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Insights of Microemulsions – A Thermodynamic Comprehension

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ABSTRACT

There is a resurgence of interest in the technological advances of liquid microdispersion formulations. Extensive research had carried on macroemulsions in the 1890's. Several theories suggesting the method of formulation and stabilization have profoundly investigated by researchers. There has been an exciting evolution of the concepts of microemulsions. Microemulsions are homogenous, transparent, optically isotropic, thermodynamically stable systems of oil and water stabilized by surfactant and cosurfactants with a size range of 5 to 100 nm. Microemulsions have a huge role in chemical, food, oil refining and pharmaceutical industries. In this article reviewed schematically on background of microemulsions, classification, components, selection criteria for excipients and theories of emulsification. The article given was importance to emphasize on thermodynamic attributes and spontaneous formation of microemulsions. The article specially introspects on stability of microemulsion with reference to thermodynamic and kinetic facets.

Keywords: Thermodynamics, spontaneous emulsification, critical packing parameter, curvature of interface, stability of film, interfacial tension.

1. INTRODUCTION

The advent of spontaneous microemulsion formation was ushered by Hoar and Schulman in 1943, by the observation of emulsion formation with the addition of a strong amphiphile (surfactant) to a water and oil system[1]. In 1959, Professor, Jack H. Schulman from Columbia University coined the term "microemulsion" to represent the transparent multicomponent system of water, oil, surfactant and alcohol[2]. Danielsson and Lindman gave the definition of microemulsion as "a system of oil, water and surfactant that is a homogenous optically isotropic solution acquiring thermodynamic stability"[3]. The microemulsion concept based application was found in washing wool using a combination of water, eucalyptus oil, soap flake, and white spirit by housewives in Australia. First use of commercial microemulsion was by Radawald in 1928. The conversion of a mixture of water and oil into a monophasic solution with the addition of surfactant was patented in the 1930's. Virbac employed commercial application of microemulsion in the dog shampoo "Allermyl"[4]. A microemulsion formulation of ibuprofen was used in the manufacture of topical ibuprofen gel at a dose of 5% and was marketed as Solvium by Chefaro (Akzo). Currently available products based on microemulsion are Sandimmune and Neoral (cyclosporine A), Norvir (ritonavir) and Fortovase (saquinavir)[5]. Progressing microemulsion technology has led to the emergence of Self Micro Emulsifying Drug Delivery Systems (SMEDDS), patented by Gattefosse in the early 90's. These are "latent" microemulsions, which are stable, water-free mixtures of surfactants, co-surfactants and lipophilic components. Microemulsions were formed while they are diluted in water or body fluids. The advantage of this system is the production of

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microemulsions with a water-free formulation, shielding sensitive API from chemical degradation in an aqueous medium. Gattefossé developed SMEDDS of simvastatin (Zocor), a successful anti-hyperlipidemic drug marketed by Merck that provided a fabulous fourfold increase in the bioavailability in dogs[6]. With the advancement in technology and methodology, microemulsion based formulations are on the increase.

2. Types of microemulsion

The types of microemulsion include oil in water type, water in oil type, and bicontinuous type.

Oil in water type: Oil droplets surrounded by a film of surfactant- cosurfactant are dispersed in water. They exhibit a larger interaction volume, as water is the external phase. The interfacial film of the surfactant monolayer is tilted in a positive curve. The hydrophilic polar heads face the external phase water and the lipophilic non-polar tails orient towards the internal phase of oil.

Example: neem oil microemulsion[7]

Water in oil type: Water droplets are dispersed in the external oily phase. They are termed 'reverse micelles' due to their orientation of polar heads and fatty oil chains. Aqueous biological systems have the ability to destabilize the w/o emulsions by increasing the phase volume of the internal phase. Phase inversion or phase separation results ultimately due to the phenomenon of percolation. An example includes water-in-virgin coconut oil microemulsion[8, 9].

Bicontinuous type: Bicontinuous microemulsions are produced as the composition of oil and water is equal. Both oil and water subsist as a continuous phase. The appearance of a 'sponge phase' is observed due to the intertwining of irregular channels of oil and water. They exhibit non-Newtonian flow and plasticity, which helps in the topical delivery of drugs or for intravenous administration of drugs[10]. An example is the blend of poly (ethyl ethylene) (PEE) and poly(dimethyl siloxane) (PDMS).

Winsor Classification[11]:

Winsor classified phase equilibria into four types based on phase behavior of water-oil-surfactant mixturesin the prevalence of diverse additives as shown in Figure 1.

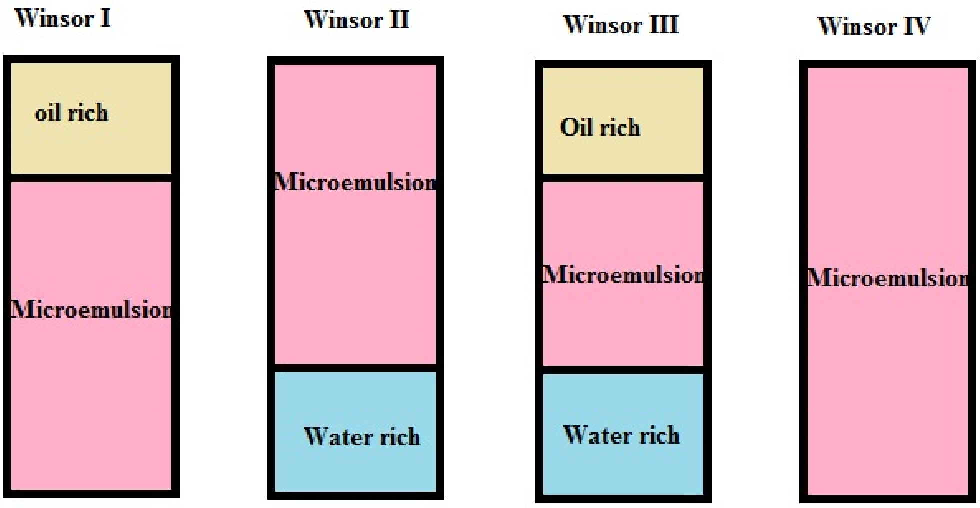

Figure (1): Winsor Classification

Winsor I: This has a lower phase with surfactant-rich water that coexists with an upper surfactant-poor oil phase.

Winsor II: In this, the upper phase with surfactant-rich oil coexists with a lower phase of surfactant-poor water.

Winsor III: Here a microemulsion exists sandwiched between water (lower) and oil (upper) surfactant-poor phases.

Winsor IV: This type is based on a monophasic homogenous mixture.

Prediction of the type of microemulsion:

Bancroft attempted to predict the type of microemulsion based on the emulsifier. Bancroft's rule states that water-soluble emulsifiers form o/w and oil soluble emulsifiers form w/o type[11].

Role of critical packing parameter (CPP):

Surfactants possess head and tail that affect the curvature of the interface. In 1976, Israelachvii proposed a relationship between the head group area (a_o) and the tail effective area ($\frac{v}{l_c}$) where v is the volume and l_c is the effective hydrocarbon chain to determine the CPP[12] as

$$CPP = \frac{v}{l_c a_o} \qquad (1)$$

A CPP value < 1/3 results in spherical micelle, 4/3 to ½ forms a rod like micelle, ½ to 1 exhibits a planar structure, > 1 forms reverse micelle and ≥ 1 corresponds bicontinuous.

Mean curvature of surface (H):

One can differentiate the type of emulsion from the value of the mean curvature of the surface. H=-1/a for water/oil interface, 1/a for oil/water interface, where 'a' is the radius of dividing surface. So if H is negative, it promotes a water in oil type of emulsion and a positive value indicates oil in water type of emulsion.

3. Composition:

Oil: Oil is considered a key determinant in microemulsion formulation, the reason being its ability to solubilize the lipophilic active moiety, enhancing drug absorption by escalating the transport via transepithelial and intestinal lymphatic systems. Drug absorption is dependent on the nature of the triglycerides used[13]. The oil component has the ability to penetrate biological membrane and promotes the swelling of the tail end of surfactant, thereby influencing the curvature. Short chain oils exhibit greater extent of penetration through biomembranes compared to long chain oils. Negative curvature of the interface increases with a reduction in effective HLB value because of this swelling of the tail group[14].

The following are suitable for forming an oil/lipid phase:

Long chain diglycerides (LCDs): corn oil, safflower oil, olive oil, soyabean oil[15]

Medium chain triglycerides (MCTs): glyceryl tricaprylate/caprate: captex 355, miglyol 810, neobee M-5

Saturated fatty acids: capric, lauric, myristic, palmitic acid

Unsaturated fatty acid: linoleic acid, linolenic acid and oleic acid

Fatty acid esters: ethyl or methyl esters of oleic acid, lauric acid and myristic acid

Propylene glycol esters: Propylene glycol dicaprylate/dicaprate[16, 17]

Surfactant:

Surfactant possesses the property of lowering surface/interfacial tension. A surfactant has a hydrophilic polar head and a lipophilic non-polar tail. Thus, it has affinity for both polar and non-polar solvents. When added to oil and water a surfactant forms a duplex film at the interface. They self-associate due to the inter-molecular and/or intra molecular forces. In addition to this, entropy also accounts for the free energy of the system. All these conditions favor thermodynamic stability. The surfactant molecules arrange themselves in a variety of shapes such as spherical micelles, rod-shaped micelles, hexagonal phase, lamellar phase, reverse micelles, and hexagonal reverse micelles. The commonly used surfactants can be categorized as, non-ionic, anionic, cationic, and zwitter ionic surfactants.

Non-ionic surfactant[18]

Nonionic surfactants do not have the ability to undergo ionization in the aqueous phase. This is because the hydrophilic group associated with nonionic surfactants is non-dissociable. Examples include alcohol, amide, ester, ether, phenol, etc. The hydrophilic nature of non-ionic surfactants is due to the polyethylene glycol chain formed by the polycondensation of ethylene oxide. They are familiar as polyethoxylated nonionics. Examples include Brij 35 and Span 80[19].

Anionic surfactant

Anionic surfactants being the most commonly used among surfactants account for about 50% of the world production. Sulfates, sulfonates, phosphates and carboxylates are the anionic functional groups at the head portions of anionic surfactants. Dioctyl sodium sulfosuccinate (DOSS) is the most widely studied anionic surfactant. Other important classes of anionic surfactants include alkyl ether sulfates, alkyl sulfates, alkyl sulfonates, aryl sulfonates, methylester sulfonates and sulfonates of alkylsuccinates. The most widely used anionic twin tailed surfactant is sodium bis-2-ethylhexylsulphosuccinate (AOT) and was reported as an effective stabiliser of w/o microemulsions[20].

Cationic surfactant

Cationic surfactants dissociate into cations and anions, which are amphiphilic, mostly of the halogen type. Nitrogenous compounds viz. amine salts of fatty acids and quaternary ammonium salts, with one or numerous alkyl long chain types constitute the major category. Alkyl ammonium halides are widely used in this arena because they are excellent hydrogen bond donors and they interact strongly with water. Quaternary ammonium alkyl salts such as cetyl trimethyl ammonium bromide (CTAB), and didodcecylammonium bromide (DDAB), the twin-tailed surfactant are the most widely used cationic surfactants[21,22].

Zwitterionic surfactant:

Zwitterionic surfactants possess groups with both positive and negative charges. They form microemulsions in the presence of co-surfactants. Naturally available zwitterionic surfactants are aminoacids and phospholipids. Examples include phospholipids like lecithin, betains like alkylbetaines, amidoalkylbetaines, and heterocyclic betaines[23].

Surfactants lessen the interfacial tension between oil and water phases, and form a protective layer preventing coalescence, while propping up the formation of an emulsion[24]. They also produce a finer droplet size, and aid the stabilization of the dispersion. The type of emulsion depends on the surfactant used.

Co-surfactant:

The stability of microemulsions is maintained by a surfactant, but a surfactant requires assistance from another component– the co-surfactant. Co-surfactants maintain the HLB value of surfactant favoring a stable microemulsion formation. The reason for this is that the head part of an ionic surfactant has significant hydrophilicity compared to other polyethylene oxide moieties. Co-surfactant acts as a second surfactant, which may be a low molecular weight amphiphile likealcohol[25].

Co-surfactants maintain stability by a further reduction of the interfacial tension. Fluidization of the surfactant duplex film increases the entropy of the system, thereby promotes thermodynamic stability. They devastate a liquid crystalline or gel structure that prevents the microemulsion formation and regulate the HLB value and spontaneous curvature of the interface by altering surfactant sectionalization trait[26]. Co-surfactants include short and medium chain alcohols like butanol, pentanol, ethanol, isopropanol and glycols like propylene glycol[27. 28].

Selection criteria for excipients:

Selection of oils:

The foremost consideration when selecting the oil phase is for the active moiety to possess high solubility in the selected oil phase that will reduce the volume of formulation of a therapeutic drug dose to be delivered in an encapsulated form. Lipophilic drugs are usually formulated as o/w type microemulsions. An oil phase also has the capability of affecting the curvature through its ability to pierce and swell the tail part of the surfactant monolayer. The outcome of tail group swelling is an increase in negative curvature which promotes the formation of a w/o microemulsion[29].

Selection of surfactants:

Hydrophilic lipophilic balance (HLB) value: The selection of a surfactant is of prime importance in the preparation of either o/w or w/o emulsions. Griffin devised hydrophilic-lipophilic balance (HLB) on an empirical basis for the selection of surfactants. It gives an approximate idea of the relative percentage of hydrophilic to hydrophobic groups of the surfactant[30]. To achieve stable emulsion, a combination of surfactants of variable low and high HLB values is recommended. The average HLB value is calculated using formula:

$$HLB = x_1HLB_1 + x_2HLB_2 \qquad (2)$$

Where, x_1 and x_2 are the fractions of weight of the surfactant 1 and 2 with HLB values of HLB_1 and HLB_2 respectively.

The variation in emulsion stability, droplet size and interfacial tension is expressed in association with the surfactants' percentage with a high HLB value as follows. With an increase in the percentage of surfactant with a high HLB number, emulsion stability increases up to a certain limit followed by a decrease and inversely affect droplet size and interfacial tension as depicted in Figure 2 [31].

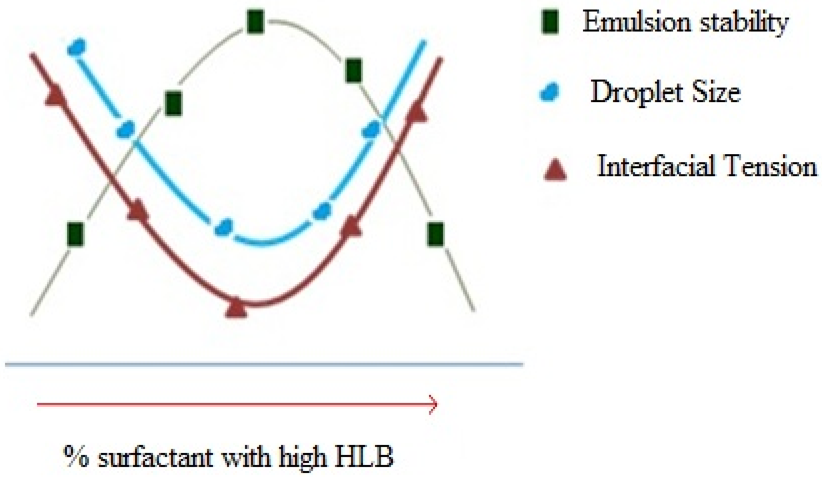

Figure (2): Effect of HLB value

Other procedures are adopted to estimate the HLB value of a surfactant. Utilization of cloud points of 5% ethoxylated surfactants to correlate the HLB values was done by Griffin. Besides this, emulsion coalescence rates were related to HLB values by Davies to assess the stability of emulsions. At each HLB value, either coalescence rate or oil separation rate was measured qualitatively to determine the stability of emulsion with respect to the HLB value of surfactant[31].

Critical packing paramete[32]:

If CPP value is between 0 and 1, it promotes a positive curvature, as the interface bends towards water favoring the formation of o/w systems. A CPP greater than 1, influences the interface to bend spontaneous towards the oil phase i.e., a negative curvature, promoting the formation of w/o microemulsions. When the CPP value is equivalent to 1, the curvature assumes a zero value indicating the formation of either bicontinuous or lamellar structures depending on the rigidity of the film.

Selection of co-surfactant:

Selection of co-surfactant depends on the length of alkanol chain, the category and the nature of co-surfactant. The most widely used co-surfactants are alcohols. If shorter chain alcohols are used as co-surfactant, o/w type emulsion is formed as alcohol swells the head region far ahead of the tail region making it to be more hydrophilic, and exhibiting a positive curvature effect. Long chain alcohols promote a negative curvature effect and forms w/o type of emulsions[33].

4. Theories of emulsification:

Different theories have been proposed on formation, stability and phase behavior of microemulsion. Noteworthy among them are interfacial, solubilization and thermodynamic theories.

Interfacial theory:

The first attempt developed to explain emulsification was the interfacial/ mixed film theory. In 1955, Bowcott and Schulman explained the significance of the interfacial film[34]. The spontaneous formation of emulsion droplets is because of the duplex film formation by surfactant or co-surfactant at the interface. It exhibits diverse properties on the water side rather than at the oil phase. Interaction of film at the interface results in the decrease of interfacial tension to very low levels perhaps to zero or even negative values. The film formed at the interface in equilibrium conditions was expected to be liquid and duplex in nature with two-dimensional spreading pressures, Π_i. The interfacial tension depends on the spreading pressure and the relationship is mathematically expressed as:

$$\gamma_i = \gamma_{o/w} - \Pi_i \qquad (3)$$

where, γ_i is the interfacial tension at interface, $\gamma_{o/w}$ is the oil/water interfacial tension without film and Π_i is the spreading pressure. The spreading pressure may be larger than $\gamma_{o/w}$ if the interface is formed by large amounts of surfactants and/or co-surfactants. At this state, interfacial tension becomes negative and forms emulsion droplets spontaneously supporting the negative interfacial tension phenomenon of spontaneous emulsification. However, the existence of negative interfacial tension is momentary and at equilibrium it becomes zero or attains a slightly positive value promoting the stability of emulsion droplets. Even though, the interfacial tension is zero it is not a certainty that a microemulsion is formed because of the possibility of formation of cylindrical and lamellar micelles[20]. The differentiation of emulsions from other liquid crystalline phases is done based on molecular interactions.

Mechanism of duplex film curvature[35]:

During the formation of droplets, the interfacial film is assumed to be curved. In the process of droplets formation, the film experiences stress due to the difference in interfacial tension and spreading pressure. The driving energy behind the curvature of film is the reduction of difference in tension on the two sides. The sides of the interface will expand spontaneously till the pressures equalize. Internal phase droplets would achieve a concave shape on the side with a higher tension. For o/w type of emulsion, bending occurs towards the water phase; in w/o type, bending occurs towards the oil phase. It is easier to form w/o microemulsion compared to o/w microemulsion as the oil side of the interface can be expanded at a faster rate than on the waterside. The direction of curvature and extent of it, and type of microemulsion and size of droplets depends on interactions in a mixed film. Based on this concept, the phase behavior theory of microemulsions was demonstrated by Robbins in 1976[36]. It is assumed that the nature, direction and degree of curvature is inflicted by the divergence trend of oil to swell the tails and water to engorge the heads.

At equilibrium conditions, the interface with a very low interfacial tension assumes optimal configuration. Spontaneous curvature ${}^{1}\!/_{R_0}$ (R_0 is the equilibrium radius of interface) which exhibits minimal bending energy is used to determine the interface bending stress as a function of curvature. The bending energy of the interface is given by a constant “curvature elasticity (K)” which indicates the ease of interfacial deformation. A large 'K' value represents a 'rigid' interface, which requires large energy to bend the interface; a small 'K' value represents a 'fluid' interface, which utilizes little energy for bending. Therefore, 'K' is also called the ‘rigidity constant’.

Factors influencing curvature[37]:

Electrolyte concentration: As electrolyte concentration increases, the shielding effect also increases reducing the area of the hydrophilic head (a_o). This leads to a more negative curvature of interfacial film with a higher CPP[38].

Oil type: The chain length (alkane) of oil affects the curvature. As the alkane chain length of oil increases, solvation of the surfactant tail group diminishes, promoting a positive curvature with lower CPP[37].

Co-surfactant: The effect of co-surfactant on the curvature is due to the alkanol chain length. The head part of the co-surfactant maintains constant ‘a_0’ and the tail phase increases the ‘v’ value with an increase in alkanol chain length, which consequently causes a raise in CPP. An increase in the alkanol length results in a negative curvature until its length equals surfactant length. Further increase promotes a greater positive curvature[37].

Temperature: With an increase in temperature, the efficiency of dissociation ionic surfactants increases, permitting a positive curvature. In the case of nonionic surfactants, owing to dehydration the head group size is diminished exhibiting a greater negative curvature[37].

Solubilization theory:

As per the solubilization theory proposed by Shinoda and Friberg, microemulsions are considered as swollen micellar spherical systems. The liaison between reverse micelles and w/o microemulsion was exemplified by Rance and Friberg with the aid of phase diagrams[39]. Relationship between the microemulsion region and the isotropic inverse micellar region was illustrated by addition of p-xylene, a hydrocarbon to inverse micellar phase resulted in a 4-component system, containing swollen inverse micellar region rather than microemulsion droplets region.

Adamson in 1969 proposed a model in which w/o emulsion is due to the balance between the Laplace and osmotic pressure[40]. The coexistence of the micellar emulsion phase with non-colloidal aqueous phase is noteworthy. It also states that the electrical double layer of the aqueous micelle interior is partially responsible for the interfacial energy, which imparts positive free energy at the interface. This concept contradicts the negative interfacial tension mechanism. Surfactants may form reverse micelles in non-polar organic media, in the incidence of water. W/O microemulsion droplet is considered as reverse micelle. The differentiation of w/o microemulsion and reverse micelle is that in a reverse micelle the amount of water is low and limits the maximum hydration capacity of surfactant hydrophilic head, thus making the pool water rigid. Both bound and free water exist in the pool if the amount of water exceeds the requirement for hydration in w/o microemulsion. The rigidity and the bend of the interfacially bound water layer affect the structure and physicochemical behaviour of the microemulsion. The ratio of [water]/[surfactant] represented as ‘w’ is the value which determines whether a reverse micelle or microemulsion was formed[41]. ‘w’ value and the corresponding system are as follows: $w < 10$ represents reverse micelle system, $w > 10$ indicates microemulsion, and the cut-off point can be $w=15$.

Microemulsions formed using polyols showed that the solubilizing capacity proportionately increases with an increase in the chain length of an alkane in alcohol and it was highest with four-carbon alcohols[42].

Thermodynamic theory:

Thermodynamic theory explains the microemulsion formation without a co-surfactant. It deals with the free energy change required for microemulsion formation. Free energy equation is $\Delta G_m=\Delta G_1+\Delta G_2+\Delta G_3-T\Delta S$ (4)

where, ΔG_m is the free energy change for microemulsion formation, ΔG_1 is the free energy change due to increase in total surface area, ΔG_2 is the free energy change due to interaction between droplets, ΔG_3 is the free energy change due to adsorption of surfactant at the oil/water interface from bulk oil or water and ΔS is the increase in entropy due to dispersion of small oil droplets.

Free energy involved in the formation of a microemulsion also depends on the lowering of interfacial tension by surfactant and the change in entropy of the system[43]. The configurational change in entropy, ΔS_{conf}, is expressed as:

$$\Delta S_{conf} = -nk_B[ln\phi + \{(1-\phi)|\phi\}ln(1-\phi)] \qquad (5)$$

Where, n is the number of droplets of dispersed phase, k_B is the Boltzmann constant and ϕ is the fraction of dispersed phase volume.

The relationship between free energy, interfacial tension and entropy is expressed by the equation[44],

$$\Delta G_f = \gamma_{AB}\Delta A - T\Delta S_{conf} \qquad (6)$$

Where, ΔG_f is the free energy change for formulation, γ_{AB} is the oil-water interface' surface tension, ΔA is the surface area change on microemulsification, ΔS_{conf} is the change in entropy of the system and T is the temperature at which emulsification is carried out.

On dispersion, the droplet number increases and ΔS_{conf} becomes positive. If the interfacial tension is reduced to an adequate minimum with a surfactant, the free energy will be relatively small and positive, thus permitting the change in the free energy value to negative, which promotes spontaneous microemulsification. It also takes into consideration, the thermal variance at the interface, in addition to the entropy of droplets, which has a key role in interfacial bending instability. Interfacial tension must be negative for the formation of microemulsion. However, a small positive value due to the entropic component is observed. This supports the contribution of entropy, which arises due to the mixing of one phase with the other promoting the formation of large number of small droplets. Other entropic contributions, which are expected to be favorable include surfactant diffusion in the interfacial layer and monomer-micelle surfactant exchange. Thus, a negative free energy of formation is desired for a large diminution in surface tension accompanied by a favorable change in the entropy. In such instances, spontaneous microemulsification occurs with thermodynamically stable dispersion[44].

Thermodynamic considerations for spontaneous microemulsification specify that the interfacial tension should be in the order of 10^{-4} to 10^{-5} dynes/cm[44]. The stability and the droplet size of microemulsion can be adjusted by altering thermodynamic detailing. This approach portrays the free energy of the electric double layer along with the van der Waal forces and the interaction potentials at electrical double layer among the droplets. The phase continuity is controlled by the interfacial charge[43]. The highest value of interfacial tension ($\Delta G=0$) at which emulsification between two phases is favourable is known as "critical interfacial tension",

$$\gamma_{AB} = -\frac{k_B T}{4\pi r^2}\left[\ln\phi_B + \left(\frac{1-\phi_B}{\phi_B}\right)\ln(1-\phi_B)\right] \qquad (7)$$

Where, r is the radius of the formed droplets and ϕ_B is the volume fraction of B.

However, the Gibbs free energy of mixing, ΔG_m must be negative for spontaneous formation and ΔG_m must, furthermore be at a minimum to maintain thermodynamical stability. By applying these conditions to microemulsions formed by an amphiphilic monolayer (which separates the polar and the non-polar regions), natural curvature and bending energy certainly affects the degree of dispersion.

5. Stability aspects:

The stability of microemulsions has been the theme of concern for diverse research groups working in this area. Researchers believe that, in addition to the reduction in the interfacial tension due to surface pressure, a complex relationship between zero interfacial tension and thermodynamic stability also provides an explanation for the formation of microemulsion systems. Thermodynamic factors include bending and tensional components of interfacial free energy, chemical potentials, and concentrations of species present in the bulk and inter-phase, enthalpy, entropy, interfacial compressibility, osmotic pressure, solubility parameters and stress gradients among others**.**

Bending effect:

Effect of the curvature on interfacial tension affects the formation of microemulsions. Surface tension and surface dilational energy are two aspects of curved interfaces. The surface dilational energy is due to the presence of surface moments. Values of these two components coincide at the surface and termed as the 'surface of tension'. In the case of microemulsions, the interface has low surface tension and the thermodynamic surface of tension is positioned away from the real transition zone between the two neighboring phases. The difference between surface tension, a tensorial quantity and surface dilational energy, a scalar quantity is more pronounced for curved interfaces due to the surface moments. Interfacial tension on curvature depends on the radii of droplet, which is compared to the Tolman parameter, the distance between the surface of tension and the equimolecular dividing surface. The Tolman parameter is large for microemulsions due to its low interfacial tension. The distribution of droplet size sis studied from bending moments. The bending moment effect plays a key role in microemulsion droplets attributed to the low interfacial tension and high curvature[46].

Work for bending of the interface:

The work for bending of the interface is,

$$dw_b = B\, dH \qquad (8)$$

where B is the bending moment and H is the mean curvature of surface. If $B < 0$; bending occurs spontaneously and dH will be greater than 0, thus negative B promotes the bending of interface around oil phase and positive B bends the interface towards aqueous phase.

Mechanism of bending effect[47]:

Bending moment develops due to the dipole moment of the adsorbed molecules, stern electric double layer, diffuse electric double layer, electrolyte contribution, and van der Waal forces. Bending moment due to surfactant and co-surfactant affects the bending of curvature. The thermodynamic equations to determine the dipole moment are as follows:

- The dipole moments of the adsorbed molecules,

$$B_{dp} = \int_0^{\Gamma} \left(\frac{\partial \mu_d}{\partial H}\right)_{\Gamma} d\Gamma \qquad (9)$$

where, B_{dp} is the bending moment due to the dipole moments of the adsorbed molecules, Γ is the surface excess and μ_d is the chemical potential due to dipole.

- The stern electric double layer,

$$B_{st} = -\zeta e \int_0^{\Gamma_s} \left(\frac{\partial \Delta\Psi_{st}}{\partial H}\right)_{\Gamma_s} d\Gamma_s \qquad (10)$$

where, B_{st} is the bending moment due to the Stern electric double layer, ζ is the zeta potential, e is the charge, $\Gamma_s$is the surface excess of surfactant and Ψ_{st} is surface potential at stern electric double layer. The negative sign of B_{st} implies that it tends to bend the interface around the oil phase.

- The Diffuse electric double layer,

$$B_{dl} = -\zeta e \int_0^{\Gamma_s} \left(\frac{\partial \Delta\Psi_{s}}{\partial H}\right)_{\Gamma_s \mu_c \mu_e} d\Gamma_s \qquad (11)$$

where, B_{dl} is the bending moment due to the diffuse electric double layer, μ_c is the chemical potential of co-surfactant and μ_e is the chemical potential of neutral electrolyte. The density of the surface charge '$\tilde{\sigma}$'is equal to$-\zeta e \Gamma_s$, if the adsorbed surfactant is completely dissociated. B_{dl} is a summation of two bending moments viz., B_{st} (bending moment contributed by stern layer) and B_{df}(bending moment generated by the diffuse part of the electric double layer). B_{dl} can be of the order of van der Waals bending moment (B_p), (≈ 10 pN) and has a negative sign that indicates the bending of the interface about the oil (gas) phase.

- The electrolyte contribution:

$$B_e = \int_0^{\Gamma_e(\mu_e)} \left(\frac{\partial \mu_e}{\partial H}\right)_{\Gamma_e} d\Gamma_e \qquad (12)$$

where, B_e is the bending moment due to neutral electrolyte and Γ_e is the surface excess of neutral electrolyte. Excess osmotic pressure created at the vicinity of the interface due to the negative adsorption of electrolyte ions is of major concern for bending moment.

- The van der Waals component of the bending moment: Bending moment due to van der Waals forces is denoted as B_p. In case of microemulsions, $B_p$value is negative and promotes the bend towards oil phase. The extent of B_p, may be in the order of 10 pN.
- Bending moment due to surfactant,

$$B_s = \int_0^{\Gamma_s} \left(\frac{\partial \mu_s}{\partial H}\right)_{\Gamma_s \mu_c \mu_e} d\Gamma_s \qquad (13)$$

where B_s is the bending moment due to surfactant. The bending modulus of the nonionic bilayer increases with the addition of ionic surfactant attributing the formation of an electrical double layer on either side of the bilayer.

- Bending moment due to cosurfactant,

$$B_c = \int_0^{\Gamma_c(\mu_c)} \left(\frac{\partial \mu_c}{\partial H}\right)_{\Gamma_c \mu_e} \mathrm{d}\Gamma_c \qquad (14)$$

where B_c is the bending moment due to surfactant.

Enthalpy:

The change in the Gibbs free energy of the system (ΔG) in terms of enthalpy and entropy can be written thermodynamically as:

$$\Delta G = \Delta H - T\, \Delta S \qquad (15),$$

*w*here, ΔG is the change in the Gibbs free energy, ΔH is the change in enthalpy, *T* is the temperature and *ΔS* is the change in entropy.

In the case of microemulsions, enthalpy is the input energy required for attaining a definite average droplet size. The enthalpy represents the internal energy during emulsification, if a change in volume is neglected. Internal energy is the work essential to increase the interfacial area (ΔW) as well as the amount of heat emerges due to wasting of a part of the energy input. The raise in the energy of an emulsion balanced against the nonemulsified components is equal to ΔW. This amount of energy must be taken into account to assess the thermodynamic instability of an emulsion.

Entropy: Configurational entropy is also known as the entropy of mixing. Lattice parameter ξ is used to calculate the entropy. As per phenomenological model, Gibb's free energy (G) is represented by

$$G = N_o\mu_o + N_w\mu_w + \gamma\Sigma - TS_{mix} \qquad (16)$$

where, N_o is total number of oil molecules in the system, N_w is total number of water molecules in the system, μ_o is chemical potentials of oil. μ_w is chemical potentials of water, γ is the interfacial tension between the mesophases and Σ is the area of the extended interface. The random mixing of oil and water phase during the formation of an emulsion results in an increase of configurational entropy resulting in a positive entropic change (ΔS) promoting the stability of microemulsions.

Osmotic pressure: The emulsions of highly concentrated droplets exhibit remarkable shear rigidity. The external osmotic pressure/surface pressure (Π) exerted on repulsive droplets is responsible for elasticity. The stability of microemulsions also depends on the droplet size distribution, which depends on Laplace pressure (Π_l). The droplet size distributions cannot be controlled; no two emulsions exhibits a similar sharing of Laplace pressures[48,49]

$$\Pi_l = \frac{2\sigma}{a} \qquad (17)$$

Where 'a' is the droplet radius or the same critical volume fractions, ϕ_c, at which droplet packing would occur. If Π(φ) come close to the Laplace pressure (Π_l) required to deform the droplets, packing of droplets and deformation occurs creating flat surfaces. A further raise in osmotic pressure results in the appearance of emulsions as a biliquid foam and φ value approaches unity. The droplets get compressed by osmotic pressure creating additional energy which may be stored by striking shear deformations. The elastic modulus is increased due to the additional droplet surface area. If the osmotic pressure drops to less than Laplace pressure, witnessed in diluted emulsions, droplets lose their rigidity and become viscous as suspending fluid[49].

Phase Inversion Temperature (PIT):

Introduced in 1969 the concept of phase inversion temperature explains the transitional interconversion of o/w and w/o type of emulsion under the influence of temperature[50, 51]. The principle involved is the alteration in the affinity of non-ionic surfactant with temperature. At low temperature, the surfactant film curvature assumes convex shape forming o/w type of emulsion and higher temperatures promote w/o emulsion by concave curvature towards water. PIT exists at a point where the curvature is neither concave nor convex. Interfacial tension reduces with temperature and accomplishes a lowest value at PIT[52]. Despite its stability, emulsification is carried out at PIT to achieve very small droplets. However, to get a fine and stable o/w emulsion, a quenching process is followed and stored at a temperature far-off from the PIT.

The stability of emulsion depends on the quenching and storage temperatures[53, 54]. To prolong the shelf-life, storage temperature is recommended at 20-65ºC which is less than PIT. Before the commencement of quenching, the oil phase is completely solubilized in the bicontinuous phase to form o/w microemulsions[55]. PIT is the average of the temperatures at which emulsions possess the highest and lowest conductivity[56]. The precise knowledge regarding PIT facilitates a researcher to select specific surfactants and determine the storage temperature to maintain the stability of the emulsions.

Marangoni effect:

It explains the additional effect of surfactants. Convective motions at the interface due to thermal and mechanical stress as well as local discrepancies in the surface concentration and play a role in the development of a gradient in interfacial tension. This interfacial tension gradient leads to the net transfer of liquid from the lower surface tension region towards higher surface tension regions. It was first identified by James Thompson; and scrupulously studied by Carlo Marangoni. Re-coalescence of emulsion droplets depends on the concentration of surfactant in the system. Upon collision, droplets tend to coalesce, if the surfactant concentration is too low to form a protective layer around them. The prevention of coalescence in formed droplets can be supported by the Gibbs-Marangoni effect, which contributes to the stability of emulsions[57].

Kinetic factors:

Electrostatic interaction and steric forces are two core factors, which affects emulsion stability. Brownian motion and the maintenance of intrinsic droplet mobility are involved in establishing kinetic stability. With a decrease in the particle size, the coalescence rate of particles increases as Brownian motion attains a significant role[58]. Concerning emulsion droplets, buoyance and gravitational force are two negligible factors in view of their tiny dimensions[59]. Velocity of droplet sedimentation described by Stokes law and droplet coagulation rate given by Smoluchowski law are the most widely used parameters to explicate kinetic consequences on emulsion stability. Stokes law equation to calculate the droplet terminal velocity[60] is

$$V_t = \frac{(D_w - D_o) g \sigma^2}{18\eta} \qquad (18)$$

where $\mathrm{D_w}$ and D_o are the aqueous and oily phase mass densities,σ is the droplet diameter and η is the oily phase viscosity. The droplet coagulation rate calculated by Smoluchowski law[61] is :

$$\frac{d\rho}{dt} = -k\rho^2 \qquad (19)$$

and the rate constant (k) is given as,

$$k = \frac{8k_BT}{3\eta} e\left[-\frac{E}{k_BT}\right] \qquad (20)$$

where, ρ is the droplet number density, E is the energy barrier to coagulation and η is the viscosity of emulsion. So, at elevated temperatures, the terminal velocity and coagulation rates are higher, and, accordingly, the emulsion instability is escalated. In thermodynamic point of view, microemulsions are more stable at a higher temperature in contrast to the kinetic aspect stability (low) at high temperature.

Factors affecting phase behavior[3]

Salinity: In o/w microemulsion, the droplet size increases at low salinity due to an augmentation of the mobilization of oil. Further increase in the concentration of brine results in the formation of a bicontinuous system at intermediate range. A continuous microemulsion will form with decreased globular size if salinity increases from the intermediate range. The outcome of further increase in salinity eventually is complete phase transition. With the addition of salt, water-in-oil emulsions are stabilized with changes in surfactant adsorption kinetics[38]. The interaction between polar groups of surfactants and ions that are dissolved in water contributes to the stabilization of the emulsion. Besides these, the decline in the Hamaker constant (van der Waals body body interaction) and the reduction of attractive force between droplets also has a remarkable role in emulsion stabilization at higher salt concentrations.

Concentration of alcohol: At increasing levels, low molecular weight alcohol as a cosurfactant results in phase transition from w/o to bicontinuous and then to o/w microemulsion. O/W type to w/o type via bicontinuous phase occurs with increase of concentration of high molecular weight alcohols[62].

Hydrophobic chain length of surfactant: As the chain length of the surfactant hydrophobic part increases, it results in the conversion of o/w type microemulsions to bicontinuous and then to w/o type.

pH: Alteration in pH regulates the phase behavior of microemulsions, if pH responsive surfactants are used in the formulation. This effect is highly prominent in the instances of acidic or alkaline surfactants. Alteration in the pH was due to carboxylic acids and amines which are favor to the conversion of w/o to o/w[63].

Nature of oil: Phase shift from o/w to w/o, arise with an increase in the aromaticity of the oil. An increase in the alkane chain length of the oil promotes the conversion of w/o type to an o/w type of microemulsions[3].

Ionic strength: With an increase of ionic strength, the o/w system which is balanced with an excess of oil passes into the middle phase and ultimately to a w/o system in an equilibrium with excess water[3].

Spontaneous formation:

The production of an emulsion requires the addition of energy at least 1000 times larger than involved in the creation of the two immiscible liquid system[64]. As an example, consider the conditions involved in the formation of an emulsion, such as the radius (r) of 1μm oil droplets in water; internal phase volume ratio Φ of 0.1 and interfacial tension (γ) of 10 mN/m. The surface free energy needed to produce this emulsion is around 3 KJ/m^3. Nevertheless, the actual energy required for emulsion formation is 3MJ/m^3, which can be provided by mechanical agitation. The spontaneous formation of emulsion is accomplished by interfacial turbulence, negative interfacial tension and diffusion with stranding[65,66].

Interfacial turbulence: When a drop of a lighter liquid is placed on a heavier liquid, unsteady motions ('kicking') can be observed at the interface. The phases penetrate into each other suggesting the principal involved is interfacial turbulence[67]. Examples include lauric acid in oil, and the sodium hydroxide, water system emulsion formation observed by Gad in 1878.

In 1888, Quincke explained the mechanism involved in the development of localized interfacial tension due to the non-uniform allocation of soap molecules on the interface. Vicious dispersal of these soap molecules creates an interfacial turbulence leading to the penetration of one liquid into the other promoting droplet formation. However, the droplets formed are stabilized by some other mechanism. Ethyl or methyl alcohol in toluene-water systems are the best example for strong spontaneous emulsification with marked interfacial turbulence mechanism. Interfacial turbulence is absolutely concealed by the addition of detergent to water, by dissolving salt in water and by distributing a protein film at the interface[66].

Negative interfacial tension: Spontaneous formation of mercury droplets in water is an excellent example for negative interfacial tension. The reduction in interfacial tension is observed when a negative potential is applied to the mercury in the quaternary ammonium salt aqueous solution. By adsorption of hydrocarbon residues and electrical attraction, the quaternary ammonium ion is very resistant to decompose at the surface of mercury, which results in a highly compressed cationic monolayer. At a potential of -2.2 V, the interfacial tension becomes negative. At a large applied negative potential, a negative interfacial tension is developed with consequent disintegration of the mercury drop into a brown cloud of colloidal mercury in water. The spontaneous emulsification is eye-catching at a potential of -8 V. In general, the interfacial tension is small or negative at relatively higher concentration of either surfactant/co-surfactant alone or in combination[66]. An example includes cetyl alcohol in toluene and sodium dodecyl sulfate system undergoing spontaneous emulsification when the amount of alcohol or detergent surpasses a particular concentration. The negative interfacial tension theory is still debated upon. The reason is the transient negative interfacial tension, which is responsible for spontaneous emulsification. Due to enormous interfacial or bulk viscosity the subsistence of negative interfacial tension can be denied. As the number of droplets increases on emulsification, the interfacial area will increase spontaneously casting out a new-fangled milieu where the interfacial tension would turn positive and the droplets would be further stabilized by the surfactant film. Hence the transient dynamic (negative) as well as equilibrium (positive) interfacial tensions have a dual role for spontaneous emulsification and stabilization.

Diffusion and stranding:

The mechanism of diffusion and stranding is unique, as in this, the value of interfacial tension has no role[68]. An example for this mechanism is a solution of ethyl alcohol and toluene in water. The creation of a three-component system in the vicinity of interface due to the diffusion of alcohol from oil into water hauling some oil is the mechanism involved in spontaneous emulsification. Alcohol further diffuses into water; because of which oil undergoes stranding in the water, up shooting fine emulsion drops. At the same time, alcohol in the oil may allow some water to dissolve leading to the appearance of water droplets on the oil side at the interface. Water is stranded in oil if alcohol passes into the oily phase. Oil with sulfonated castor oil and sodium oleate undergoes emulsification in water by diffusion and stranding mechanism as sodium oleate diffuses into water carrying oil.

The possible emulsification mechanism in the case of methanol/ ethanol in toluene/ water is as follows. Interfacial turbulence mechanism can be contradicted with an addition of surfactants or salts diminishing the interfacial turbulence. The equilibrium surface tension is around 10mN/m, which is positive denying the negative interfacial tension mechanism. Thus, the possible mechanism here is diffusion and stranding. Spontaneous emulsification is not observed by presaturating the toluene-alcohol mixture with water. This suggests that the diffusion of alcohol from oil into water and/or water into oil is a prerequisite condition for spontaneous emulsification through diffusion/stranding mechanism[68].

Phase transition due to temperature changes, osmotic pressure gradient effects, myelinic structures at the oil-water interface, sequential changes in the structure due to concentration gradient, Rayleigh instability and droplet explosion and spreading were recently proposed mechanisms for spontaneous emulsification[69,70]. The Plateau-Rayleigh instability explains the mechanism involved in the formation of lesser surface area droplets from a stream of fluid when it is broken into smaller packets of same volume. The driving force for spontaneous emulsification by Rayleigh instability is surface tension, which leads to the minimalization of surface area.

Irrespective of the mechanism, caution should be exercised, when selecting the initial composition of the system so that spontaneous emulsification occurs without mechanical energy. Spontaneous emulsification is exhibited by a few precise surfactant systems. Two surfactant systems reported so far which are involved in spontaneous emulsification include sodium bis (2-ethylhexyl) sulfosuccinate AOT, an anionic surfactant used to stabilize microemulsions, and hexaethylene glycol monododecyl ether, $C_{12}E_6$, a non-ionic surfactant which props up spontaneous emulsification, if a co-solvent soluble in oil as well as water is used[71]. Though spontaneous emulsification is not a thermodynamic equilibrium process, conditions such as the initial composition of the system i.e., oil and water is of major concern. The mechanism involved in the transfer of drug from emulsions to the cells is through aqueous diffusion and collisional mechanisms[72].

Aqueous diffusion mechanism: The drug passes through the aqueous pores in cell membranes. The transfer of the drug in between the lipid compartments is affected by the amount of lipophilic drug present in the aqueous medium[72].

Collisional mechanism: The transfer of drug is a consequence of direct collision of emulsion droplets with the cells. A significant level of lipophilic compound is not required to be present in the aqueous medium, a condition that suits highly lipophilic compounds[72].

Conclusion:

With the advent of latest technologies, lipid based formulations are gaining importance. Stability is the major concern in these formulations. The selection of excipients should be carried out with utmost care. Surfactants should be selected based on their HLB value and CPP. The chain length of an alcohol has to be carefully considered in the selection of co-surfactants. Interfacial tension should be zero/slightly positive to maintain stability whereas a negative value promotes spontaneous microemulsification. The nature, extent and direction of curvature, and the type of bonding dictate the type of miroemulsion formed. A change in the free energy of the system that depends on enthalpy, entropy, and an altered surface tension contributes considerable stability to microemulsions. The PIT concept is exploited to assess the stability of microemulsion at storage conditions. Prevention of coalescence can be explained by the Gibbs/Marangoni effect. Kinetic factors like droplet sedimentation velocity and the droplet coagulation rate must be determined to ensure stability. Thermodynamic and kinetic parameters are to be evaluated to formulate a stable microemulsion.

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إضاءة على المستحلبات الميكروية- فهم للثيرموديناميكية الحرارية

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ملخص

يمكن وصف المستحلبات الميكروية بأنها أنظمة زيتية ومائية محتوية على عوامل فاعلة سطحياً وعوامل مساعدة للفاعلية السطحية ذات تجانس وشفافية ضوئية متعادلة وثباتية ثيرموديناميكية يتراوح قياس الطور المتوزع فيها من (5 إلى 100 نانوميتر). تلعب المستحلبات الميكروية دوراً كبيراً في الصناعات الكيميائية والغذائية والدوائية وتصفية النفط.

تقوم هذه الورقة بمراجعة منظمة للمستحلبات الميكروية من حيث تصنيفها ومكوناتها ومعايير اختيار مكوناتها ونظريات الاستحلاب وثباتها من ناحية ثيروديناميكية وحركية.

الكلمات الدالة: المستحلبات الميكروية، الثيرموديناميكية الحرارية، الأنظمة الزيتية، الصناعات الكيميائية، تصفية النفط.

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