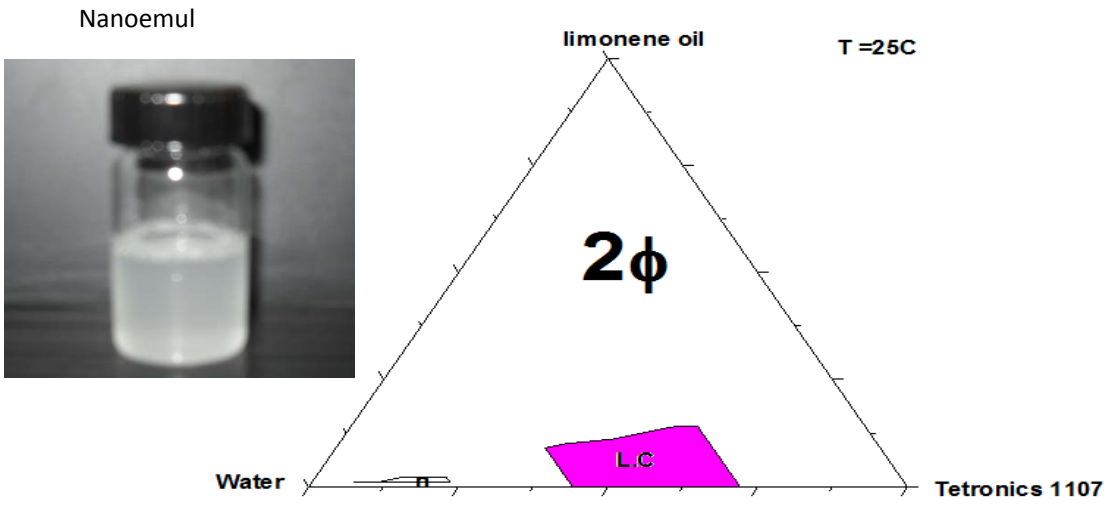


Figure4.7 :the isothermal phase diagram of three component system Tetronic1107 / limonene oil / water at 25C . LC and n represent liquid crystal region and nanoemulsion area respectively

Finally, when we used buffer solution (pH=9.0) , the study of the ternary phase diagram of Teronics1107/ limonene oil /buffer solution reveled that the aggregation of surfactant is difficult at high pH, and the liquid crystal region is disappear as shown in phase diagram figure 4.8

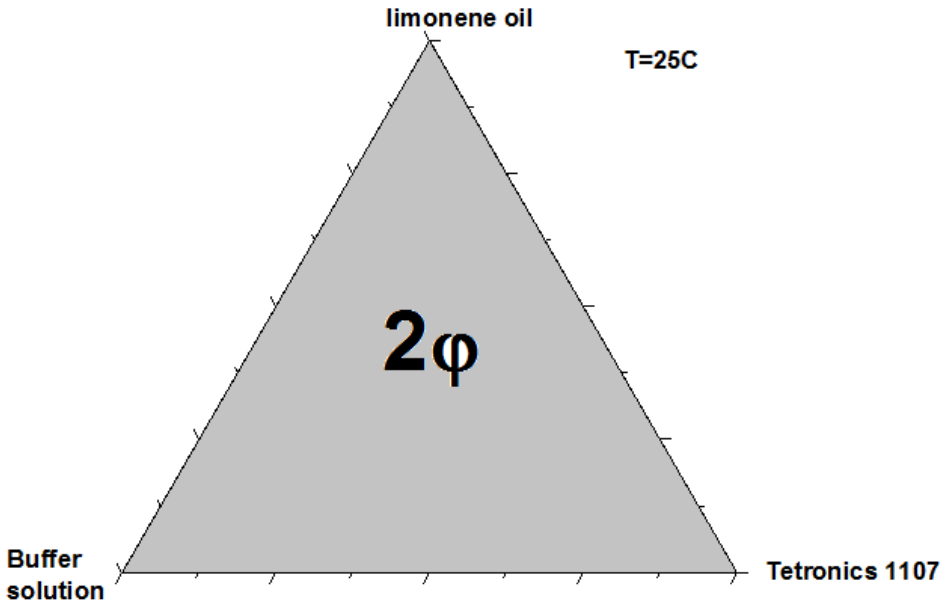


Figure4.8 : the isothermal phase diagram of three component system Tetronic

1107 / limonene oil / buffer solution at 25C .

From these result, we will be noted that the aggregation behavior of Tetronics 1107 is difficult at high pH, these result deal with previous study, that the physicochemical conditions of the medium, particularly pH, can alter the extent of protonation of the ethylenediamine central group so it effect the aggregation behavior of surfactant. In previous study the diprotonated form is the predominant one at pH values below 4, and its concentration is greater than that of the nonprotonated form up to pH 5.8.

The monoprotonated form predominates in the pH range from 4.0 to 7.9.

The Coulombic repulsions among the positively charged amine groups at the center of the PPO chains constrains the self-aggregation. [Jaime Gonzalez-Lopez , et al.,2008][33].

The positive charge of both the diamine center (diprotonated) at high pH ,create strong electrostatic repulsion, which constrain the blocks to stay away disfavoring the aggregation.

On the contrary, the presence of single charge in the copolymer at pH=4.14 and pH =6.43 permits to obtained aggregates (liquid crystal and nanoemulsion region).

In previous study, they found that the Tetronics1107, under low acidic condition pH=2.7 the aggregation is difficult to the same reason at high pH .[Rosario De Lisi, et al .,2010][41] .

4.4 Biocompatible microemulsion using Tetronics1107/biocompatible oil single or mix / propylene glycol with water at ratio 1:2

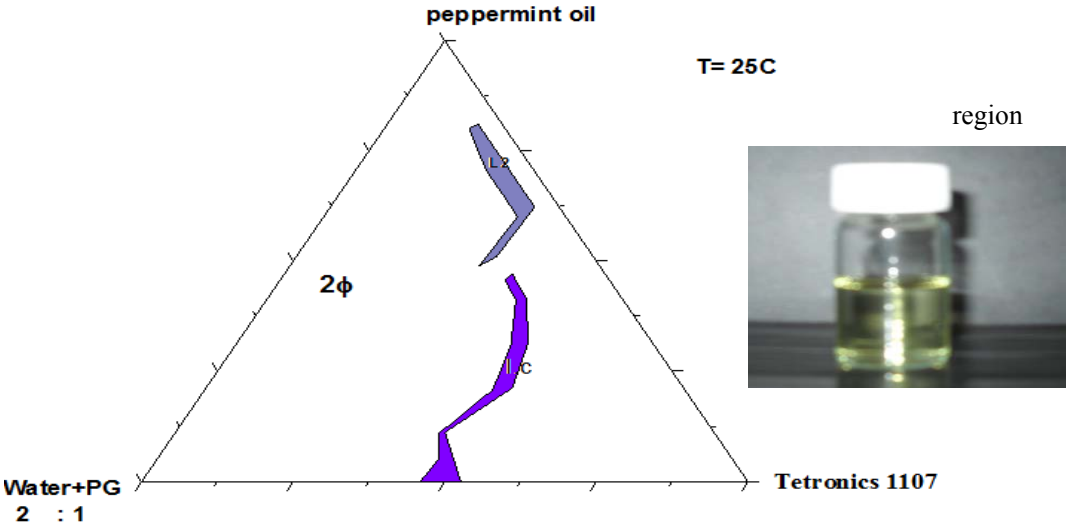


Figure 4.9 : pesudoternary phase diagram of Tetronics1107/peppermint oil / propylene glycol with water at ratio 1:2 . L2 and LC represent inverse micelle and liquid crystal regions respectively

Figure 4.9 present pesudoternary phase diagram of Tetronics 1107/peppermint oil / propylene glycol with water at ratio 1:2. We will be noted that the Tetronics1107 forming very small regions of microemulsion (inverse micelle) and isotropic liquid crystal .

At the point of 39% tetronics1107 , 49% peppermint oil, and 12 % water ,additional peppermint oil will change the isotropic liquid crystal to inverse micelle structure.

To increase the area of microemulsion region, in our lab we tried by using cosurfactant 1-Pentanol, and by using mixing oil to enhance the microemulsion region .

4.5 Effect of addition 1.Pentanol on the phase behavior of Tetronics1107 /peppermint oil/ water

In previous phase diagram, the inverse micelle and liquid crystal regions were very small .

The inverse micelle area and liquid crystal area are increased when mixed 50% peppermint oil with 50% 1-pentanol more than when used peppermint oil without 1-pentanol.

The region of L2, LC represent the reversed micelle and the isotropic liquid crystal respectively.

At the point of 40% Tetronics1107, 44% peppermint oil with 1-pentanol, and 16 % water, additional surfactant will change the liquid crystal to inverse micelle structure figure 4.10.

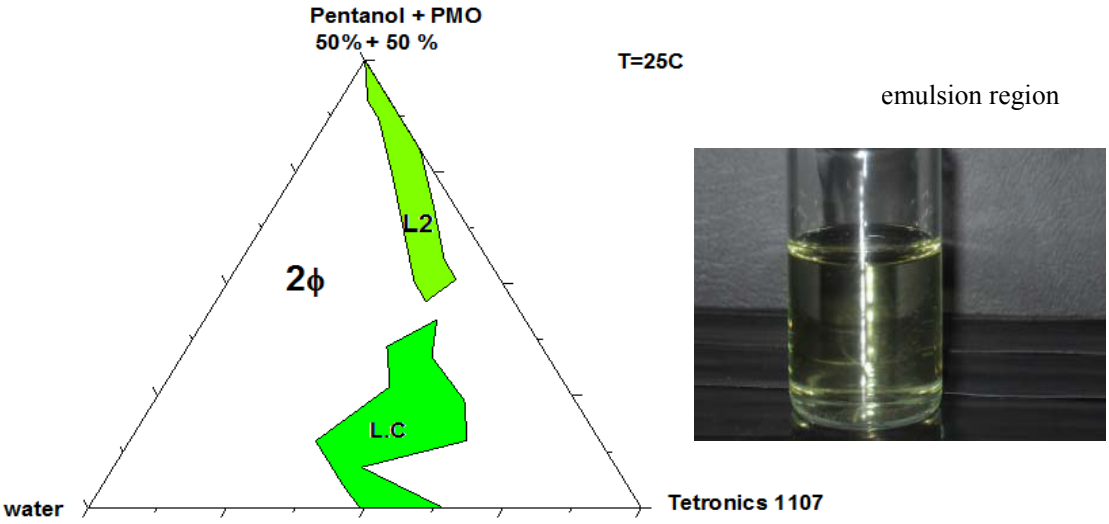


Figure4.10 : the isothermal phase diagram of four component system Tetronics1107 / peppermint oil +1-pentanol (50%:50%) respectively / water at 25C . L2 represent Inverse micelle area and LC represent liquid crystal .

During the past years various researchers have tried to find the exact role of alcohols in microemulsions. medium chain of 1-pentanol making strong hydration of Tetronics1107 head groups leads to a stronger repulsive interaction with oil, which reflects itself in a strong adsorption

at water/oil interfaces, and the formation of (inverse) micelles [Daliya S ,et.al,2006][42] .

4.6 pesudoternary phase diagram of Tetronics1107 with (isopropyl myristate) as oil or mixing oil (isopropyl myristate +limonene oil) or (peppermint oil + isopropyl myristate) .

when used (isopropyl myristate) as oil or mixing oil (50% isopropyl myristate + 50% limonene oil) or (50% peppermint oil +50% isopropyl myristate), to gain microemulsion region or to increase this region in previous phase diagram with peppermint oil .

The microemulsion and isotropic liquid crystal region disappeared and is, replaced by emulsion region which is kinetically stable figure 4.11,4.12,4.31. Tetronics1107 have high hydrophilic lipophilic balance, so it difficult to emulsifying as noted in this research .

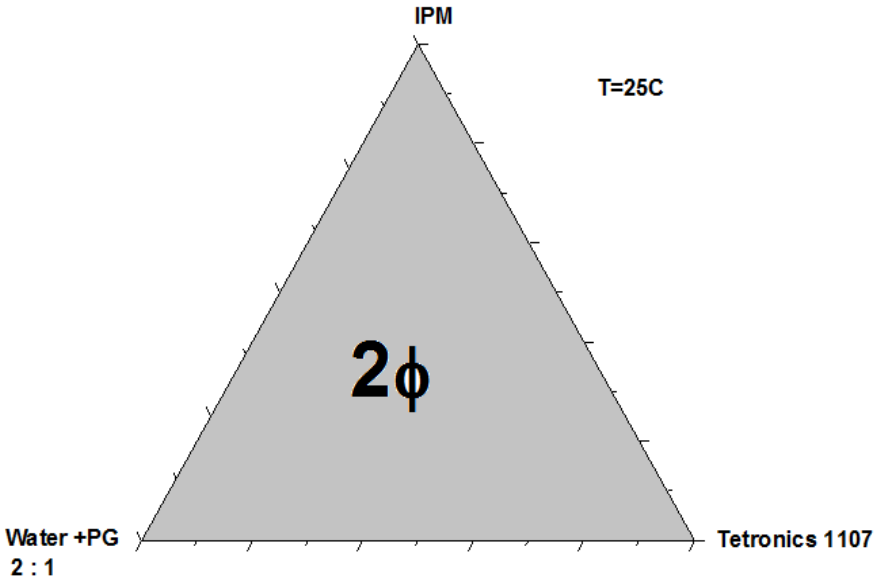


Figure 4.11 : pesudoternary phase diagram of Tetronics1107/isopropylmyristate / propylene glycol with water at ratio 1:2 . 2Φ represent emulsion region .

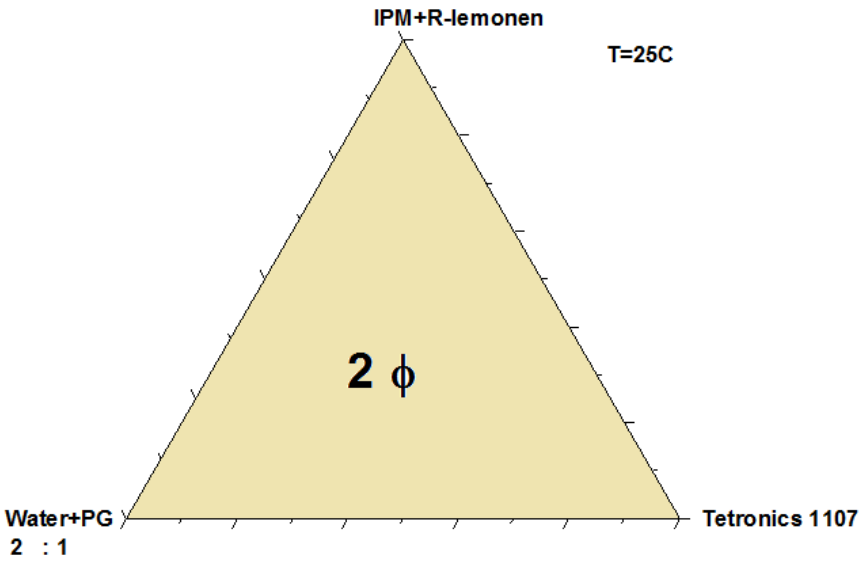


Figure4.12 : pesudoternary phase diagram of Tetronics1107/isopropylmyristate+R- limonene / propylene glycol with water at ratio 1:2 . 2Φ represent emulsion region .

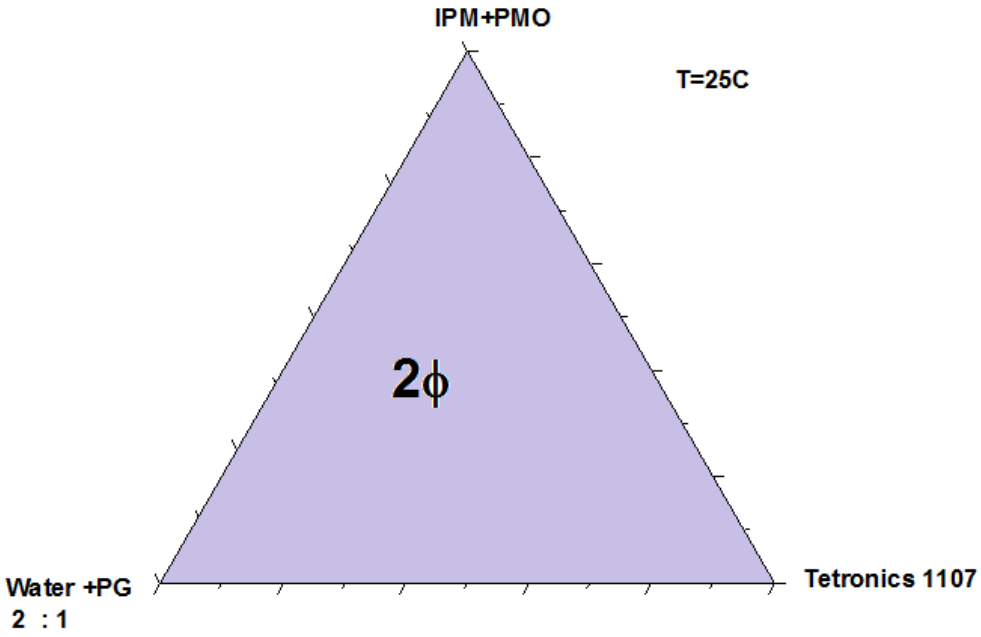


Figure4.13 : pesudoternary phase diagram of Tetronics1107/isopropylmyristate+ peppermint oil / propylene glycol with water at ratio 1:2 . 2Φ represent emulsion region .

4.7 Solublization of Isotretinoin in microemulsion and liquid crystal (Cubic) .

Microemulsion where formed by peppermint oil and liquid crystal formed by limonene oil, were used to enhance solubility of Isotretinoin .

The amount of drug solublized in microemulsion region is approximately 17.9 mg /1gm microemulsion.

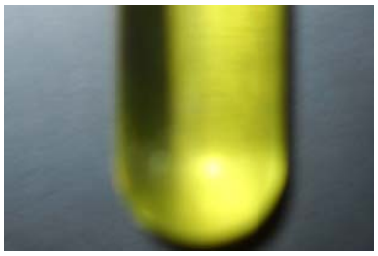


Figure 4.14 : solublizing Isotretinoin in microemulsion forming by (19 wt.% tetronics1107 , 76 wt .% peppermint oil, and 5 wt.% water) .

The amount of drug solublized in liquid crystal region is approximately 10 mg / 1 gm liquid crystal .

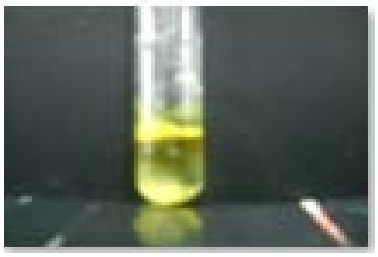


Figure 4.15 : solublizing Isotretinoin in liquid crystal forming by (42 wt.% tetronics1107 , 10 wt .% limonene , and 48 wt.% water) .

Chapter Five
Conclusion And Recommendation

5.1 Conclusion

The present study investigated thoroughly the phase behavior of star copolymer tetronics1107 with different oil and the effect of addition cationic surfactant tetra butyl ammonium bromide on phase behavior of tetronics1107. The cosolvent/surfactant effects in the phase behavior are related to the preference of the cosolvents/surfactants, depending on their polarity, to locate in different domains of the self assembled microstructures formed by the block copolymers.

Phase behavior studies indicate that, propylene glycol is polar water miscible solvents are able to maintain the ternary composition range of stability of a given structure up to high solvent/water ratios. Polar water miscible propylene glycol may have some preference to locate in the PPO-rich domains but cannot induce the formation of water-in-oil structures (with negative curvature).

Addition of Tetra butyl ammonium bromide, to tetronics1107 at different concentration leads to the destruction of the liquid crystalline phases .

The physicochemical conditions of the medium, particularly the pH , can alter the extent of protonation of the ethylenediamine central group, perturbing the hydrophobic interactions that govern the self-assembly process. result of this study deal with previous study that under low pH=2.7and high pH=9.0, the aggregation is difficult due to coulombic repulsions among the positively charged amine groups at the center of the PPO chains constrains the self-aggregation .

Regardless of the impact that these structural parameters have on their performance, the information currently available is limited to a few varieties under some specific conditions, and a comprehensive and comparative investigation of behavior of the Poloxamines is still lacking.

Microemulsion and liquid crystal regions forming by copolymer tetronics1107, are used to enhance solubility of *Isotretinoin*. the results show us that, the potential use of tetronics1107 as nanocarriers in pharmaceutical formulations. although it difficult to emulsifying .

5.2 Recommendation

Poloxamine surfactant are less studied in the biomedical and pharmaceutical fields, so we need to focus investigation of Tetronics to use it as nanocarrier for enhancing solubility of drugs.

Surface-adsorbed Tetronic can provide steric stabilization and modify the biodistribution of orally or topically administered drug-loaded nanoparticles.

For any of these purposes, the efficiency of a surfactant is intimately linked to its ability to interact with water, which determines the solubility, the free/bound water ratio, and the self associative phenomena. In the case of Tetronics the paucity of data is notable. So, we should be further more study for Tetronics groups.

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ميكروواملشن حيوي وكيفية تشكله وسلوكه وبعض استخداماته

إعداد : أصالة نصري نصار الجندي

إشراف: البروفيسور إبراهيم الكيالي

الملخص :

تناولت هذه الدراسة دراسة سلوك الكوبولمر الذي يستخدم كسلفاكتنت و يسمى تيترنوك1107, حيث انه يتكون من أربعة اذرع تتكون من البولي بروبلين اوكسيد والبولي اثلين اوكسيد ويحتوي في مركزه على مجموعة اثلين داي امين , ونظرا لهذا التركيب الفريد فانه يتأثر بالوسط الذي يتواجد فيه , حيث انه وتحت (pH= 2.7or pH= 9.0) يكون (aggregation) صعب جدا نظرا لوجود (Ethlyene diamine group) , حيث يحدث لها ما يسمى (protonation) وتحت (pH=2.7 or pH=9.0) يحدث (Diprotonation) لمجموعة (ethylene diamine group) مما يؤدي إلى تنافر شديد الأمر الذي يجعل (aggregation) صعب .

وتمت في هذه الدراسة دراسة سلوك (tetronics1107) مع المذيب القطبي (propylene glycol) , وتم الحصول على (Lα, I, L1) , وتم تعين منطقة (Anisotropy) بواسطة ميكروسكوب الاستقطاب (polarize microscopy) .

و تمت دراسة تأثير إضافة (tetra butyl ammonium bromide) على سلوك (Tetronics1107) , حيث كشفت هذه الدراسة انه كلما زاد تركيز tetra butyl ammonium bromide يؤدي إلى اختفاء منطقة (liquid crystal) في الرسم الثلاثي الأطوار ternary phase diagram للنظام(Tetronics1107/propylene glycol / water) .

أيضا تم دراسة سلوك (tetronics1107) مع الزيوت التي تدخل أجسامنا , مثل زيت النعناع وزيت الليمون في محاولة لعمل (microemulsion) واستخدمه لتحسين ذائبية الدواء التي تعد من أهم المشاكل التي تعاني منها الادوية , وقد تم الحصول على (microemulsion) بواسطة زيت النعناع , وتمت زيادة هذه المنطقة باستخدام الكحول (1-pentanol) وتم الحصول على جل (isotropic gel region cubic) عند استخدام زيت الليمون , وتم استخدام هاتان المنطقتان لتحسين الذائبية لدواء (*Isotretinoin*) حيث تمت إذابة 17.9 ملغ دواء/غرام ميكروواملشن أما في (isotropic gel region cubic) فقد تم إذابة 10ملغ دواء /1غرام ميكروواملشن .