Pharmaceutical Microemulsion-A review

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***Abstract*- Microemulsion are clear, thermodynamically stable, isotropic liquid mixtures of oil, water and surfactant, frequently in combination with a cosurfactant. The aqueous phase may contain salt(s) and/or other ingredients, and the "oil" may actually be a complex mixture of different hydrocarbons and olefins. In contrast to ordinary emulsions, microemulsions form upon simple mixing of the components and do not require the high shear conditions generally used in the formation of ordinary emulsions. The three basic types of microemulsions are direct (oil dispersed in water, o/w), reversed (water dispersed in oil, w/o) and bicontinuous.**

In ternary systems such as microemulsions, where two immiscible phases (water and 'oil') are present with a surfactant, the surfactant molecules may form a monolayer at the interface between the oil and water, with the hydrophobic tails of the surfactant molecules dissolved in the oil phase and the hydrophilic head groups in the aqueous phase.

Microemulsions are one of the best candidates as novel drug delivery system because of their long shelf life, improved drug solubilization with ease of preparation and administration. Microemulsions are thermodynamically stable and optically isotropic liquid solutions of oil, water and amphiphile. They have emerged as novel vehicles for drug delivery which allow controlled or sustained release for ocular, percutaneous, topical, transdermal, and parenteral administration of medicaments.

***Index terms*- Micro emulsion, stability study, preparation method, identification test**

MICRO EMULSION

DEFINITION:

"A micro emulsion is a system of water, oil and an amphiphile which is a single optically isotropic and thermodynamically stable liquid solution".

INTRODUCTION

In some respects, micro emulsions can be considered as small-scale versions of emulsions, i.e., droplet type dispersions either of oil-in-water (o/w) or of water-in-oil (w/o), with a size range in the order of 5−50 nm in drop radius. Such a description, however, lacks precision since there are significant differences between micro emulsions and ordinary emulsions (or macro emulsions).

In particular, in emulsions the average drop size grows continuously with time so that phase separation ultimately occurs under gravitational force, i.e., they are thermodynamically unstable and their formation requires input of work. The drops of the dispersed phase are generally large (> 0.1 μm) so that they often take on a milky, rather than a translucent appearance. For micro emulsions, once the conditions are right, spontaneous formation occurs.

As for simple aqueous systems, micro emulsion formation is dependent on surfactant type and structure. If the surfactant is ionic and contains a single hydrocarbon chain (e.g., sodium dodecyl sulphate, SDS) micro emulsions are only formed if a co-surfactant (e.g., a medium size aliphatic alcohol) and/or electrolyte (e.g., 0.2 M NaCl) are also present. With double chain Ionics (e.g., Aerosol-OT) and some non-ionic surfactants a co-surfactant is not necessary. This results from one of the most fundamental properties of micro emulsions, that is, an ultra-low interfacial tension between the oil and water phases, $\gamma_{o/w}$.

The main role of the surfactant is to reduce $\gamma_{o/w}$ sufficiently − i.e., lowering the energy required to increase the surface area − so that spontaneous

dispersion of water or oil droplets occurs and the system is thermodynamically stable. As described in Section 3.2.1 ultra-low tensions are crucial for the formation of micro emulsions and depend on system composition.

Micro emulsions were not really recognized until the work of Hoar and Schulman in 1943, who reported a spontaneous emulsion of water and oil on addition of a strong surface-active agent. The term "micro emulsion" was first used even later by Schulman et al.

THEORY OF FORMATION AND STABILITY

Interfacial Tension in Microemulsions

A simple describing microemulsion formation is to consider a subdivision of the dispersed phase into very small droplets. Then the configurationally entropy change, can be approximately expressed as the equation Boltzman's equation

Kinetic Stability

Internal contents of the microemulsion droplets are known to exchange, typically on the millisecond time scale. They diffuse and undergo collisions. If collisions are sufficiently violent, then the surfactant film may rupture thereby facilitating droplet exchange, that is the droplets are kinetically unstable. However, if one disperses emulsions sufficiently small droplets (< 500 Å), the tendency to coalesce will be counteracted by an energy barrier. Then the system will remain dispersed and transparent for a long period of time (months). Such an emulsion is said to be kinetically stable. (reference :- Danielsson, I.; Lindman, B. Colloids Surf. A 1981, 3, 391. Pg. No. 61)

PHYSICOCHEMICAL PROPERTIES

Predicting microemulsion type

A well-known classification of microemulsions is that of Winsor who identified four general types of phase equilibria:

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

Surfactant film properties

An alternative, more physically realistic, approach is to consider mechanical properties of a surfactant film at an oil−water interface. This film can be characterized by three phenomenological constants: tension, bending rigidity, and spontaneous curvature. Their relative importance depends on the constraints felt by the film. It is important to understand how these parameters relate to interfacial stability since surfactant films determine the static and dynamic properties of microemulsions (and emulsions). These include phase behaviour and stability, structure, and solubilisation capacity.

Spontaneous curvature

Spontaneous (or natural or preferred) curvature C_o is defined as the curvature formed by a surfactant film when a system consists of equal amounts of water and oil. Then, there is no constraint on the film, which is free to adopt the lowest free energy state. Whenever one phase is predominant, there is a deviation from C_o. In principle, every point on a surface possesses two principal radii of curvature, R_1 and R_2 and their associated principal curvatures are $C_1 = 1/R_1$ and $C_2 = 1/R_2$. Mean and Gaussian curvatures are used to define the bending of surfaces.

Mean curvature: $C = ½ (1/R_1 + 1/R_2)$

Gaussian curvature: $\kappa = 1/R_1 \times 1/R_2$

C_1 and C_2 are determined as follows: every point on the surface of the surfactant film has two principal radii of curvature, R_1 and R_2 as shown in Figure 3.5. If a circle is placed tangentially to a point p on the surface and if the circle radius is chosen so that its second derivative at the contact point equals that of the surface in the direction of the tangent (of normal vector, n), then the radius of the circle is a radius of

curvature of the surface. The curvature of the surface is described by two such circles chosen in orthogonal (principal) directions.

Surfactant type

Nature of the polar head group, also influences C_o through different interactions with the polar (aqueous) phase:

For ionic surfactants electrolyte content and temperature affect the spontaneous curvature in opposite ways. An increase in salt concentration screens electrostatic head group repulsions − i.e., decreases head group area so the film curves more easily toward water, leading to a decrease in C_o.

Raising temperature has two effects:

(1) An increase in electrostatic repulsions between head groups due to higher counter ion dissociation, so C_o increases;

(2) More gauche conformations are induced in the surfactant chains, which become more coiled, resulting in a decrease in C_o. Therefore the combined effects of temperature on the apolar chains and on electrostatic interactions are competitive. The electrostatic term is believed to be slightly dominant, so C_o increases weakly with increasing temperature.

For non-ionic surfactants, unsurprisingly, electrolytes have very little effect on C_o, whereas temperature is a critical parameter due to the strong dependence of their solubility (in water or oil) on temperature. For surfactants type as temperature increases water becomes a less good solvent for the hydrophilic units and penetrates less into the surfactant layer. In addition, on the other side of the film, oil can penetrate further into the hydrocarbon chains, so that increasing temperature for this type of surfactant causes a strong decrease in C_o. This phenomenon explains the strong temperature effects on the phase equilibria of such surfactants.

Phase behaviour

Solubilisation and interfacial properties of microemulsions depend upon pressure, temperature and also on the nature and concentration of the components. The determination of phase stability diagrams (or phase maps), and location of the different structures formed within these water(salt)−oil−surfactant−alcohol systems in terms of variables are, therefore, very important.

Phase rule

The phase rule enables the identification of the number of variables (or degrees of freedom) depending on the system composition and conditions. It is generally written as:

$F = C - P + 2$

Where F is the number of possible independent changes of state or degrees of freedom, C the number of independent chemical constituents, and P the number of phases present in the system. A system is called invariant, mono variant, bi variant, and so on, according to whether F is zero, 1, 2, and so on. For example, in the simplest case of a system composed of three components and two phases, F is uni variant at a fixed temperature and pressure.

PREPARATION AND METHODS

Phase Titration Method

Microemulsions are prepared by the spontaneous emulsification method (phase titration method) and can be depicted with the help of phase diagrams. Construction of phase diagram is a useful approach to study the complex series of interactions that can occur when different components are mixed. Microemulsions are formed along with various association structures (including emulsion, micelles, lamellar, hexagonal, cubic, and various gels and oily dispersion) depending on the chemical composition and concentration of each component. The understanding of their phase equilibrium and demarcation of the phase boundaries are essential aspects of the study. As quaternary phase diagram (four component system) is time consuming and difficult to interpret, pseudo ternary phase diagram is often constructed to find the different zones including microemulsion zone, in which each corner of the diagram represents 100% of the particular component.

The region can be separated into w/o or o/w microemulsion by simply considering the composition that is whether it is oil rich or water rich. Observations should be made carefully so that the meta stable systems are not included.

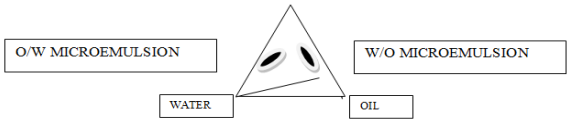

Figure 4.1: - Pseudotemary Phase Diagram of oil, water & surfactant.

PHASE INVERSION METHOD

Phase inversion of micro emulsions occurs as a result of addition of excess of the dispersed phase or in response to temperature. During phase inversion drastic physical changes occur including changes in particle size that can affect drug release both in vivo and in vitro. These methods make use of changing the spontaneous curvature of the surfactant. For non-ionic surfactants, this can be achieved by changing the temperature of the system, forcing a transition from an o/w micro emulsion at low temperatures to a w/o micro emulsion at higher temperatures (transitional phase inversion). During cooling, the system crosses a point of zero spontaneous curvature and minimal surface tension, promoting the formation of finely dispersed oil droplets. This method is referred to as phase inversion temperature (PIT) method. Instead of the temperature, other parameters such as salt concentration or pH value may be considered as well instead of the temperature alone. Additionally, a transition in the spontaneous radius of curvature can be obtained by changing the water volume fraction. By successively adding water into oil, initially water droplets are formed in a continuous oil phase. Increasing the water volume fraction changes the spontaneous curvature of the surfactant from initially stabilizing a w/o micro emulsion to an o/w micro emulsion at the inversion locus. Short-chain surfactants form flexible mono layers at the o/w interface resulting in a bi continuous micro emulsion at the inversion point.

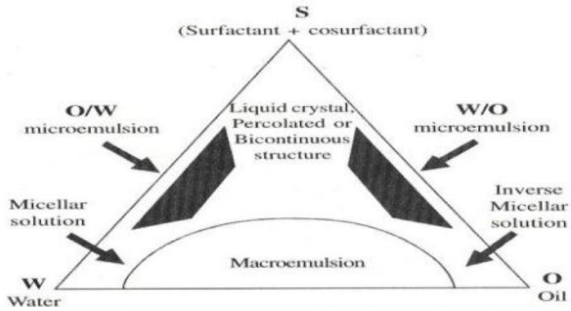

Figure 4.2: Hypothetical Phase region of Micro emulsion system

From above figure, we can see that,

- When there is high concentration of oil, surfactant forms reverse micelles capable of solubilising more water molecules in their hydrophilic interior.
- Continued addition of water in this system may result in the formation of W/O micro emulsion in which water exists as droplets surrounded and stabilized by interfacial layer of the surfactant / co-surfactant mixture
- at a limiting water content, the isotropic clear region changes to a turbid, bi refringent one
- Upon further dilution with water, a liquid crystalline region may be formed in which the water is sandwiched between surfactant double layers.
- Finally, as amount of water increases, this lamellar structure will break down and water will form a continuous phase containing droplets of oil stabilized by a surfactant / co-surfactant (O/W micro emulsions).

FACTORS AFFECTING FORMATION AND PHASE BEHAVIOUR OF MICROEMULSION

1. Factor affecting formation of Microemulsion system

The formation of oil or water swollen microemulsion depends on the packing ratio, property of surfactant, oil phase, temperature, the chain length, type and nature of co-surfactant.

Packing ratio:- The HLB (Hydrophilic Lipophilic Balance) of surfactant determines the type of microemulsion through its influence on molecular packing and film curvature. The analysis of film curvature for surfactant associations leading to microemulsion formation has been explained by Israclachvili et al (1976) and Mitchell and Ninham (1977) in terms of packing ratio, also called as critical packing parameter.

Critical Packing Parameter (CPP) = v/a×l

Where,

v is the partial molar volume of the hydrophobic portion of the surfactant, is the optimal head group area and l is the length of the surfactant tail.

- If CPP (0-1) interface curves towards water (positive curvature) and o/w systems are favoured.
- CPP is greater than 1, interface curves spontaneously towards oil (negative curvature) so w/o micro emulsions are favoured
- At zero curvature, when the HLB is balanced (p is equivalent to 1), then either bi continuous or lamellar structures may form according to the rigidity of the film (zero curvature).

Property of Surfactant, Oil Phase and Temperature:- The type of microemulsion formed depends on the nature of surfactant. Surfactant contains hydrophilic head group and lipophilic tail group. The areas of these groups, which are a measure of the differential tendency of water to swell head group and oil to swell the tail area, are important for specific formulation when estimating the surfactant HLB in a particular system. When a high concentration of the surfactant is used or when the surfactant is in presence of salt, degree of dissociation of polar groups becomes lesser and resulting system may be w/o type.

The Chain Length, Type and Nature of Co-Surfactant:- In the formation of alcohols are widely used as a co-surfactant in micro emulsions. Addition of shorter chain co-surfactant gives positive curvature effect as alcohol swells the head region more than tail region so, it becomes more hydrophilic and o/w type is favoured, while longer chain co-surfactant favours w/o type w/o type by alcohol swelling more in chain region than head region.

2. Factor Affecting Phase Behaviour
Salinity:- At low salinity, the droplet size of o/w microemulsion increases. This corresponds to increase in the solubilisation of oil. As salinity further increases, the system becomes bi- continuous over an intermediate salinity range. Increase in salinity leads to formation of continuous microemulsion with reduction in globule size. Further increase in salinity ultimately results in complete phase transition.

Alcohol concentration:- Increasing the concentration of low molecular weight alcohol as a co surfactant leads to the phase transition from w/o to bi continuous and ultimately to o/w type micro emulsion. Exactly opposite phase transition is noticed in case of high molecular weight alcohol.

Surfactant Hydrophobic Chain Length:-
The increase in length of hydrophobic chain length of the surfactant shows the change of o/w micro emulsion to w/o via bi continuous phase.

pH:- Change in pH influences the micro emulsions containing pH sensitive surfactants. This effect is more pronounced in case of acidic or alkaline surfactants. Carboxylic acids and amines change the phase behaviour from w/o to o/w by increasing the pH.

Nature of Oil:- Increase in the aromaticity of oil leads to phase transition from o/w to w/o and is opposite to that of increase in the oil alkane carbon number.

Ionic Strength:- As the ionic strength increases the system passes from o/w micro emulsion in equilibrium with excess oil to the middle phase and finally to w/o micro emulsion in equilibrium with excess water.

EVALUATION OF MICRO EMULSION

Visual Inspection
For visual inspection microemulsion can be inspect visually for homogeneity, optical clarity, and fluidity.

Examination under Cross-polarizing Microscope
The microemulsion systems are subjected to examination under cross polarizing microscope for the absence of birefringence to exclude liquid crystalline systems.

Limpidity Test (Percent Transmittance)
The limpidity of the microemulsion can be measured spectro photometrically using spectrophotometer.

Accelerated Stability Tests
Centrifugation stress testing:- Stability studies is time consuming process, so accelerated stability test is preferred. Microemulsion are centrifuged at 5000 and 10,000 rpm for 30 min were applied in order to assess the physical instabilities like phase separation, phase inversion, aggregation, creaming and cracking of the

formulations. Previously thermally tested formulation are taken in centrifuge sample tubes and placed in the centrifuge basket at a well-balanced equilibrium position at ambient temperature conditions.

Freeze-Thaw Cycles (FTC):- To access any change in stability of microemulsion they are subjected to stored at 25°C for 24 h and followed by 24 h at −5°C, the cycle is repeated three times and change is noted.

Long Term Stability:- Stability can be examined according to ICH guidelines. The Micro emulsion are stored under ambient conditions for 6 months, and the system was examined periodically after 1, 3, and 6 months by visual inspection and measurement of percent transmittance, pH, specific gravity, and rheological evaluation.

Specific gravity testing at 28°C:-
To determine the specific gravity, a capillary gravity bottle method is used. Washed and dried, the precaution was necessary during the drying of the gravity bottle as a little amount of moisture could increase the errors in the data of the specific gravity of the samples.

IDENTIFICATION TESTS FOR MICRO EMULSION

1) Dilution test
If the continuous phase is added in micro emulsions, it will not crack or separate into phases. If water is added in o/w type of micro emulsions it will remain stable.

2) Staining test
Water soluble dye such as methylene blue or amaranth is added in water and micro emulsion is prepared with oil and surfactant. A drop of Micro emulsions is observed under microscope. Background is found to be blue / red and globule will appear colourless respectively.

3) Dilute ability test
The Micro emulsions formed is diluted in 1:10, and 1:100, ratios with double distilled water to check if the system shows any signs of separation.

4) Zeta potential measurement
It must be negative or neutral, which indicate that droplets of micro emulsion having no charge and hence the system is stable. Zeta potential is determined by using Zetasizer. Zeta potential is essentially useful for assessing flocculation since electrical charges on particles influence the rate of flocculation.

5) Poly dispersity
This property is characterized by Abbes refractometer.

APPLICATIONS OF MICRO EMULSION

1) Pharmaceutical Applications
During the last two decades, microemulsions have been promisingly used as drug delivery system for its advantages include their thermodynamic stability, optical clarity and ease of penetration. The role of microemulsion as drug delivery system shall be discussed herein.

2) Oral delivery:-
The development of effective oral delivery systems has always been challenging to researchers because drug efficacy can be restricted by instability or poor solubility in the gastrointestinal fluid. Microemulsions have the potential to enhance the solubilisation of poorly soluble drugs (particularly BCS class II or class IV) and overcome the dissolution related bioavailability problems. Due to the presence of polar, non-polar and interfacial domains, hydrophilic drugs including macromolecules can be encapsulated with varying solubility. These systems have been protecting the incorporated drugs against oxidation, enzymatic degradation and enhance membrane permeability. Presently, Sand immune Neoral(R) (Cyclosporine A), Fortovase(R) (Saquinavir), Norvir(R) (Ritonavir) etc. are the commercially available microemulsion formulations. Microemulsion formulation can be potentially useful to improve the oral bioavailability of poorly water soluble drugs by enhancing their solubility in gastrointestinal fluid.

3) Parenteral delivery:-
The formulation of Parenteral dosage form of lipophilicand hydrophilic drugs has proven to be difficult. O/w microemulsions are beneficial in the

Parenteral delivery of sparingly soluble drugs where the administration of suspension is not required. They provide a means of obtaining relatively high concentration of these drugs which usually requires frequent administration.

Other advantages are that they exhibit a higher physical stability in plasma than liposome's or other vehicles and the internal oil phase is more resistant against drug leaching. Several sparingly soluble drugs have been formulated into o/w microemulsion for parenteral delivery. An alternative approach was taken by Von Corse want and Thoren in which C3-C4 alcohols were replaced with parenterally acceptable cosurfactants, polyethylene glycol (400) / polyethylene glycol (660) 12-hydroxystearate / ethanol, while maintaining a flexible surfactant film and spontaneous curvature near zero to obtain and almost balanced middle phase microemulsion.

4) Topical delivery:-

Topical administration of drugs can have advantages over other methods for several reasons, one of which is the avoidance of hepatic first-pass metabolism, salivary and degradation of the drug in stomach and related toxicity effects. Another is the direct delivery and targetability of the drug to affected areas of the skin or eyes.

5) Ophthalmic delivery:-

In conventional ophthalmic dosage forms, water soluble drugs are delivered in aqueous solution while water insoluble drugs are formulated as suspension or ointments. Low corneal bioavailability and lack of efficiency in the posterior segment of ocular tissue are some of the serious problem of these systems.

6) Nasal delivery:-

Recently, microemulsions are being studied as a delivery system to enhance uptake of drug through nasal mucosa. In addition with mucoadhesive polymer helps in prolonging residence time on the mucosa. Lianly et al. investigated the effect of diazepam on the emergency treatment of status epilepticus. They found that the nasal absorption of diazepam fairly rapid at 2 mg kg-1 dose with maximum drug plasma concentration reached within 2-3 min.

ADVANTAGES

1. Micro emulsions are thermodynamically stable system and allows self-emulsification of the system.
2. Micro emulsions act as super solvents for drug, can solubilise both hydrophilic and lipophilic drugs including drugs that are relatively insoluble in both aqueous and hydrophobic solvents.
3. The dispersed phase, lipophilic or hydrophilic (oil-in-water, O/W, or water-in-oil, W/O micro emulsions) can act as a potential reservoir of lipophilic or hydrophilic drugs, respectively. Drug release with pseudo-zero-order kinetics can be obtained, depending on the volume of the dispersed phase, the partition of the drug and the transport rate of the drug.
4. The mean diameter of droplets in micro emulsion is below 0.22 mm. This yield a large interfacial area, from which the drug is released rapidly into external phase when absorption (in vitro or in vivo) takes place, maintaining the concentration in the external phase close to initial levels.

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