Introduction

Solution is an intimate mixture of two or more chemical substances. In solution, the dissolving agent is the solvent (dispersion medium) and the substance which dissolves is the solute (dispersed phase). The state of matter of a solution may be solid, liquid or gas which are in the form of atoms, ions, or molecules. According to Scottish chemist Thomas Graham (1861), depending on the size of solute particles, the solutions are classified as ;.

1.1 True solutions

A true solution is a homogeneous solution in which the solute particles have diameters lesser than 1 nm i.e., the solute particles are of molecular dimensions. Such dispersed particles dissolve in solution to form a homogenous system. These do not settle down when the solution is left standing. The particles are invisible even under powerful microscopes and cannot be separated through filter paper, parchment paper or animal membranes, e.g. sodium chloride in water, sugar in water.
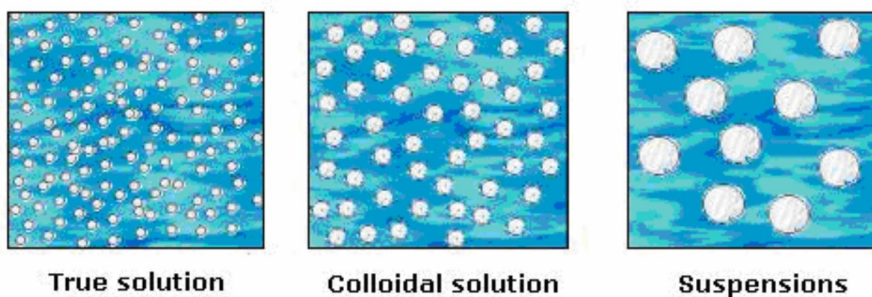

True solution **Colloidal solution** **Suspensions**

Figure. 1.1 Types of solutions

1.2 Suspensions

Suspensions consist of particles of a solid suspended in a liquid medium. Suspensions are systems with two distinct phases. The particles in suspensions are bigger than 1000 nm. visible to the naked eye or under a microscope. Suspensions are heterogeneous systems. They stay only for a limited period i.e. these are not stable as the particles have a tendency to settle down under the influence of gravity. The particles of a suspension can neither pass through ordinary filter paper nor through animal membranes, e.g. sand in water, oil in water.

1.3 Colloids

Colloids or Colloidal solutions, in chemistry, are a substances in which one substance of microscopically dispersed insoluble particles is suspended throughout another substance. Sometimes the dispersed substance alone is called the colloid;(1,2). represent an intermediate kind of a mixture between true solution and suspension (3). The size of a colloidal particle lies roughly between 1-1000 nm(4, 5) Colloids are also a two-phase heterogeneous system consisting of the dispersed phase (internal or discontinuous phase) and dispersion medium (external or continuous phase). Since the dispersed phase in a colloidal system is uniformly distributed in the dispersion medium, the colloidal state appears homogenous to the naked eye or even an ordinary microscope (due to particles being invisible). However it is a heterogeneous dispersion of two immiscible phases by viewing it under an ultra-microscope, where the light reflected by colloidal particles can be seen. Colloidal particles do not settle down under gravity. Colloids can pass through ordinary filter paper but do not pass through animal membranes, e.g. a colloidal solution of gold. Total interface area of the colloidal dispersed particles is very large due to their submicroscopic size. The huge area-to-volume ratio determines specific properties and behavior of colloids. In other words, as in the colloids the amount of dispersed particles is very large, their overall surface is very large too and by consequence the interaction of the two phases is important. Because of the wide surface of contact between the two phases, often the colloids are studied with the surface phenomena. Adsorption processes occurring on the interface between the dispersed and continuous phases exert considerable effect on the colloid physical properties, chemical reactions in the system and its stability. Surface active substances added to a colloid modify its properties. Colloidal solutions, depending upon the nature of interactions between dispersed phase and the dispersion medium, are classified into two types as lyophilic (solvent loving) and lyophobic colloids (solvent hating).

1.3.1 Lyophilic colloids:

The colloidal solution in which the particles of the dispersed phase have a great affinity for the dispersion medium, are called lyophilic collodis." In such colloids, the dispersed phase does not precipitate easily and the colloids are quite stable. If the dispersion medium is separated from the dispersed phase, the colloids can be reconstituted by simply remixing with the dispersion medium (4) Hence, these colloids are reversible in nature, e.g. colloids of gum, polymers in organic solvents.

1.3.2 Lyophobic colloids.

The colloidal solution in which there is no affinity between particles of the dispersed phase and the dispersion medium are called lyophobic colloids." These colloids are easily precipitated on addition of small amount of electrolytes, by heating or by shaking and therefore are not stable. Once precipitated, it is not easy to reconstitute the colloid by simple mixing with the dispersion medium. Hence these colloids are irreversible in nature, e.g. colloids of metals. Depending upon the physical state of dispersed phase and dispersion medium whether these are solids, liquids or gases, eight types of colloidal systems are possible as given in the table 1.1[5]

Table 1.1 Types of colloidal systems

medium/phase		Dispersed phase		
		Gas	liquid	solid
Dispersion medium	Gas	**None** (All gases are mutually miscible)	**Liquid aerosol** Examples :fog,Hair sprays	**Solid aerosol** Examples :smoke, Cloud, air particulate
	Liquid	**Foam** Examples : Shaving cream	**Emulsion** Examples : Milk, hand cream	**sol** Examples : Pigmented ink blood
	solid	**Solid foam** Examples : aerogel	**Gel** Examples : Jelly, silica gel	**Solid sol** Examples : glass

1.4 Formation of Colloids

There are two basic methods for formation of colloids:

1.4.1 Dispersion method

where in the reduction of larger particles to colloidal size occurs, e.g. by mechanical subdivision of larger particles or by dissolution in the case of lyophilic sols.

1.4.2 Condensation method

where in condensation of smaller particles (e.g., molecules) into colloidal particles occurs, e.g. from supersaturated solutions or as the product of chemical reactions. Some substances (e.g. glue) are easily dispersed (in the proper solvent) to form a colloid; this spontaneous dispersion is called peptization. Condensation of smaller particles to form a colloid usually involves chemical reactions—typically displacement, hydrolysis, or oxidation and reduction. When a condensation method is applied, molecules (or ions) are deposited on nuclei, which may be of the same chemical species as the colloid (homogeneous nucleation) or different (heterogeneous nucleation).

1.5 Shape of colloidal particles

It is general observation that the colloidal particles acquire spherical shape. This is explained by the excess free surface energy. It is known that among the bodies of different geometrical shapes, a sphere has the smallest surface energy, and the process of sphere formation occurs spontaneously in accordance with the second law of thermodynamics. In a spherical drop all the surface molecules are indistinguishable from one another and also differ from the bulk ones in their orientation. The excess free energy makes the colloidal solutions thermodynamically unstable. The process of lowering the excess free energy and reducing the dispersity are the fundamental characteristics of all colloidal solutions. If a colloidal solution remains unchanged in its chemical composition, but changes its free energy characteristics, then this will result in a change in colloidal properties.

Table 1.2 common colloid types

Colloid type	Substance Dispersed	Dispersing Medium	Examples
Aerosol	Solid	Gas	Smoke
Aerosol	Liquid	Gas	Fog
Solid foam	Gas	Solid	Marshmallow
Foam	Gas	Liquid	Whipped cream
Emulsion	Liquid	Liuid	Milk, mayonnaise
Solid emulsion	Liquid	Solid	Cheese, butter
sol	solid	liquid	Paint, gelatin

1.6 **Emulsifying agent**

Emulsifying agent or surfactant may be defined as" a compound that lowers the surface tension and forms a film at the interface of two immiscible liquids making them miscible". Some commonly used emulsifying agents are shown in Table 1.3 The efficiency of an emulsifying agent is related to its chemical structure, solubility, pH and physical properties. There are two types of emulsifying agents on the basis of their effect;

1.6.1 Primary agents (true emulsifying agents) can form and stabilize emulsions by themselves.

1.6.2. Auxiliary agents (stabilizers) alone do not form fine emulsions but assist the primary emulsifying agents(6). Classification of emulsifying agents on the basis of charged groups is as shown in Table 1.4.

Table 1.3 Some commonly used emulsifying agents,

their HLB values, characteristics and functions.

Chemical name	HLB	Miscible with Water	function
Oleic acid	1.6	immiscible	antifoam
Sorbitan tristrarate	2.1	immiscible	antifoam
Ethyleneglycol monostearate	2.9	immiscible	antifoam
Glyceryl monostearate	3.8	Disperses with difficulty	W/O emulsifier
Sorbitan monostearate	4.7	Disperses with difficulty	W/O emulsifier
Sorbitan monopalmitate	6.7	Foam milky dispersion	W/O emulsifier
PEG-4 dilaurate	6	Foam milky dispersion	W/O emulsifier
Sucrose dipalmitate	7.4	Foam milky dispersion	W/O emulsifier
PEG-4 monooleate	8	Foam milky dispersion	W/O emulsifier
PEG-4 monolaurate	9.8	Foam milky stable dispersion	W/O emulsifier
Polysorbate85	11	Foam clear dispersion	W/O emulsifier
PEG-8 monooleate	11.4	Foam clear dispersion	W/O emulsifier

Table 1.4 . **Classification of emulsifying agents on the basis of presence of formally charged groups in their heads**

S/N	Surfactant class	Surface charge	Example
01	Anionic((based on sulfate, sulfonate or carboxylate anions)	The charge is negative	Perfluorooctanoate (PFOA or PFO) Perfluorooctanesulfonate (PFOS) Sodium dodecyl sulfate (SDS), ammonium lauryl sulfate, and other alkyl sulfate salts Sodium laureth sulfate, also known as sodium lauryl ether sulfate (SLES) Alkyl benzene sulfonate Soaps, or fatty acid salts
02	Cationic (based on quaternary ammonium cations)	The charge is positive	Cetyl trimethylammonium bromide (CTAB) a.k.a. hexadecyl trimethyl ammonium bromide, and other alkyltrimethylammonium salts Cetylpyridinium chloride (CPC) Polyethoxylated tallow amine (POEA) Benzalkonium chloride (BAC) Benzethonium chloride (BZT)
03	Zwitterionic (amphoteric)	Two oppositely charged groups	Dodecyl betaine Cocamidopropyl betaine Coco ampho glycinate
04	Nonionic	No charge groups	Alkyl poly(ethylene oxide) Alkylphenol poly(ethylene oxide) Copolymers of poly(ethylene oxide) and poly(propylene oxide) (commercially called Poloxamers or Poloxamines) Alkyl polyglucosides, including: octyl glucoside and decyl maltoside Fatty alcohols, including: cetyl alcohol and oleyl alcohol Cocamide MEA Polysorbates, including: Tween 20 and Tween 80

1.7 Characteristic Feature of Surfactants

Surface-active agents are organic molecules that, when dissolved in a solvent at low concentration, have the ability to adsorb (or locate) at interfaces, thereby altering significantly the physical properties of those interfaces. The term "interface" is commonly

employed here to describe the boundary in liquid/liquid, solid/liquid and gas/liquid systems, although in the latter case the term "surface" can also be used. This adsorption behaviour can be attributed to the solvent nature and to a chemical structure for surfactants that combine both a polar and a non-polar (amphiphilic) group into a single molecule. To accommodate for their dual nature, amphiphiles therefore "sit" at interfaces so that their lyophobic moiety keeps away from strong solvent interactions while the lyophilic part remains in solution. Since water is the most common solvent, and is the liquid of most academic and industrial interest, amphiphiles will be described with regard to their "hydrophilic" and "hydrophobic" moieties, or "head" and "tail" respectively.

Adsorption is associated with significant energetic changes since the free energy of a surfactant molecule located at the interface is lower than that of a molecule solublised in either bulk phase. Accumulation of amphiphiles at the interface (liquid/liquid or gas/liquid) is therefore a spontaneous process and results in a decrease of the interfacial (surface) tension. However, such a definition applies to many substances: medium- or long-chain alcohols are surface active (e.g., n-hexanol, dodecanol) but these are not considered as surfactants. True surfactants are distinguished by an ability to form oriented monolayers at the interface (here air/water or oil/water) and, most importantly, self-assembly structures (micelles, vesicles) in bulk phases. They also stand out from the more general class of surface-active agents owing to emulsification, dispersion, wetting, foaming or detergency properties.

Both adsorption and aggregation phenomena result from the hydrophobic effect (7); i.e., the expulsion of surfactant tails from water. Basically this originates from water−water intermolecular interactions being stronger than those between water−tail. Finally another characteristic of surfactants, when their aqueous concentration exceeds approximately 40%, is an ability to form liquid crystalline phases (or lyotropic mesophases). These systems consist of extended aggregation of surfactant molecules into large organized structures. Owing to such a versatile phase behaviour and diversity in colloidal structures, surfactants find application in many industrial processes, essentially where high surface areas, modification of the interfacial activity or stability of colloidal systems are required. The variety of surfactants and the synergism offered by mixed-surfactant systems [8] also explains the ever-growing interest in fundamental studies and practical applications. Listing the various physical properties and associated uses of surfactants is beyond the scope of this chapter. However, a few relevant examples are presented in the following section, giving an idea of their widespread industrial use.

1.8 Classification and Applications of Surfactants

1.8.1 Types of surfactants

Numerous variations are possible within the structure of both the head and tail group of surfactants. The head group can be charged or neutral, small and compact in size, or a polymeric chain. The tail group is usually a single or double, straight or branched hydrocarbon chain, but may also be a fluorocarbon, or a siloxane, or contain aromatic group(s). Commonly encountered hydrophilic and hydrophobic groups are listed in Tables 1.5and 1.6 respectively.

Since the hydrophilic part normally achieves its solubility either by ionic interactions or by hydrogen bonding, the simplest classification is based on surfactant head group type, with further subgroups according to the nature of the lyophobic moiety. Four basic classes therefore emerge as:
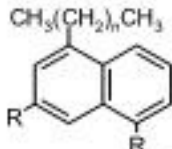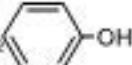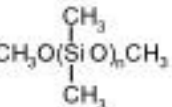
• the anionics and cationics, which dissociate in water into two oppositely charged species (the surfactant ion and its counterion).

• the non-ionics, which include a highly polar (non charged) moiety, such as polyoxyethylene ($-OCH_2CH_2O-$) or polyol groups.

• the zwitterionics (or amphoterics), which combine both a positive and a negative group.

With the continuous search for improving surfactant properties, new structures have recently emerged that exhibit interesting synergistic interactions or enhanced surface and aggregation properties. These novel surfactants have attracted much interest, and include the catanionics, bolaforms, gemini (or dimeric) surfactants, polymeric and polymerisable surfactants [9, 10]. Characteristics and typical examples are shown in Table 1.5. Another important driving force for this research is the need for enhanced surfactant biodegradability. In particular for personal care products and household detergents, regulations [11] require high biodegradability and non-toxicity of each component present in the formulation.

Table 1.5 hydrophilic groups found in commercially available surfactantS

Class	General structure
Sulfonate	$R\text{--}SO_3^- \ M^+$
Sulfate	$R\text{--}OSO_3^- \ M^+$
Carboxylate	$R\text{--}COO^- \ M^+$
Phosphate	$R\text{--}OPO_3^- \ M^+$
Ammonium	$R_xH_yN^+X^-$ (x = 1-3, y = 4-x)
Quaternary ammonium	$R_4N^+X^-$
Betaines	$RN^+(CH_3)_2CH_2COO^-$
Sulfobetaines	$RN^+(CH_3)_2CH_2CH_2SO_3^-$
Polyoxyethylene (POE)	$R\text{--}OCH_2CH_2(OCH_2CH_2)_nOH$
Polyols	Sucrose, sorbitan, glycerol, ethylene glycol, etc
Polypeptide	$R\text{--}NH\text{--}CHR\text{--}CO\text{--}NH\text{--}CHR'\text{--}CO\text{--}...\text{--}CO_2H$
Polyglycidyl	$R\text{--}(OCH_2CH[CH_2OH]CH_2)_n\text{--}...\text{--}OCH_2CH[CH_2OH]CH_2OH$

Table 1.6 Common hydrophobic groups used in commercially available surfactants

Group	General structure	
Natural fatty acids	$CH_3(CH_2)_n$	n = 12-18
Olefins	$CH_3(CH_2)_nCH = CH_2$	n = 7-17
Alkylbenzenes	$CH_3(CH_2)_nCH_2$⟨benzene ring⟩	n = 6-10, linear or branched
Alkylaromatics	$CH_3(CH_2)_nCH_3$, R-substituted naphthalene (R, R)	n = 1-2 for water soluble, n = 8 or 9 for oil soluble surfactants
Alkylphenols	$CH_3(CH_2)_nCH_2$⟨phenol⟩—OH	n = 6-10, linear or branched
Polyoxypropylene	$CH_3CHCH_2O(CHCH_2)_n$ with X and CH_3	n = degree of oligomerisation, X = oligomerisation initiator
Fluorocarbons	$CF_3(CF_2)_nCOOH$	n = 4-8, linear or branched, or H-terminated
Silicones	$CH_3O(SiO)_nCH_3$ with CH_3 groups	

A typical example of a double-chain surfactant is sodium bis(2-ethylhexyl)sulfosuccinate, often referred to by its American Cyanamid trade name Aerosol-OT, or AOT. Its chemical structure is illustrated in Figure 1.2, along with other typical double-chain compounds within the four basic surfactant classes.
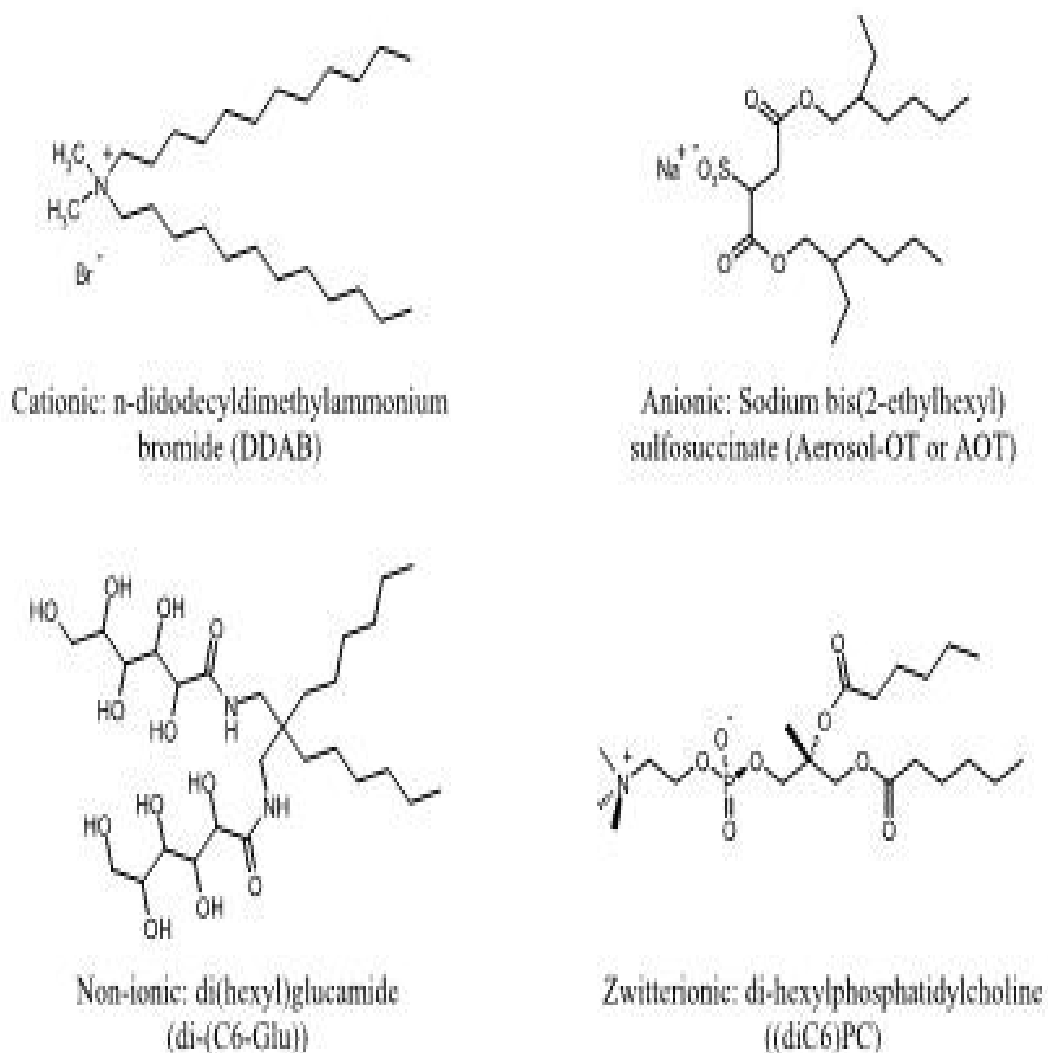

Cationic: n-didodecyldimethylammonium bromide (DDAB)

Anionic: Sodium bis(2-ethylhexyl) sulfosuccinate (Aerosol-OT or AOT)

Non-ionic: di(hexyl)glucamide (di-(C6-Glu))

Zwitterionic: di-hexylphosphatidylcholine ((diC6)PC)

Figure 1.2 Chemical structure of typical double-chain surfactants.

Surfactants may be from natural or synthetic sources. The first category includes naturally occurring amphiphiles such as the lipids, which are surfactants based on glycerol and are vital components of the cell membrane. Also in this group are the so-called "soaps", the first recognized surfactants [12]. These can be traced back to Egyptian times; by combining animal and vegetable oils with alkaline salts a soap-like material was formed, and this was used for treating skin diseases, as well as for washing. Soaps remained the only source of natural detergents from the seventh century till the early twentieth century, with gradually more varieties becoming available for shaving and shampooing, as well as bathing and laundering. In 1916, in response to a World War I-related shortage of fats for making soap, the first synthetic detergent was developed in Germany. Known today simply as detergents, synthetic detergents are washing and cleaning products obtained from a variety of raw materials. Nowadays, synthetic surfactants are essential components in many industrial processes and formulations [9-11]. Depending on the precise chemical nature of the product, the properties of, for example emulsification, detergency and foaming may be exhibited in varying degree. The number and arrangement of the hydrocarbon groups together with the nature and position of the hydrophilic groups combine to determine the surface-active properties of the molecule. For example C12 to C20 is generally regarded as the range covering optimum detergency, whilst wetting and foaming are best achieved with shorter chain lengths. Structure-performance relationships and chemical compatibility are therefore key elements in surfactant-based formulations, so that much research is devoted to this area.

Amongst the different classes of surfactants, anionics are often used in applications, mainly because of the ease and low cost of manufacture. They contain negatively charged head group, e.g., carboxylates, used in soaps, sulfate, and sulfonates groups. Their main applications are in detergency, personal care products, emulsifiers and soaps.

Cationics have positively charged head groups – e.g., trimethylammonium ion and are mainly involved in applications related to their absorption at surfaces. These are generally negatively charged (e.g., metal, plastics, minerals, fibres, hairs and cell membranes) so that they can be modified upon treatment with cationic surfactants. They are therefore used as anticorrosion and antistatic agents, flotation collectors, fabric softeners, hair conditioners and bactericides.

Non-ionics contain groups with a strong affinity for water due to strong dipole-dipole interactions arising from hydrogen bonding, e.g., ethoxylates (). One advantage over ionics is

that the length of both the hydrophilic and hydrophobic groups can be varied to obtain maximum efficiency in use. They find applications in low temperature detergents and emulsifiers.

Zwitterionics constitute the smallest surfactant class due to their high cost of manufacture. They are characterized by excellent dermatological properties and skin compatibility. Because of their low eye and skin irritation, common uses are in shampoos and cosmetics.

1.9 Poly ethylene glycol (PEG) Ester surfactants

PEG Ester surfactants are manufactured by reacting a polyethylene glycol with a fatty acid. The polyethylene glycol comprises the hydrophilic part of the surfactant and the fatty acid the lipophilic part. By varying the molecular weight of the PEG and the fatty acid, surfactants covering a wide range of HLB values can be produced. Typically, those with an HLB below 13 are oil soluble and water dispersible while those above are water soluble

The traditional application areas for PEG ester surfactants have mainly utilised their excellent water/oil emulsifying properties, e.g. as: Lubricants in textile processing Cutting oils and metalworking fluids Solvent cleaners and emulsifiable degreasers Emulsifiers for self-emulsifying herbicides, insecticides and fungicides Emulsifiers for cosmetic creams and toiletry emulsions Emulsifiers for polymer latex production.

Table 1.7 PEG Monoleate Surfactants Corresponding nonylphenol ethoxylates

Name	Type	HLB No.	
EE 354	200 MO(PEG4 Mono oleate)	8.0	NP3, NP4
EE 344	300 MO	10.5	NP5, NP6
EE 364	400 MO	11.4	NP7
EE 374	600 MO	13.5	NP10
EE 404	800 MO	14.5	NP13, NP14
EE 414	1000 MO	15.4	NP18
EE 424	1500 MO	17.0	NP30

Other applications have utilised their wetting/dispersing properties, e.g. as: Pigment dispersants for both organic and inorganic pigments in aqueous and non-aqueous systems. Plasticizers/viscosity modifiers in mastics, adhesives, emulsion paints and PVC plastisols because : PEG esters, particularly PEG oleates and stearates, are excellent emulsifiers, better than alcohol ethoxylates or nonyl phenol ethoxylates, Low foaming tendency, Good wetting/dispersing properties, Readily biodegradable, No hazard labelling required for transport or use.but Hydrolysed under hot alkaline conditions.

The environmental effects associated with NPE's are now well documented and their replacement by alternatives is being strongly encouraged. It is considered that PEG oleate surfactants are a closer match to NPE's with respect to solubility and emulsifying characteristics than are alcohol ethoxylate surfactants.

The attached table lists a series of PEG Oleates and their corresponding NPE's based on HLB No. Tables are also included comparing PEG cocoate and stearate surfactants with their corresponding alcohol ethoxylates(16).

1.10 Emulsion

An emulsion may be defined as a biphasic system consisting of two immiscible liquids, one of which (the dispersed phase) is finely and uniformly dispersed as globules throughout the second phase (the continuous phase). Since emulsions are thermodynamically unstable system, a third agent, the emulsifier is added to stabilize the system (17). Emulsifier stabilizes the system by forming a thin film around the globules of dispersed phase Either the dispersed phase or the continuous phase may vary in consistency from that of a mobile liquid to semisolid Thus, pharmaceutical emulsions range from lotions (low viscosity) to creams (high viscosity). The particle size of the dispersed phase commonly ranges from 0.1 to 100 μm (17-18).

1.11 Types of Emulsion
1.11.1 Oil in water emulsion

Pharmaceutical emulsions usually consist of mixtures of aqueous phase with various oils and waxes. If the oil droplets are dispersed throughout the aqueous phase, the emulsion is termed oil-in-water (O/W) as shown in Figure 1.3 Fats or oils for oral administration, either as medicaments in their own right, or as vehicles for oil soluble drugs, are always formulated as oil in water (O/W) emulsions (19). They are non greasy and are easily removable from the skin surface and they are used externally to provide cooling effect and internally to also mask the bitter taste of oil. Water soluble drugs are more quickly released from O/W emulsion. O/W emulsion give a positive conductivity test as water, the external phase is a good conductor of electricity (9).
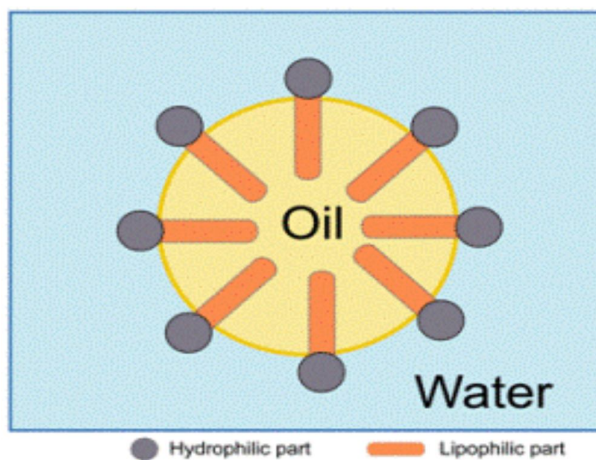
Figure 1.3 . O/W emulsion.

1.11.2 Water in Oil Emulsion

A system in which the water is dispersed as globules in the oil continuous phase is termed water-in-oil emulsion (W/O) as shown in Figure 1.4 Water-in-oil emulsions will have an occlusive effect by stratum corneum inhibiting vaporation   hydrating the and have an occlusive effect by of eccrine secretions drugs from W/O emulsions. It has an effect on the absorption of W/O emulsion is also useful for the skin of oil soluble dirt although its greasy texture is no   alys cosmetically acceptable (19)They are greasy and not water   washable and are used externally to prevent evaporation of the moisture from the surface of skin e.g. cold cream. Oil soluble drugs are more quickly released from W/O emulsion. They are preferred for formulation meant for external use like cream W/O emulsion is not given a positive conductivity tests, because oil is the external phase which is a poor conductor of electricity[20]
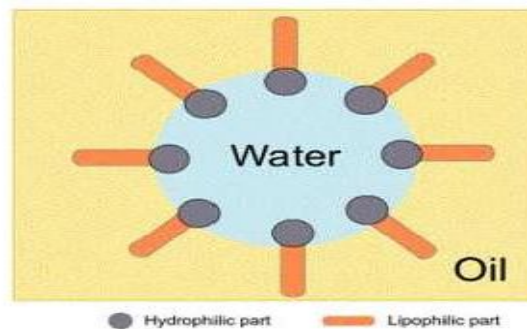
.

Figure 1.4 O/W emulsion

1.11.3 Multiple emulsions

Multiple emulsions are complex systems. They can be considered as emulsions of emulsions, and have been shown to be secured in cosmetic pharmaceutical and separation sciences (21). It is a complex type of emulsion system in which the oil-in-water or water-in-oil emulsions are dispersed in another liquid medium. In this way an oil-in-water-in-oil (O/W/O) emulsion consists of very small droplets of oil dispersed in the water globules of a water-in-oil emulsion and a water-in-oil-in-water (W/O/W) emulsion consists of droplets of water dispersed in the oil phase of an oil-in water emulsion (1). Their pharmaceutical applications include taste masking, adjuvant vaccines, an immobilization of enzymes and sorbent reservoir of overdose treatments, and sometimes for the augmentation of external skin or dermal absorption. Multiple emulsions have been formulated as cosmetics, such as skin moisturizer. Prolonged release can also be obtained by means of multiple emulsions. These systems have some advantages, such as the protection of the ensnared substances and the possibilities of incorporating several actives ingredient in the different compartments. Regardless of their importance, multiple emulsions have limitations because of thermodynamic instability and their complex structure (5).

1.12 Pharmaceutical applications of emulsion

Both macroemulsions and microemulsions are generally well documented as carriers for hydrophilic and lipophilic drugs. Recently, attention has been made on controlling the size distribution and understanding the stabilization phenomenon, which creates novel horizons; this had resulted in great attention for these liquid dispersion systems. The main advantage of such systems is that they increase the solubility and bioavailability of therapeutic drugs as well as the ability to favour the topical transport of hydrophilic drugs. Multiple emulsions, especially W/O/W emulsions are admirable candidate for controlled and sustained release of drugs. Multiple emulsions are used as an alternate to liposomes as delivery system. Microemulsions are isotropic mixture of oil, water and surfactant often with cosurfactant. It has been shown that microemulsions can be formed spontaneously and are thermodynamically stable; on one hand, they improve drug solublization and bioavailability, and on the other hand, they act as potential drug delivery systems by integrating a wide range of drug molecules. O/W and W/O/W emulsions are generally employed for intravenous route. Lipid emulsions are used for parenteral nutrition, intravenous drug administration and as oxygen carriers. Emulsions have been used for many centuries for treating local skin

diseases. Oil-in-water emulsions are used for lamentation of skin lacerations. The main advantage of using the topical emulsions is to avoid gastrointestinal environment and first pass metabolic effect. Emulsions are also available for oral route. They are mainly used for enteric nutrition or laxative preparations (22).

In addition to the aforementioned applications, emulsions may also be used, to stabilize hydrolytically susceptible drugs for sustained release, reduction of irritation or toxicity, possible targeted delivery of drugs to various organs and possible enhanced pharmacological effect (23).

1.13 the hydrophylic-lipophylic balance (HLB)seyetem for emulsion formation

Griffin (1954) introduced a very useful system for the classification of surfactants on the basis of their solubility in water. The numerical values in this system are called hydrophylic-lipophylic balance (HLB) that denotes the relative affinity of the surfactant for oil and water. Emulsifying agents with HLB values of 3 to 6 are used for w/o emulsions. Whereas emulsifying agents with HLB values of 7 to 20 are used for o/w emulsions (24). According to Alfred the type of emulsion is a function of the relative solubility of the surfactants, thus the phase in which the surfactant is more soluble gives rise to the continuous phase This phenomenon is sometimes referred to as "The Rule of Bancroft" (25).

1.14 Emulsification process

Milk is a natural emulsion, which consists of fatty globules surrounded by a layer of casein, suspended in water. The theory of emulsification is based on the study of milk. When a pharmaceutical emulsion is to be prepared the principal consideration is the same as that of milk(26).

1.14.1 General method

Generally, an O/W emulsion is prepared by dividing the oily phase completely into minute globules surrounding each globule with an envelope of emulsifying agent and finally suspends the globules in the aqueous phase. Conversely, the W/O emulsion is prepared by dividing aqueous phase completely into minute globules surrounding each globule with an envelope of emulsifying agent and finally suspending the globules in the oily phase (26).

1.14.2 Phase inversion method

In this method, the aqueous phase is first added to the oil phase so as to form a W/O emulsion. At the inversion point, the addition of more water results in the inversion of emulsion which gives rise to an O/W emulsion (27)

1.14.3 Continental and dry gum method

Extemporaneously emulsions are usually made by continental or dry gum method. In this method, the emulsion is prepared by mixing the emulsifying agent (usually acacia) with the oil which is then mixed with the aqueous phase. Continental and dry gum methods differ in the proportion of constituents (26).

1.14.4 Wet gum method

In this method, the proportion of the constituents is same as those used in the dry gum method; the only difference is the method of preparation. Here, the mucilage of the emulsifying agent (usually acacia) is formed. The oil is then added to the mucilage drop by drop with continuous trituration (26).

1.14.5 Membrane emulsification method

It is a method, which is based on a novel concept of generating droplets "drop by drop" to produce emulsion. Here, a pressure is applied direct to the dispersed phase which seeps through a porous membrane into the continuous phase and in this way the droplets formed are then detached from the membrane surface due to the relative shear motion between the continuous phase and membrane surface (28).

1.15 Stability

Although emulsion stability is not a concept with a well agreed upon definition, it is always linked either to the persistence or to the decay of the dispersed system under certain circumstances. As a matter of fact it is a fundamental emulsion property and a lot of attention has been dedicated to its study (29-30) 1. Involved Phenomena The first question to answer is stability against what? In fact, an emulsion can remain unchanged under certain circumstances while it will break readily under others. Of particular importance are the eventual changes in temperature that have a formulation effect as seen in the previous chapter. Other emulsion breaking processes could include physical effects like artificial gravity, Brownian motion or stirring. However, the most common case however is when an emulsion is kept in a container to rest at constant temperature under normal gravity conditions. This is the one to be dealt with here and later to be considered as a reference based on which other cases could be discussed. This breaking process comprises several steps:

(a) long-distance approach between drops or between drop and flat interface,

(b) interdrop film drainage; and, finally

 (c) coalescence (30-31).

Since the continuous and dispersed phase have generally different densities, there is a neat Archimedes pull on the dispersed phase drops that drives a separation process called *settling*. This separation tends to gather the drops in a region that becomes a high internal phase ratio emulsion, sometimes referred to as a *cream.*

The settling process is essentially similar in nature to Stokes falling sphere sedimentation problem, eventually modified according to Hadamard's work (32) to account for the fluid motion inside the drop. The Stokes calculation of limiting falling velocity is solved by equating the gravity force to the friction force, which is taken as proportional to velocity (creeping flow) and proportional to the radius of the sphere R Thus the limiting velocity turns out to be:

$$v = \frac{\alpha\,R^3\,D_r}{\dot{\eta}\,R} = \frac{\alpha\,R^2\,D_r}{\dot{\eta}}$$

where α is a constant ($2\prod/9$ in the case of Stokes' law), D_r is the density difference, and $\dot{\eta}$ the continuous phase viscosity Since Stokes problem addresses the case of a single rigid sphere sedimentation in an infinite medium, the actual problem with plenty of falling spheres (with different diameters, thus different velocities) could be depicted only qualitatively by such a law. For instance, the simultaneous falling of many drops results in a countercurrent in the external phase that would reduce the actual falling velocity. The interaction of falling drops with one another is also a factor that would reduce the falling velocity. Even more serious objections rise from the possible retardation effect produced by tension gradients along the drop surface (24).

This means that the value of the constant is of course to be determined experimentally in each case, and that Stokes' law is only indicative, and may turn out to be wrong when the internal phase proportion is high. In any case Stokes' law indicates that the approach of the drops would be facilitated and accelerated whenever the drop size or density difference increases, while it would be slowed down by an increase in external phase viscosity. In the macroemulsion range (1-100 μm) the settling may be rather quick unless the external phase is viscous or the density difference is very small. In the miniemulsion range (100-500 Å) the settling is generally very slow because of the importance of the squared radius factor. Thus, it may be said that an extremely small drop size would slow down the first step of the breaking process, and as such would slow down the whole process. This statement is true in the event that the second step (drainage) is rather quick, i. e., when the surfactant does not provide the

appropriate stabilization conditions, so that the first step controls the decay. The maximum internal phase ratio that can be attained without deforming the drop spherical shape depends upon the drop size distribution. For mono dispersed rigid spheres, the most dense tessellation is the hexagonal packing at about 74 % of internal phase. As an example, for randomly settled mono dispersed spheres it could be 65 %. For very polydispersed emulsions it might be higher than 90 % (34).

The final arrangement of the drops in the cream depends upon the segregation process between drops. In effect, if the density difference is large, the R^2 factor results in a considerably increased force on the large drops that would settle more quickly and end up accumulating at the far end of the cream. The shape of the settling vessel is also important in the segregation process because the segregation could be large if the settling path is long and vice versa. Of course, if the emulsion contains more than 60-70% of internal phase, particularly with small drops, the settling would not take place significantly. In any case the Brownian motion or other unusual effects may provide some driving force for the drop-drop interaction to be dealt within the next paragraph (32,-35).

When the drops are close together, whatever the driving force that makes them approach, the film that is located in between neighboring drops exhibits a complex drainage process that involves several different mechanisms, and this controls the second step of the emulsion decay. Some of them depend upon the drop volume like the Van der Waals attractive forces, or the Archimedes pull, while others depend on the interdrop film physical properties such as viscosity, or on the interfacial phenomena that occur whenever two interfaces approach at sub micrometer range. The first class of interfacial phenomena deals with static attractive or repulsive forces, like electrical, steric or entropic repulsions, while the second one has to do with dynamic processes like the steaming potential and interfacial viscosity effects, as well as the more classical hydrodynamic considerations (36,37).

In some cases the interdrop film becomes very thin, only a few micellar or molecular sizes across. It decreases not continuously but stepwise, layer by layer, and could end up in a surfactant bilayer with no solvent content (sometimes referred to as black film because of its color). Such extremely thin films could exhibit a high resistance to rupture as it occurs in so-called foam emulsions (38,39).

In most cases, there exists an electrical double layer near the interface, even in absence of charged surfactant, in which case the differential adsorption of OH- and H_3O+ ions results in a net charge per unit area. As a matter of fact nonionic surfactants often produce a negatively charged interface at neutral pH because the smaller OH- is more abundant in the vicinity of

interface than the hydrated proton. In any case it can be considered that the double layer is a very general feature at liquid interfaces. Of course the charge separation occurs in a very thin region near the interface, whereas the whole electrical balance per unit area is neutral. Today it contributes as a model for emulsion stability on a qualitative basis, since the drop size is much bigger than a colloidal particle, so that DLVO interaction calculations do not apply straighforwardly. Moreover it is now recognized that the repulsion between approaching drops may come from other (non-DLVO) interactions such as the steric repulsion between adsorbed molecules, which is the most common case with nonionic surfactant and polymer emulsifiers both in water and in oil (40,41). There is first an enthalpic contribution that has been referred to as osmotic repulsion as well, because it has to do with the departure of the chemical potential of the in the region where adsorbed surfactant layers overlap (42). On the other hand, there exits another repulsion mechanism, often called entropic, that is related to the molecular organization or degree of freedom with respect to interactions of surfactant or polymer molecules with the solvent that change as the two interfaces get closer (43). Figure 1-5 illustrates the different cases of repulsion: electrical repulsion in presence of ionic surfactants and steric repulsions with nonioic surfactants, such as the polyethoxylated ones. The third type, i. e., entropic repulsion, for instance occurs when polymeric amphiphilic molecules are forced to rearrange and sometimes to loose solvatation as they are compressed. As in DLVO theory, the overall balance of repulsive and attractive forces may result in different cases, since their variations are not necessarily at the same scale nor manner. For instance molecular attractive forces act at short range while electrical ones are rather long range forces.
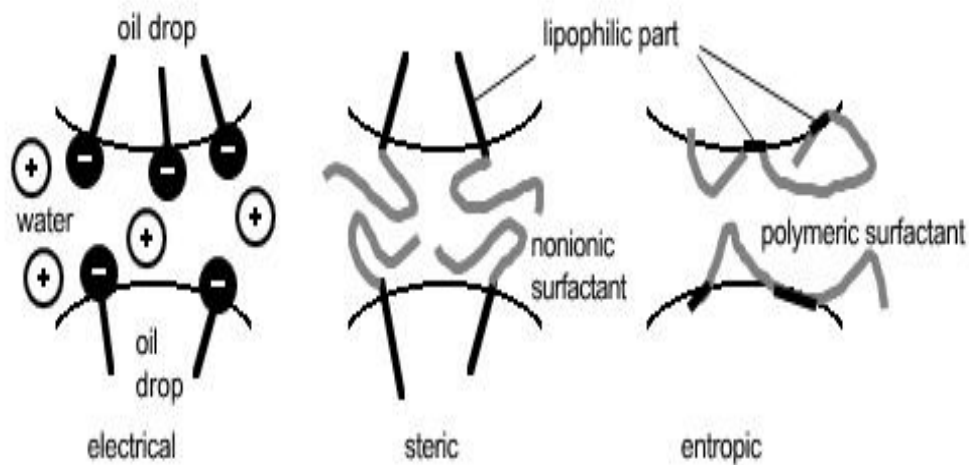
Figure 1-5: Three cases of interdrop repulsion

Steric and entropic forces do not produce any effect until some kind of contact takes place between adsorbed antagonist layers, at which point they can increase slowly or rapidly depending upon the compressibility or elasticity of the adsorbed layer. In many cases several effects can contribute. There are essentially three cases as in DLVO theory, that are characterized by the shape of the repulsive-attractive potential vs. distance (see Figure 1-6). In the first case (left) the attractive forces dominate at all distance and thus the two approaching interfaces will get into contact sooner or later depending upon kinetic phenomena, as seen later on. The minimum of the curve (maximum attractive potential) corresponds to the notion of contact and occurs at an essentially zero distance (exaggerated in the figure). A further reduction in distance would be opposed by the compressibility of matter, and would result in a strong repulsion.
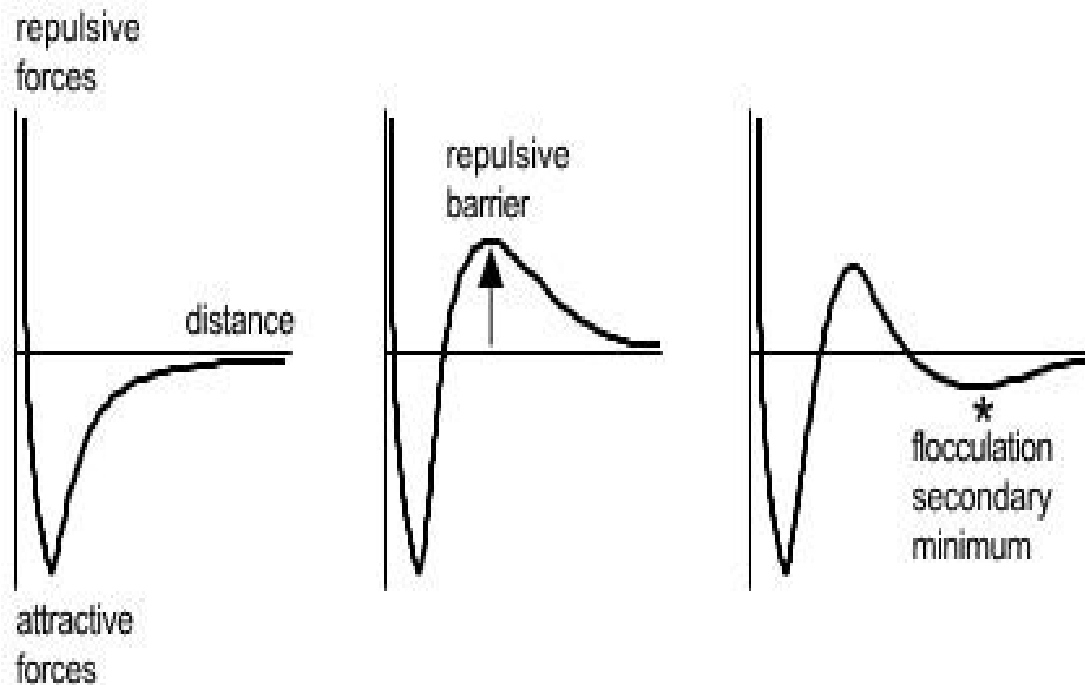
Figure 1-6: Three cases of variation of the interdrop forces versus intedrop distance according to the extension of the DLVO theory

A very important parameter for emulsion products is their stability; however, the evaluation of emulsion stability is not easy (44). Pharmaceutical emulsion stability is characterized by the absence of coalescence of dispersed phase, absence of creaming and retaining its physical characters like elegance, odor, color and appearance. The instability of emulsion may be classified into four phenomenons: Flocculation, creaming, coalescence and breaking as shown in Figure 1-7.
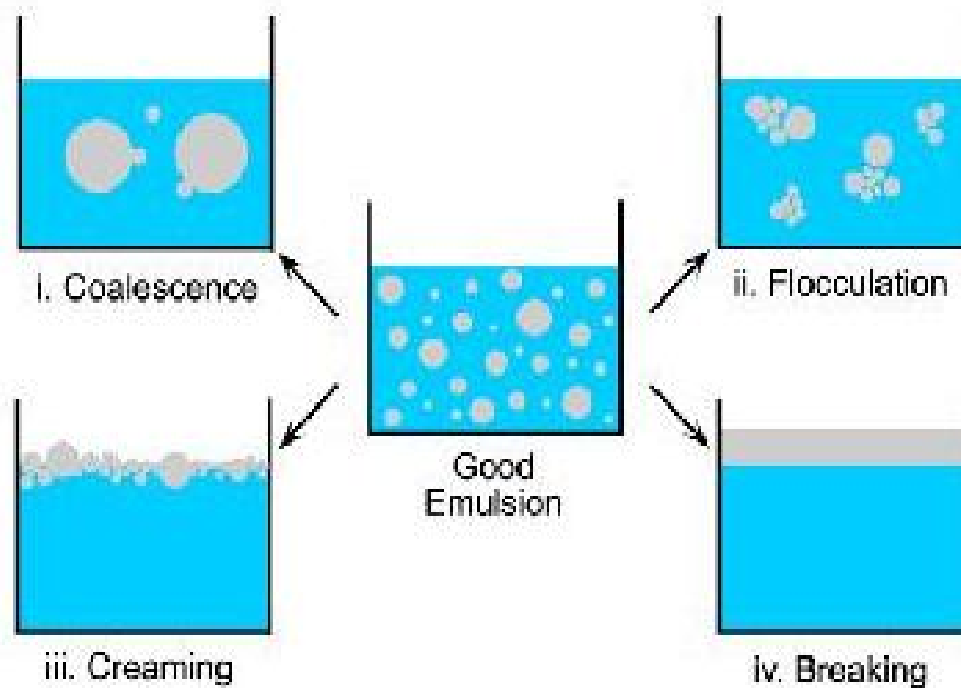
Figure 1.7 Instability types of emulsion.

1.15.1 Flocculation

It is the association of small emulsion particles to form large aggregate which is redispersable upon shaking. It is a reversible process in which the droplets remain intact. Flocculation is considered as the precursor of coalescence (45). This is because the presence of excess surfactant in the continuous phase of an emulsion can lead to flocculation of emulsion droplets. The flocculation of emulsion droplets by excess surfactant occurs because of the so-called "depletion effect". The depletion mechanism can be explained as, a system containing excess surfactant in the form of micelles, when the dispersed emulsion droplets approach each other to distances closer than the diameter of the surfactant micelles, segregation of micelles from the interparticle space that occurs because of the loss in configurational entropy of the micelles. This phenomenon results in an attractive force between the droplets due to the lowering of osmotic pressure in the region between the droplets, and accordingly, flocculation of

droplets occurs .

1.15.2 Creaming

Creaming is the phenomenon in which the dispersed phase separates out, forming a layer on the top of the continuous phase. It is notable that in creaming, the dispersed phase remains in globules state so that it can be redispersed on shaking. Creaming can be minimized if the viscosity of the continuous phase is increased (26). The rate of creaming is determined by Stoke's law as follows:

$$V = \frac{D^2 \, (\rho s - \rho o) \, g}{18 \eta}$$

where V is the velocity in cm/s, D is the diameter of particles of dispersed phase in cm, ρs is the dispersed phase density, ρo is the continuous phase density, η is the continuous phase viscosity and g is the gravitational acceleration. O/W emulsions generally face upward creaming when the globules of the dispersed phase are less dense thanthe continuous phase. In contrast, W/O emulsions face downward creaming when the globules of the dispersed phase are denser than the continuous phase (46).

1.15.3 Coalescence (synonyms: breaking or cracking)

A more subtle type of emulsion instability, coalescence occurs when the mechanical or electrical barrier is insufficient to prevent the formation of progressively larger droplets (46). Stabilization against coalescence may be achieved by the addition of high boiling point or high molecular weight components to the continuous phase (47) Newman (1914) and Schulman and Cockbain (1940) experimentally concluded that W/O emulsions are formed only when the film of emulsifying agent in the interface is uncharged and rigid as a result of complex formation. They were of the view that a W/O emulsion cannot be stabilized against flocculation by charge on the dispersed phase of water droplets, because an electric diffuse layer cannot be built up as oil being a nonionizing medium. A surface potential considerably higher than 25 mv is not sufficient to stabilize the droplets of dispersed phase with a radius ≥ 1 μ against flocculation. This is because of the high sedimentation velocities(48).

1.15.4 Stability of W/O emulsions against coalescence

According to Newman (1914) and Schulman and Cockbain (1940) a charged film is not able to prevent coalescence, because due to the repulsion between emulsifying molecules in the interface, no interlinked solid thick film can be formed (39). thick film can be formed.

1.16 The Effects of Different Process Variable on Emulsion Stability

The preparation of stable W/O emulsion is critical for the efficient production of final dosage form. The important parameter that can affect emulsion stability is the stirring intensity. It has been concluded that the interfacial area increases with the increase of rotational speed and diameter of the stirrer keeping the diameter of container tank low. Temperature indirectly affects the emulsification as a result of changing the interfacial tension, adsorption of emulsifying agent and viscosity. Higher temperature is favorable for emulsification as both viscosity and interfacial tension decrease with increase in temperature. It has been evidenced that a minute decrease in temperature may cause coagulation of particles thereby result in worsening the emulsion (49).

1.16.1 Effect of emulsifier concentration

The amount of emulsifying agent is one of the most important factors having an influence on the emulsion stability. Emulsifier concentration has a great impact on emulsion stability. A concentration window existed, out of which the emulsion stability is quickly declined. At low emulsifier concentration, the emulsion is unstable because of agglomeration of the oil droplets. At high emulsifier concentration emulsion instability occurs because of rapid coalescence (49).

1.16.2 Effect of oil/water ratio

Ostwald concluded that a phase volume above 0.74 for the continuous phase may result either in phase inversion or breaking (49).

1.16.3 Effect of stirring intensity

Various types of procedures may be applied for emulsification. Emulsification is usually achieved by applying mechanical energy. In such a process, initially, the interface between the two phases is deformed to extents that large droplets are formed which are subsequently broken into small particles. Stirring is done to form a stable and homogeneous emulsion by converting large droplets into small ones. It is clearly indicating that a more stable emulsion can be prepared with a higher stirring speed but less than 2500 RPM as more than 2500 RPM will lead the emulsifier to break away from the oil-water interface (49).

1.16.4 Effect of mixing temperature

Emulsions prepared at low temperature are stable; however, more stable emulsions can be prepared at a temperature of 30°C. It is cleared that the surface tension of most liquids decreases with the increase of temperature. Due to this high kinetic energy, the surface molecules tend to overcome the attractive force of bulk liquid. Furthermore, at critical

temperature value, the cohesive forces between the liquid molecules become zero; therefore, the surface tension will fade off at critical temperature value (49).

1.16.5 Effect of mixing time

Mixing time is a key factor during emulsification. According to Gonglun and Daniel, (2005), the radii of the droplets of the dispersed phase decrease with the increase of stirring speed and mixing time. Long mixing time increase the effectiveness of emulsifying agents; however, too much long mixing time will cause a decrease in the effectiveness of emulsifying agents, because severe stirring will cause the emulsifying agents to drop out from liquids interface (49).   .

1.17 Emulsification equipments

Various types of equipments are available for emulsification both for laboratory scale and commercial scale. Usually equipment for emulsification is selected on the basis of resulting emulsion. Equipment for emulsification works on the mechanism to break up or distribute the dispersed phase into the continuous phase so that the size of the droplets of the dispersed phase is sufficiently small to avoid coalescence and instability(27)

1.17.1 Small scale processing

For the laboratory scale or prescription department emulsification of fixed/volatile oils, the most frequently used equipments are Wedgwood or porcelain mortars and pestles (50).

1.17.2 Shaker mixers/agitators

In shaker mixers for small scale production, the material in the container is agitated by oscillator, whereas for large scale production, the material in the container is agitated by rotary movement similar to that of ball mills (24).

1.17.3 Turbine mixers

Turbine mixers are used for mixing the high viscosity emulsions. They are rotated at a slow rate as compared to the propellant mixers. They are provided generally in a circular disc impeller attachment to short straight or curved blades (24).

1.17.4 Homogenizers

Modern emulsions can be prepared by a variety of various emulsification equipments, all are working nearly on similar mechanism that is agitated (51). Among all the equipments for emulsification, rotor/stator high pressure homogenizer is the most continuously operated device. High pressure homogenizers are provided with a high pressure pump and homogenizing nozzle. The high pressure pump raises the pressure up to 50 to 500 bar (52).

During emulsification, the dispersion of two liquids is carried out by forcing them through a small orifice at a high pressure(53). The rotor/stator assembly of the homogenizer consists of a rotor with blades and a stator with openings. As the rotor rotates, a vacuum is created drawing the liquid in and out of the assembly, resulting in liquid circulation. The size of the dispersed phase is reduced;

1. Due to the mechanical collision against the walls of homogenizer because of high liquid acceleration and

2. Due to the shear force occurring within the gap between rotor and stator (51).

1.17.5 Ultrasonifiers

Ultrasonifiers, the transduced piezoelectric instruments are used for laboratory scale emulsion production, however, they have limited output and are expensive. Their mechanism of work is that the dispersion is forced through an orifice at a medium pressure of 150 to 350 psi and is allowed to collide upon a blade(53). Ultrasonifiers provide an easy way of agitation for the laboratory scale preparation of constant and reproducible oil-in-water (o/w) emulsions (54).

1.17.6 Colloid mills

Colloid mills are suitable for the preparation of emulsions on a continuous basis. Due to intense shearing force, the emulsions produced by colloid mills are of very small globule size (Aulton, 1988). Colloid mills are mostly used for the milling of solids and for the dispersion of very poorly wetable suspensions; however, colloid mills are very useful for the preparation of relatively high viscous emulsions (53)

1.17.7. Whisks/churns

These are used for emulsion preparation involving the agitation of emulsion ingredients by blenders fitted in the container. Sometime, the containers may be fitted 1.17.8with a jacket if heating/cooling effects are required (55).

Silverson mixer consists of an emulsifying head with blades which are surrounded by stainless steel fine mesh sieves. The emulsifying head is adjustable for insertion into the containers to be used for emulsification. An electric motor is used for rotating the head. The liquid to be emulsified if sucked by the fine mesh sieve into the emulsifying head where they are subjected to intense mixing due to the rotation of blades of emulsifying head(24).

1.18 Foaming during agitation process

The foaming and emulsifying characteristics of emulsion are important characteristics during the production stage, storage, transport and consumer observation of quality and

appearance of emulsions. Foaming and emulsifying characteristics and the stability of the resulting dispersion depend on the properties of the emulsifying agent in the system .The reason for the formation of foam is that during emulsification, the emulsifying agent also reduces the surface tension at the air-water interface .To avoid foam formation, the emulsification must be carried out in closed system or under vacuum. In addition, continuous mechanical stirring during cooling stage of emulsion may also affect in preventing foam formation (53).

1.19 Emulsion Stability Assessment

Emulsion stability must be regarded in terms of physical stability of emulsion system examined and the physical and chemical stability of the emulsion components(8)

1.19.1 Macroscopic examination

The degree of creaming or coalescence occurring perunit period of time can give the assessment of emulsion physical satiability. This procedure is carried out by calculating the ratio of the volume of the creamed part (separated part) of the emulsion and the total volume of the product (3).

1.19.2 Determination of particle size

count/globule size analysis Determination of changes in the average particle size is one of the parameters used for assessing emulsion stability. Optical microscopy, Andreasen apparatus and Coulter counter apparatus are used for this purpose(4).

1.19.3 Determination of electrophoretic properties

Zeta potential is an important parameter used for assessing emulsion stability, since electric charges on the particles affect the rate of flocculation (4). Electrostatically emulsion stabilization is due to the mutual repulsion between electrical double layer of both phases. Such type of stability is very sensitive to the ionic strength of solution, as the concentration of electrolyte increases the electrical double layer compressed and the distance of electrostatic repulsion is reduced resulting in flocculation (Jayme et al., 1999).

1.20 Tests for Identifying Emulsion Type

Several tests are used for identifying the emulsion type. Although, such tests may be applied rapidly, the results must be interpreted with caution. It may be possible that such tests can not indicate whether a multiple emulsion has been produced? Such contro-versies may be resolved by microscopic examination (56).

1.20.1 Dilution test/miscibility test.

Miscibility test involves the addition of continuous phase, e.g. in case of O/W emulsion; the emulsion remains stable upon unlimited addition of water but will become unstable upon unlimited addition of oil, that is, the oil will separate. Vice versa is the case with W/O emulsion (55).

1.20.2 Electrical conductivity test

Water is a good conductor of electricity; hence, an emulsion with water continuous phase will readily conduct electricity while that with oil continuous phase will not (18).

1.20.3 Staining test/dye-solubility test

In this test, a small amount of water soluble dye, such as methylene blue is added to the emulsion, now if water is the continuous phase (O/W emulsion), dye will dissolve uniformly throughout the system. If oil is the continuous phase (W/O emulsion), dye will remain as cluster on the surface of the system (25)

1.21 . How to Measure Stability

It said that an emulsion is stable when it does not change its aspect in three years or so, and that it is unstable if it has completely separated after a few minutes. Anything in between these extremes requires a quantitative measurement of the emulsion evolution with time. The unique absolute measurement would be to count the number of drops in a given container, an information that cannot be collected without altering the system, so that only a single measurement may be done, which is not very sagacious anyway. The second choice would be to analyze a sample of the emulsion from time to time to determine whether the drop size average and/or distribution is changing. This could be done with some accuracy, but a lot of inaccuracy may come from the sampling process. In effect, if the emulsion is left to rest in the gravity field, the settling would result in a segregation by size according to a vertical distance. Thus, the sample drop is likely to depend upon the location where the sample is withdrawn. The answer to this problem is to not take the sample at the same location, since such a tactic could backfire. For instance, if the sampling is taken exactly at the middle of a test tube that contains an emulsion containing small and big oil drops in water, the first change to be observed could be an increase drop size because of the transit of the big drops that were initially in the lower part of the test tube, then a return to the initial average size, then finally a decrease in drop size after all big drops have settled into the upper part. It is obvious that such a segregation could completely hide the way the drop size changes because

of coalescence. The experimenter could be rid of this obstacle by completely remixing the whole system before taking a sample. However, such a procedure would destroy the rest state of the emulsion by interrupting any segregation or flocculation process. The final solution of this problem, is to prepare several small samples in separated vials to be kept exactly in the same conditions until each of them is opened and fully mixed before carrying out a drop size measurement. This may not be satisfactory for some unconventional studies that would require large emulsion amounts to be kept or turned upside down in a jar or submitted to heating-cooling cycles as in real life occurrence. In many instances the concept of emulsion stability is linked with a visual change in appearance or tactility, i.e., because some portion of one or the two phases separates from the emulsion, or because some other crucial property such as viscosity is significantly altered. If the emulsion is not too stable this may be a nice way to follow up the decay. If it takes too long a time to get visible measurable changes, then some time acceleration tactics would be advised. Figure 1-8 indicates the typical variation of separated oil or water volume from the emulsion as times elapses. The separated volume V_x could come from the internal phase drops that have coalesced or could be the external phase which has been cleared from settling drops. V_∞ is the same phase volume value at infinite time, i. e., after complete settling, so that the V_x/V_∞ ratio varies from zero to unity.

The second occurrence (external phase clearing) is not necessarily a measurement of instability since the gathering of drops in a cream without coalescence could be reversed by an appropriate slow mixing. This clearing and creaming is common in low-internal-phase-ratio emulsions, in which there is a large density difference and large drops. If the experimenter is looking for a solid basis to study formulation effects for instance, a unit W\O ratio is advised as well as the making of rather small drops to eliminate this eventuality. If this is not possible, the monitored phase separation should refer to the internal phase only.

the rate of separation is determined by stoke law as follow :

$$V = \frac{D^2 (\rho_s - \rho_o) g}{18\eta}$$

where is the velocity in cm/s, D is the diameter of particles of dispersed phase in cm, ρ_s is the dispersed phase density, ρ_o is the continuous phase density, η is the continuous phase viscosity and g is the gravitational acceleration.

So the rate V equal the separated volume(V_x) divided by time

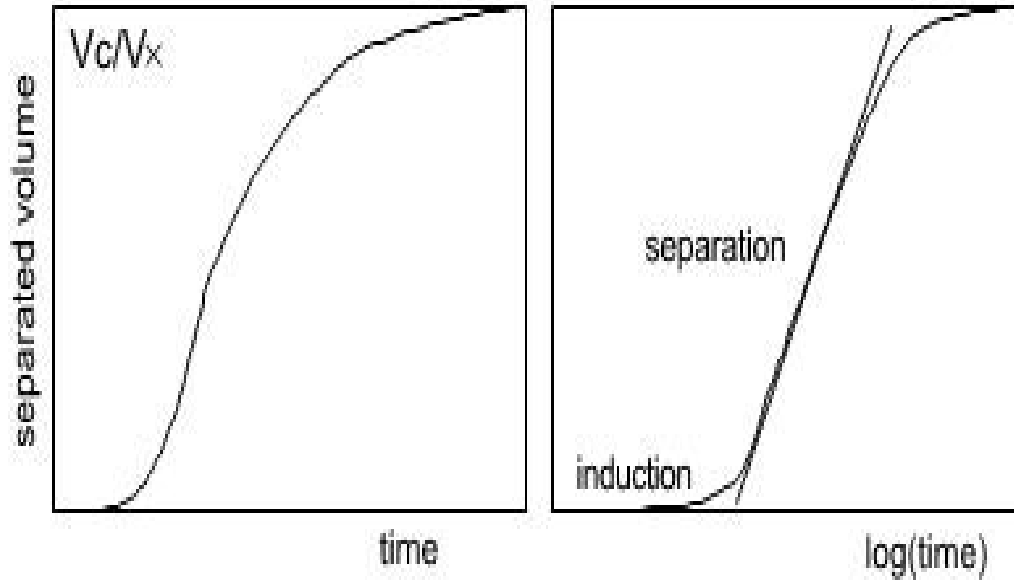$$V = \frac{D^2 (\rho s - \rho o) g}{18\eta}$$

Figure 1-8: Variation of the separated phase volume vs. time.

Coming back to Figure 1-8, it is seen that the apparent decay occurs in three periods. First, there is a period of time in which no separation takes place. This induction period may be related to the drop approach and film drainage, with no coalescence occurrence, so that no drop big enough to settle quickly is formed.

In the second period the separated volume increases steadily with time according to a S shaped curve as indicated in Fig 1.8 This is when most of the coalescence takes place at a steady rate. The third period is some kind of asymptotic behavior during which the last and smaller droplets complete their separation. This could trail quite a long time since the scarcity of droplets shrinks the probability of encounter and coalescence. Often, the central part of the separation curve is found to be linear vs. a logarithmic time scale, and the use of such a scale is advised to compare emulsified systems with very different stability(57)

1.21.1 . Acceleration Tactics to Measure Stability

Some emulsions are sometimes so stable that they require an extremely long time to start separating, which is quite inconvenient when experimental time is money. It is thus worthwhile to try to artificially accelerate the emulsion breakup in order to compare

formulation effects at a shorter time scale. The first thing that comes to mind is to use a centrifuge to speed up both early sedimentation and ensuing creaming, and to augment the force that pushes the drops against one another and thus helps in the film drainage. This will in general accelerate the separation process, but it may also convey false or misleading information. In effect, some emulsions would never coalesce in normal gravity, while they would do it under artificial gravity, because of different relative strengths between gravity and repulsive forces. In other cases, the creamed emulsion often will not coalesce either with natural or artificial gravity because the gravity pull has very little or no effect upon the surfactant role in slowing down the interdrop film drainage that commands the second and often crucial step in the separation process. The separation under centrifugation is thus a useful technique but not a necessarily successful even for comparison purpose. Another method is to make an emulsion with a larger drop size so that the settling process is accelerated. A larger drop size also means a smaller surface to volume ratio, that is a lower repulsive effect (that depends upon the adsorbed surfactant at interface) vs. a higher attractive force (that depends upon the drop volume). This will lead to a reduction in separation time, although probably no more than one order of magnitude, which might be too little in many instances. This method influences the separation second step and is thus more reliable than centrifugation to predict trends.

A clever method is to reduce the stabilizing agent concentration at interface so that all the stabilizing phenomena taking place in the second step (that dominates the decay of stable emulsions) would be weakened. A reduction in surfactant concentration in the whole system is not appropriate to produce such a reduction in surfactant adsorption. In effect, it is known that the surfactant adsorption starts occurring at very low concentration, much lower than its critical micellar concentration CMC, while the surfactant concentration in stable emulsions is often much higher in order to insure a quick drop coverage during emulsification. Accordingly, a reduction in surfactant concentration is likely to first produce alterations in the emulsification process, and thus the emulsion would be quite different from the one that must be studied It is preferred to reduce the interfacial surfactant concentration without reducing the surfactant concentration in the bulk phase. This may be done by introducing a co-surfactant that would compete with the surfactant for interfacial occupancy, but would not provide the stability features the surfactant molecules do. The most likely candidates for such a purpose are short chain alcohols in the three- to five-carbon range. In order to occupy a larger interfacial area, the alcohol should not be too hydrophilic or lipophilic. The best intermediate choice seems to be in-between n-propanol and n-butanol, the first one being

rather hydrophilic and the second more lipophilic. A mixture of these two n-alcohols, as well as secondary butanol, and even tertiary pentanol, would do the job fairly well at a 2-3.% wt concentration level in the system. It is worth noting that these alcohols will exhibit a neutral hydrophilic-lipophilic tendency that will not significantly affect the formulation at interface. [57].

difference between oil and water. Higher alcohols (n-butanol to n-hexanol) would dilute the surfactant at interface, but would shift the formulation toward more lipophilicity, and thus alter the physicochemical formulation of the system. Even more lipophilic alcohols (above hexanol) are found to be mostly miscible with oil with little adsorption at interface, so that their diluting capability vanishes. However, they are known to produce an interesting effect in the oil side of the interface either as a lipophilic linker or as a polar oil. If some alcohol is already present in the emulsion, the addition of 1 or 2% of sec-butanol might be effective or not depending on the effect of the alcohol added in the first place. The recommended addition of up to 3% sec-butanol could be realized before or after emulsification, but preferably before as an admixture to the aqueous phase, since it guarantees the best homogenization. In many cases the addition of sec-butanol is found to considerably reduce (100-fold or 1000-fold) the time scale of the emulsion decay without altering its characteristics. However, the actual "accelerating" factor cannot be forecast by any means.[57].

1.21.2 Quantifying Stability Measurements

There are two ways to quantify the notion of stability from the separated volume data as indicated in Figure 1-9 , where the coalesced volume V_x(referred to as a fraction of its maximum value V_∞) i s plotted vs. time .for two emulsions labeled A and B. From the first glance it is obvious that the same trends apply to both emulsions, but earlier in the case of emulsion A which may be qualified as less stable. The way to quantify this concept is to intercept the two curves by a single line.

$$V_x/V_\infty \quad VS \quad Time$$

where V_x is separate volume at time t, V_∞ is separate volume at infinite time
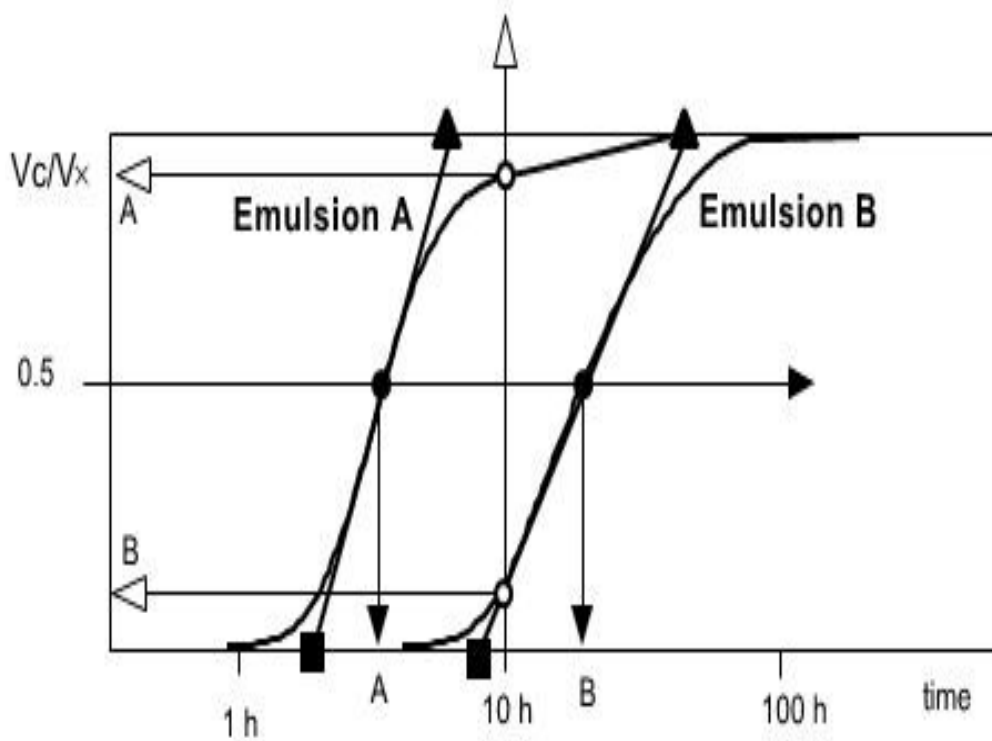
Figure 1-9 : Comparison of the stability of two emulsions (A and B) according to the criterion defined in figure 1.8 .

. For instance the (vertical) white head arrow located at a fixed time (here 10 h) intercepts both curves at a point (white dot) whose ordinate indicates the coalesced volume after ten hour. It is larger for emulsion A, which is thus less stable. In the present case there is quite

a difference in coalescence fraction V_x/V_∞ between the two emulsions. However this is not the general case, since the emulsion coalesced volume fraction does not vary but over a sometimes narrow period of time. For instance, if the interception is made at 100 h instead of 10 h, then both emulsions are completely coalesced, while after 1 h none of them has started to coalesce. Thus at 1 h and 100 h the diagnostic is the same for both criteria, in discrepancy with the actual difference. This is why the preferred method is to intercept the curve with a horizontal line, e. g., the (horizontal) black head arrow located at V_x/V_∞ = 0.5. The

corresponding (black circle) intercepts indicate the times required for both emulsions to exhibit one-half settling. It is worth noting that since the curves are very similar in shape (with a logarithmic time scale), the result is essentially the same whatever the position of the intercept line. In some cases the incipient (respectively final) separation is the critical criterion and a 10% (respectively 90%) separation may be taken instead. Since in most cases the lower and upper regions of the curve do not exhibit abundant experimental points, an extrapolation of the central linear trend to zero and total separation (squares and triangles) could lead to a good comparison criterion.[57] .

1.22 objectives

Because The environmental effects associated with nonylphenolethoxylates (NPE's) are now well documented and their replacement by alternatives is being strongly encouraged. It is considered that PEG oleate surfactants are a closer match to NPE's with respect to solubility, readily biodegradability , and emulsifying characteristics than are alcohol ethoxylate surfactants. This study aims to:

* Synthesize PEG4 oleate by general method

* Test the functionality of the prepared surfactant in emulsification of water\n-hexane w\o emulsion

Materials and methods

2-1 .materials

2.1.1 chemicals.

Oleic acid ,   sulfuric acid,   sodium bicarbonate,   sodium chloride

distilled water,   n-hexane .

2.1.2 apparatus

250ml beaker, 250 ml round bottom,   magnetic stirrer, vacuum pressure pump, hotplate,   separation funnel, burette,   test tube,   graduated cylinder,   Litmus paper and IR spectrometer   . All chemicals used were of anal. R grade.

2.2 method

2.2.1 Preparation of surfactant

in 250 ml round-bottom flask with continuous stirring . Esterification of oleic acid and PEG4 had been taken place at 130˚C for 6 hours with 3% wt(1.65ml) sulfuric acid as catalyst. Oleic acid was used in excess and fed step –wise to the reactor. The first portion of oleic acid and the whole amount of PEG4 were added at the start of the reaction.. The molar ratio of PEG4 to oleic acid was 1: 1.8 (34.65ml : 62.35ml) . Water was continuously removed from the   reactor in order to favorable shift the equilibrium .For this purpose a vacuum pressure   was applied to obtain the high selectivity of diester . The reaction mixture then allowed to cool at room temperature and removed from the reaction system to isolation process. For this purpose the reaction mixture was neutralized by 2% Sodium bicarbonate indicating to that by litmus paper. Then the un reacted PEG4 was extracted with saturated   sodium chloride solution at high temperature using a separation funnel .The retained product which contain mainly diester was then dried to clear products and IR was done to the last product .then   HLB was calculated using griffin method .(59).

2.2.2 Determining the HLB of a surfactant

William Griffin, in the late 1940s, introduced the Hydrophilic-Lipophilic Balance system (HLB) as a way of figuring out which emulsifier would work best with the oil phase of an emulsified product . All emulsifiers have a hydrophilic head (water loving) that is generally composed of a water soluble . Atypical nonionic emulsifier (PEG4 oleate) contains an ethylene oxide groups or polyethylene glycol hydrophilic portions with a fatty acid (oleic)hydrophobic portion. The HLB for a nonionic surfactant can be calculated by griffin method as follows:

$$HLB = 20 * M_h/M$$

where M_h is the molecular mass of the hydrophilic portion of the molecule, and M is the molecular mass of the whole molecule, giving a result on a scale of 0 to 20. An HLB value of zero   corresponds to a completely lipophilic/hydrophobic molecule, and a value of 20 corresponds to a completely hydrophilic/lipophobic molecule.

Mw of poly ethylene glycol divided by mw of poly ethylene oleate all divided by 5

HLB = Weight % Hydrophile/5

= (Mw of PEG4 \MW of all PEG 4 oleate)100\5

2.2.3 –Emulsion formation

With ratio presented in the table below (table 2.1) ,in 250 ml beaker all amount of oil and all amount of surfactant was added with continuous stirring(1600rpm) on magnetic stirrer heated to 50˚ C. From a burette distilled water was added drop wise then left on stirring for 2 hour (the total volume was 100 ml) . (62) ,(60).

Table 2.1 the phases and surfactant ratio in emulsion.

	n-hexane v\v%	Surfactant v\v%	WATER v\v%
A	78.7	2.55	18.75
B	77	3	20
C	77.45	2.55	20

2.2.4 Dilution test to test Emulsion type

into two 25ml test tube A, B . 10 ml of prepared emulsion was taken. For A test tube 5ml of acetone was added , to B test tube 5ml of distilled water was added. gently shaken and left for an hour (55).

2.2.5 Emulsion stability

From the three emulsion prepared above A,B and C,. 25 ml of each emulsion was put in graduated flat bottom test tubes labeled A,B,C, tightly sealed with their glass cup then stored for 7 days at ambient room temperature. [58] .The internal phase sediment was measured in interval of time then the variation of separated phase volume(V_x) and the fraction (f_r) of (V_x) to its maximum value (V_∞) plotted VS time (57).

Result and discussion

3.1 IR Interpretation:

The surfactant was prepared by esterification of poly ethylene glycol oleic acid by general method . The IR of this surfactant was done at Khartoum university lab to investigate if esterification happened or not .The IR(figure 3.1) show a peak at 2923.88cm^{-1} and 2854.45 cm^{-1} due to saturated (-C-H) stretching peak .The bending peak of methylene group (-C-H) at 1461.94cm^{-1},,bending peak of methyl group at 1360.08 cm^{-1} ,one at 1739.67 cm^{-1} due to (C=O) , and at 1137.92 cm^{-1} due to(C-O) these peaks indicate presence of ester .The peak at 723.26 cm^{-1} indicates along chain structure .The broad peak at 3446.55cm^{-1} due to (-O-H) of moisture or may be of trace of un separated glycol. .

3-2 –HLB calculation

HLB = (Mw of PEG4/MW OF all PEG 4 oleate)100/5

3-2-1 HLB calculation for PEG4 monoleate

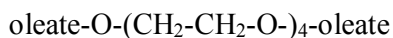$$H-O-(CH_2-CH_2-O-)_4-oleate$$

Mw of PEG4 (190 – 200 as labeled on the bottle) so average = 195

Mw oleate = 282.

MW PEG4 monoleate surfactant = 195+282 = 477

HLB = Weight % Hydrophile/5 = (mw of PEG4/mw of (PEG oleate)100/5.

= (195/477)100/5 = 8.17

3-2-2 HLB calculation for PEG4 dioleate.

$$oleate-O-(CH_2-CH_2-O-)_4-oleate$$

Mw of PEG4 = 195

Mw of 2mole oleate = 564

MW PEG4 dioleate surfactant =   195 + 564 = 759

HLB = (195/759)100 /5 = 5.138

The HLB system, does not indicate the overall efficiency of the surfactant, it does tell "what it will do" i.e. what kind of an emulsion or product to expect. By so doing, it enables us to compare various chemical types of surfactants at their optimum balance.   Here the synthesized surfactant is a mixture of both PEG4 monoleate (HLB = 8.176) and PEG4dioleate (HLB = 5.138) surfactants . so the expected HLB lay between (5.138 to 8.176) this HLB value promote w\o emulsion (table 1.3).

3.3 Emulsion type test

Table 3.1 Emulsion diluted with acetone and water

Test tube No	notification
A	Diluted stable homogenous emulsion
B	Aggregation and then quick phase separation

According to the result (table 3.1). emulsion is w\o type because the emulsion must be remain stable upon unlimited addition of continues phase (55)

3.4 Emulsion stability

Figure 3.2 which is the relation (V_x Vs   Time) where V_x is separated volume at time t. this curve indicates the typical variation of separated water volume from emulsion as time elapse.

The separated volume (V_x) comes from internal phase drops that have coalesced. there is a period of time in which no separation take place (12 hour for emulsion A and C, 24 hour

for emulsion B) this induction period may be related to the drop approach and film drainage with no coalescence occurrence so no drop big enough to settle. In the second period the separated volume increase steadily with time making S shaped curve . At the last period when each emulsion reach V_∞ which is the same volume value at infinite time after complete settle .

Table 3.2 variation of separated volume (Vx) vs time h

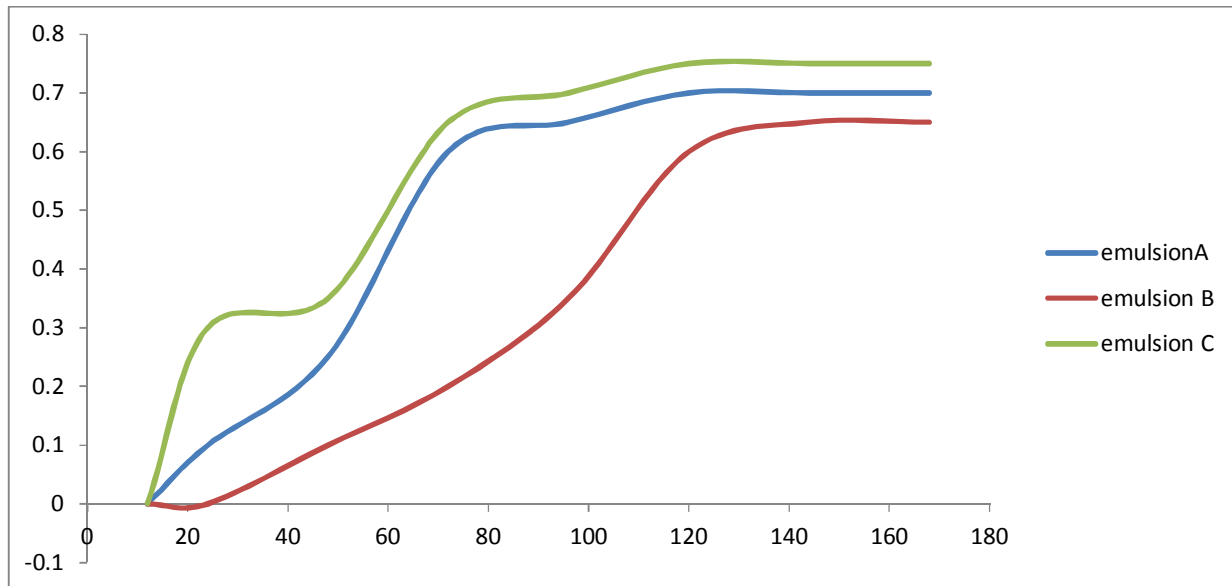| time h	12	24	48	72	96	120	144	168
A cm	0	0.1	0.25	0.6	0.65	0.7	0.7	0.7
B cm	0	0	0.1	0.2	0.35	0.6	0.65	0.65
C cm	0	0.3	0.35	0.65	0.7	0.75	0.75	0.75

Figure 3.2 variation of separated volume V_x Vs time

figure 3.2 indicate that emulsion B is more stable one this is related to high emulsifier concentration which give low interfacial tension then give small droplet size which take a long time to settle because smaller droplet size means higher surface to volume ratio, that is lower repulsive effect which depend upon the adsorbed surfactant at interface . or may of making thick film . emulsion A with low water content is more stable than C emulsion .

table 3.3 V_x/V_∞ ratio with time

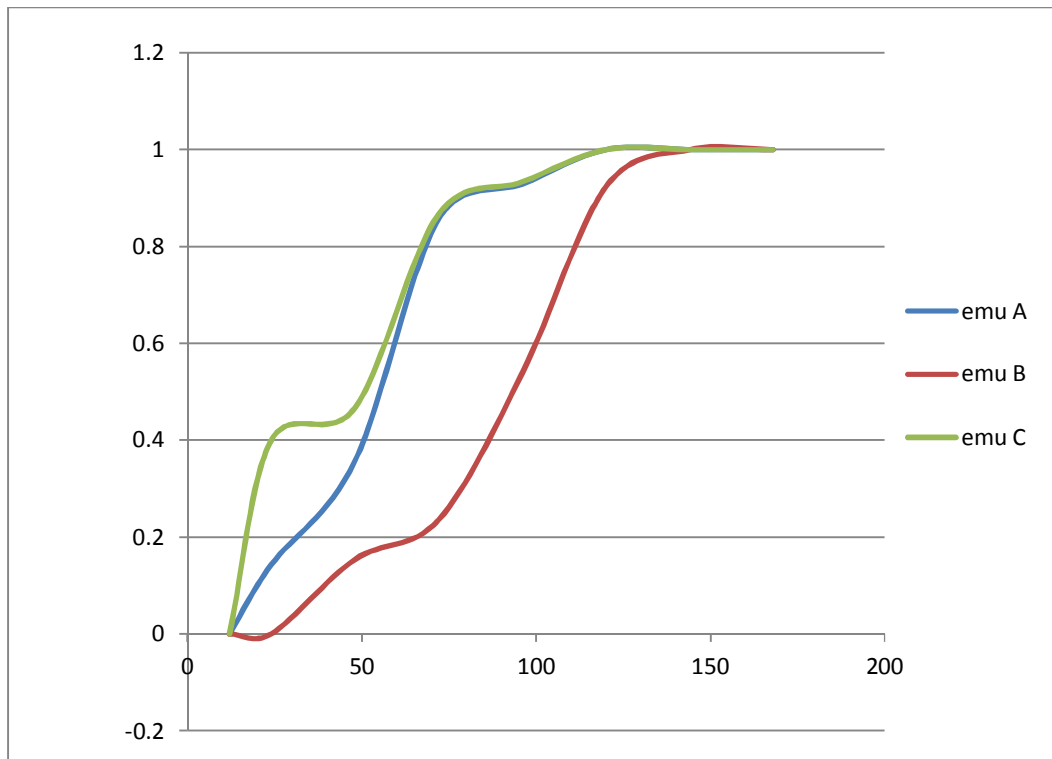| TIME h	12	24	48	72	96	120	144	168
A (V_x/V_∞)	0	0.1429	0.3571	0.8571	0.9286	1	1	1
B $(V_x/V_\infty$	0	0	0.1538	0.2353	0.5384	0.923	1	1
C $(V_x/V_\infty$	0	0.4	0.4666	0.8666	0.9333	1	1	1

Figure 3.3 comparison of the stability of the three emulsion according

to criterion defined in in figure 3.1 . V_x/V_∞ against time

From the figure 3.3 the V_∞ is the phase volume value at infinite time after complete settling so that V_x/V_∞ ratio (where V_x/V_∞ varies from zero to unity) . The preferred method is to intercept the curve with a horizontal line located at $V_x/V_\infty= 0.5$. The corresponding intercept indicate the times required for three emulsions to exhibit one-half

settling and used as criterion to emulsion stability .The curve show that the one-half time for emulsion B is 91 hour, 56 hour for A   and 49.99 hour for C emulsion.   .

3.5 Conclusion

* The PEG4 ester surfactant can be easily, safely and efficiently synthesisized

*The PEG4 ester surfactant mono and di oleate (HLB 8.176 and 5.138 respectively can promote moderate stable w/o emulsion and the stability can be increased by optimizing emulsification conditions

* The PEG4 ester surfactant can make more stable emulsion between oils of a high density and water .the deference in density between n- hexane and water high (0.3452 g/ml) So the emulsion separation occur.

Recommendation :-

We recommend that addition of weighing agent to match the density deference effect

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