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MICROEMULSION: A NOVEL APPROACH FOR DRUG DELIVERY SYSTEM

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ABSTRACT : 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 isotropic system, which are difficult to formulate than ordinary emulsions because their formulation is a highly specific process involving spontaneous interactions among the constituent molecules. Microemulsions are clear, thermodynamically stable, isotropic liquid mixture of oil, water and surfactant, frequently in combination with a cosurfactant. An API has high solubility and oil may also have more or less pharmacological property, so it may assist the therapeutic action of API. Microemulsions have an advantage easily prepared and require no energy contribution during preparation this is due to better thermodynamic stability. Microemulsion evaluated by various methods. The main objective of this review paper is to discuss microemulsion as drug carrier system.

Key words: Microemulsion, novel drug delivery, thermodynamic stability, cosurfactants.

1. INTRODUCTION

Microemulsions are isotropic system, which are difficult to formulate than ordinary emulsions because their formulation is a highly specific process involving spontaneous interactions among the constituent molecules. Microemulsions are clear, thermodynamically stable, isotropic liquid mixtures of oil, water and surfactant, frequently in combination with a cosurfactant. The aqueous phase may contain salt 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 simply mixing of the components and do not require the high shear conditions generally used in the formulation of ordinary emulsions [(1).] The solubility potential of microemulsion is a major factor in enhancing absorption of drugs. Mostly microemulsions have favorable solvent properties due to the potential incorporation of large fraction of lipophilic and/or hydrophilic phases [(18)]. 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 [(20).] In case of emulsion, it contains three components, namely oil, water and surfactant; whereas microemulsions generally require a forth component that is co-surfactants, which include alcohol of medium chain length that is miscible with water [(24).]

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Microemulsions have specific physical and chemical properties such as transparency, low viscosity, and homogeneity. Hence, since their discovery, several applications for microemulsions have been implemented in the in industry which includes pharmaceutical drug delivery, enhanced oil recovery and nanoparticle synthesis [(25).] Microemulsions have been widely studied to enhance the bioavailability of poorly water soluble drug. They offer a cost effective approach in such cases [(26).] Poorly aqueous soluble drug need to have solubility in dispersed oil phase to form efficient o/w microemulsion system. Even with increase in oil content in o/w microemulsions leads to increase in droplet size [(27).] 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 ordinary emulsions. 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 group in the aqueous phase. In a microemulsion the domains of the dispersed phase are either globular or interconnected (to give a bicontinuous microemulsion) [(2).]

2. MICROEMULSIONS: POST AND CURRENT STATE

The word microemulsion was originally proposed by Schulman et al. They prepared a quaternary solution of

water, benzene, hexanol, and K-oleate which was stable, homogenous and slightly opalescent. These systems became clear as soon as a short chain alcohol was added. In the years between 1943 and 1965 Schulman and co-workers described how to prepare these transparent systems. Basically a macroemulsion was prepared and the system was then titrated to clarify by adding a second surface active substance (co-surfactant). When the combination of the four components was right, the system cleared spontaneously. Most of the work reported by Schulman dealt with four component system. Schulman had previously published extensively in the field of monolayer's and applied what he had learnt in that field to explain the formation of microemulsions. He proposed that the surfactant and co-surfactant, when properly selected, form a mixed film at the oil/water interface, resulting in an interfacial pressure exceeding the initial positive interfacial tension. To summarize, the basic observation made by Schulman and co-workers that when a co-surfactant is titrated into a coarse microemulsion composed of a mixture of water/surfactant in a sufficient quantity to obtain micro droplet, the result may be a system which is low in viscosity, transparent, isotropic, and very stable. The titration from opaque emulsion to transparent solution is spontaneous and well defined. It was found that these systems are made of spherical micro droplets with a diameter between 600 and 8000 nm. It was only in 1959 that Schulman proposed to call these systems microemulsions. Previously he used terms such as transparent water and oil dispersion, oleophatic hydromicelles or hydropathic oleomicelles [3].

3. TYPES OF MICROEMULSIONS

These are stable system that are broadly categorized into three types

A) Oil-in-water (O/W) microemulsions
B) Water-in-oil (W/O) microemulsions
C) Bicontinuous microemulsions

A) Oil-in-water (O/W) microemulsions:

In Oil-in-water type of microemulsions droplets of oil is surrounded by a surfactant (and may be co-surfactant) film that forms the internal phase distributed in water, which is the continuous phase. This type of microemulsion generally has a larger interaction volume than the w/o microemulsion.

B) Water-in-oil (W/O) microemulsions

In water-in-oil type microemulsion droplets of water surrounded by a continuous oil phase. These are recognized as "reversemicelles", where the polar head groups of the surfactant are facing into the droplets of water, with the fatty acid tails facing into the oil phase. A w/o microemulsion used orally parenteralyy may be destabilized by the aqueous biological system.

C) Bicontinuous microemulsion

In bicontinuous microemulsion system the amount of water and oil present are similar, in case, both water and oil exist as a continuous phase. An irregular channel of oil and water are combined, and looks like a "sponge-phase". Transitions from o/w to w/o microemulsions may pass through this bicontinuous state. Bicontinuous microemulsion, may show non-Newtonian flow and plasticity. These properties make them especially useful for topical delivery of drug or for intravenous administration.

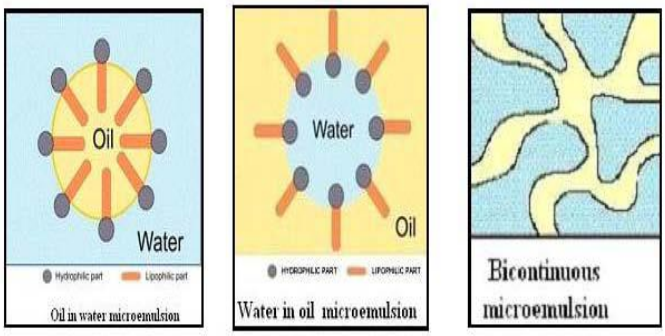

Fig no. 1. Type of microemulsion (28)

4. THEORIES OF MICROEMULSION FORMATION

Historically, three approaches have been used to explain microemulsion formation and stability. They are as follows:

- Interfacial or mixed film theories.
- Solubilization theories.
- Thermodynamic treatments.

The free energy of microemulsion formation can be considered to depend on the extent to which surfactant lowers the surface tension of the oil water interface and change in entropy of the system such that,

$$Gf = \gamma a - Ts$$

Where,

Gf = free energy of formation; A = change in interfacial area of microemulsion; S = change in entropy of the system T = temperature ;γ = surface tension of oil water interphase It should be noted that when a microemulsion is formed the change in A is very large due to the large number of very small droplets formed. In order for a microemulsion to be formed (transient) negative value of was required, it is recognized that while value of is positive at all times, it is very small and it is offset by the entropic component. The dominant favorable entropic contribution is very large dispersion entropy arising from the mixing of one phase in the other in the form of large number of small droplets. However there are also expected to be favorable entropic contributions arising from other dynamic processes such

as surfactant diffusion in the interfacial layer and monomer-micelle surfactant exchange. Thus a negative free energy of formation is achieved when large reductions in surface tension are accompanied by significant favorable entropic change. In such cases, microemulsion is spontaneous and the resulting dispersion is thermodynamically stable [5].

5. ADVANTAGES OF MICROEMULSION SYSTEM

1) Microemulsions are easily prepared and require no energy contribution during preparation this is due to better thermodynamic stability.
2) The formation of microemulsion is reversible. They may become unstable at low or high temperature but when the temperature returns to the stability range, the microemulsion reforms.
3) Microemulsions are thermodynamically stable system and allow self-emulsification of the system.
4) Having the ability to carry both lipophilic and hydrophilic drugs.
5) Microemulsions act as super solvents for drug, can solubilise both hydrophilic and lipophilic drugs including drugs that are insoluble in both aqueous and hydrophobic solvents.
6) The dispersed phase, lipophilic or hydrophilic (O/W, or W/O microemulsions) can act as a potential reservoir of lipophilic or hydrophilic drugs, respectively.
7) The use of microemulsion as delivery systems can improve the efficacy of a drug, allowing the total dose to be reduced and thus minimizing side effects(6).
8) It has low viscosity compared to primary and multiple emulsions.
9) It can improve the efficacy of a drug, minimizing side effects with reduced total dose [22].

6. DISADVANTAGES OF MICROEMULSION SYSTEM

1) Microemulsion having limited solubilizing capacity for high melting substances.
2) Microemulsion require large amount of Surfactants for stabilizing droplets.
3) Microemulsion stability is influenced by environmental parameters such as temperature and pH [6].

7. LIMITATIONS OF MICROEMULSIONS SYSTEM

Factors which limit the use of microemulsion in pharmaceutical applications.

1) The concentration of surfactants and co-surfactants used must be kept low for toxicological reasons.
2) Microemulsion also suffers from limitations of phase separation [21].
3) For intravenous use, the demand of toxicity on the formulation is rigorous and very few studies have been reported so far.
4) Use of those surfactants which are included in "generally regarded as safe" (GRAS) category can reduce toxicity [22].

Table no. 1. Physical characteristics of micelles, microemulsion, emulsion, and liposomes [17]

Delivery system	Advantages	Disadvantages
Micelles	Low viscosity Small droplet size Easy preparation Long shelf life	Low solubillization Potential toxicity of surfactant
Microemulsion	High solubility of drug Small droplet size Easy preparation Long shelf life	Large amount of surfactant Potential toxicity of surfactant Drug solubility influenced by environmental conditions
Emulsion	Small amount of surfactant High solubility of drug into carrier	High viscosity Instability Short shelf life Larger droplets
Liposomes	Made from lecithin and cholesterol also present in the body	High viscosity Difficult to prepare Often disintegrate once administered
Nanoparticles	Long storage life In vaccination, slow degradation in body	Limited solubility of drug Difficult to prepare Difficult to control size Polymer which represents constituent are usually not bioacceptable

Table no 2. Comparison of microemulsion with macroemulsion:

Emulsions (Macroemulsions)	**Microemulsions**
	
Emulsions consist of roughly spherical droplets of one phase dispersed into the other.	They constantly evolve between various structures ranging from droplet like swollen micelles to bi-continuous structure.
They are lyophobic.	They are on the borderline between lyophobic and lipophilic colloids [24].
Droplet diameter: 1 – 20 mm.	10 – 100 nm
Require intense agitation for their formation.	Generally obtained by gentle mixing of ingredients
They may remain stable for long periods of time, will ultimately undergo phase separation on standing to attain a minimum in free energy. They are kinetically stable thermodynamically unstable.	More thermodynamically stable than macroemulsions and can have essentially infinite lifetime assuming no change in composition, temperature and pressure, and do not tend to separate.
Ordinary emulsion droplets, however small exist as individual entities until coalescence or Ostwald ripening occurs.	Microemulsion droplet may disappear within a fraction of a second whilst another droplet forms spontaneously elsewhere in the system.
Most emulsions are opaque (white) because bulk of their droplets is greater than wavelength of light and most oils have higher refractive indices than water.	Microemulsions are transparent or translucent as their droplet diameter are less than ¼ of the wavelength of light; they scatter little light (20).

8. PHARMACEUTICAL FORMULATION OF MICROEMULSIONS:

Components of microemulsion formulations

A large number of oils and surfactants are available which can be used as components of microemulsion system but their toxicity, irritation potential and unclear mechanism of action limit their use. One must choose formulation components that are biocompatible, non-toxic, and clinically acceptable. Again the use of those formulation components is limited to acceptable concentration range. The emphasis is, therefore, on the use of generally regarded as safe (GRAS) excipients.

1 Oils:

These constitute of the oil phase of the emulsions. Various externally applied emulsions, mineral oils, either alone or in combination with soft paraffin or hard paraffin, are widely used for their occlusive and sensory characteristics as well as used as vehicle for the drug. The non-biodegradable mineral and castor oils are widely used in the oral preparations and these provide a local laxative effect, and fish liver oils or various fixed oils of vegetable origin (e.g., arachis, cottonseed, and maize oils) as nutritional supplements. Microemulsion for transdermal delivery of terbina fine was developed by employing oleic acid as oil phase [7].

2 Surfactants:

The amount of surfactant in emulsions is very small, 0.1% to 1.0% of the total emulsion weight. The amount of surfactant in a microemulsion is a minimum of 10% of the total ME weight. Such large surfactant levels are essential because of the large increase in interface area between the aqueous and oil phase. Selection of a proper surfactant is the key to the formation of any Microemulsion. In general, hydrophobic surfactants will be suitable for the formation of w/o microemulsions (ME), and the hydrophilic surfactants will form o/w ME. In industrial applications, it is common to use inexpensive ionic surfactants but in food, pharmaceutical, and cosmetic applications, the ionic surfactant toxicity limits their use. The most common anionic surfactants are the sodium di-isooctylsulfosuccinate (AOT) and the sodium dodecylsulfate (SDS). Nonionic surfactants are very often used in pharmaceutical microemulsion formation. Tweens (ethoxylatedsorbitan esters) are well known and widely used. They are water-soluble and have high HLB values and, therefore, are used mainly for making o/w microemulsions. Ethoxylated (with up to 40 EO units castor oil, ECO-40) and hydrogenated ethoxylated castor oil (HECO) with 8 to 40 EO group attached to the hydroxyl group on the side chain of the triglyceride are regarded a very efficient surfactants [8].

Table no 3: Showing HLB ranges and the typical application of surfactant related to it [19]

HLB value	Application
1-3.5	Antifoams
3.5-8	Water in oil emulsion
7-9	Wetting and spreading agent
8-16	Oil in water emulsion
13-16	Detergents
15-40	Solubilizers

3 Co-surfactant

Co-surfactants play a very important role in microemulsions. They help the surfactant reduce the interfacial tension to very low values to achieve thermodynamic stability. They both modify the curvature of the interface by incorporating additional polar groups and provide more fluidity to the film, preventing crystallization of the tails of the surfactants, which could result in the formation of lyotropic liquid crystals. Co-surfactants are considered to be liquid crystal structure breakers. They are of less help to surfactants with unsaturated (double) bonds in their tails. However, they are especially essential when the surfactant has a saturated tail. In most cases, the co-surfactants are short (ethanol) and medium-chain (propanol, octanol) alcohols. In some pharmaceutical applications (transdermal, ocular), we use mostly those that do not present irritation. Other molecules, such as amino acids and short organic acids, have also been utilized [9].

4 Aqueous phase

This form the aqueous phase of the microemulsion. Commonly used agents are water, alcohol etc. For drugs that cannot be formulated as an aqueous solution, emulsions and microemulsions have typically been cost-effective and provided for ease of administration [10].

9. METHOD OF PREPARATIONS:

A) Phase titration method

B) Phase inversion method

A) 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 emulsions, 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 metastable systems are not included [11].

B) Phase inversion method

Phase inversion of microemulsions is formed either by adding excess of dispersed phase (Phase Inversion Concentration) or in response to temperature (Phase Inversion Temperature). The phase inversion method makes drastic physical changes in the system such as changes in particle size. In phase inversion temperature (PIT) method, the interfacial tension is the key factor. On cooling, the interfacial tension get lowered and can be found in the phase inversion region from water-in-oil (W/O) microemulsion to an oil-in-water (O/W) microemulsion. In the phase inversion region, this low interfacial tension helps in the spontaneous formation of finely dispersed, blue shining O/W PIT microemulsion. In case of nonionic ethoxylated surfactants, as the temperature increases, their hydrophobicity increases strongly therefore all practical applications of PIT microemulsions are based on the use of ethoxylated surfactants. Further, changing the water volume fraction causes a transition in the spontaneous radius of curvature. By continuously adding water into oil, initially water droplets are developed in a continuous oil phase. As the water volume increases, the changes occurred in the spontaneous curvature of surfactant causes transition from a W/O microemulsion to an O/W microemulsion at the inversion point. Since the phase inversion occurs at definite water concentration within the intermediate microemulsion like phase, the resulting emulsion is called phase inversion concentration (PIC) microemulsion. A bicontinuous microemulsion is formed at the inversion points because of the flexible monolayer of short chain surfactants at the O/W interface [23].

10. PSEUDO TERNARY PHASE DIAGRAM

Microemulsion domains are usually characterized by constructing ternary phase diagrams. Three components are the basic requirement to form a microemulsion: two immiscible liquids and a surfactant. The emulsion regions

are usually characterized by constructing ternary-phase diagrams as shown in Figure no. 2. Three components are the basic requirement to form nano-emulsion: an oil phase, an aqueous phase and a surfactant. If a co-surfactant is used, it may sometimes be represented at a fixed ratio to surfactant as a single component, and treated as a single "pseudo-component". The relative amounts of these three components can be represented in a ternary phase diagram. Gibbs phase diagrams can be used to show the influence of changes in the volume fractions of the different phases on the phase behavior of the system. The three components composing the system are each found at an apex of the triangle, where their corresponding volume fraction is 100 %. Moving away from that corner reduces the volume fraction of that specific component and increases the volume fraction of one or both of the two other components. Each point within the triangle represents a possible composition of a mixture of the three components or pseudo-components, which may consist (ideally, according to the Gibbs' phase rule) of one, two or three phases. These points combine to form regions with boundaries between them, which represent the "phase behavior" of the system at constant temperature and pressure [12].

The series of concentrations of oils, Surfactants, and Co-surfactants were used to construct the system. A visual observation was made immediately for spontaneity of emulsification, phase separation and precipitation. Twenty compositions of each group with varying concentrations were prepared in this investigation. The methods are used to plot Ternary phase diagrams are namely Dilution method and Water Titration method [13].

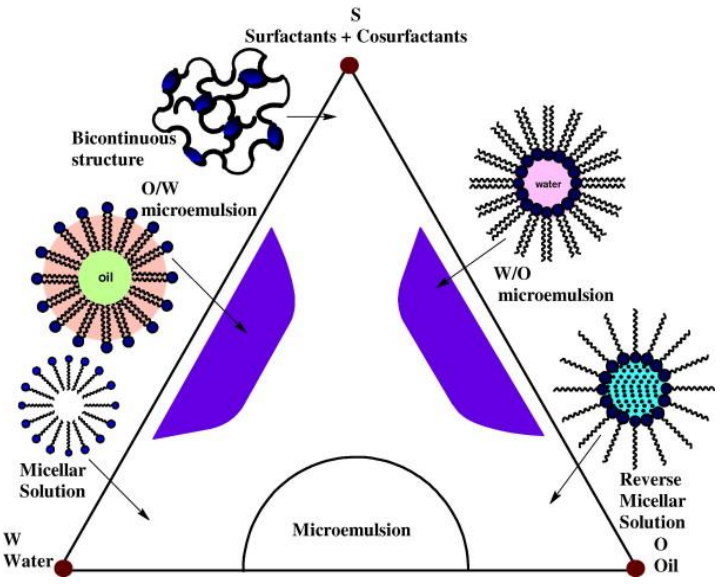

Fig no. 2: Constructing ternary-phase diagrams

11. DILUTION METHOD

Ternary mixtures with varying compositions of surfactant, co-surfactant and oil will be equipped. The surfactant concentration will diverge from 30 to 75% (w/w), oil concentration will diverge from 25 to 75% and co-surfactant concentration will diverge from 0 to 30% (w/w). For any mixture, the total of surfactant, co-surfactant and oil concentrations always added to 100%. For example, in the experiment, first mixture consisted of 75% of surfactant, 25% of the oily phase and 0% of co-surfactant [14]. Further, the co-surfactant was increased by 5% for each composition, oily phase concentration will keep constant and the surfactant concentration will adjust to make a total of 100%. Forty-two such mixtures with varying surfactant, co-surfactant and oil concentrations will prepare. The percentage of surfactant, co-surfactant and oil used herein will decide on the basis of the requirements. Compositions are evaluated for nano-emulsion formation by diluting appropriate amount of mixtures with appropriate double distilled water. Globule size of the resulting dispersions will be determined by using spectroscopy technique. Dispersions, having globule size 200 nm or below will consider desirable. The area of nano-emulsion formation in Ternary phase diagram will identified for the respective system in which nano-emulsions with desire globule size were obtain [15].

12. CHARACTERIZATION OF MICROEMULSION:

a) Viscosity:

Viscosity is measure by Brookfield rotational viscometer. Viscosity provides an indication of rod like or worm like micelles and type of microemulsion.

b) pH

Digital pH meter is the instrument use for measurement of pH of microemulgel and results are taken into triplicate then averages of the results are taken into consideration. The pH of microemulsion is also required to because change in pH may affect zeta potential and finally affect the stability of product.

c) Drug content determination:

Drug content in microemulgel will be measured by dissolving 1gm of microemulgel in solvent by sonication. Absorbance will be measured after dilution at λmax nm using UV Spectrophotometer.

d) Centrifugation:

Centrifugation will be measured to evaluated physical stability of microemulsion. Microemulsion will be centrifuged at ambient and 500 rpm for 10-60 min to evaluated the system for creaming pr phase separation. System will be observed visually for appearance.

e) Conductivity:

Conductivity measurement using Digital conductometer provide a means of determining whether the

microemulsion is oil continuous or water continuous. The results are taken into triplicate and average is taken [29].

f) Dilution test:

If continuous phase into microemulsion, it will not crack or separate into phases. A total inyo 50 to 100 aqueous dilution of microemulsion are carried out and visually checked for phase separation and clarity. Result are into triplicate and average is taken.

g) % Transmittance Measurement

The % transmittance of formulation was measured using UV visible spectrophotometer at a specific wavelength using UV visible spectrophotometer against continuous phase as blank. Microemulsion will be diluted 50-100 with continuous phase. Results are taken into triplicate and average is taken.

h) Zeta potential and particle size analysis:

Particle size, size distribution and potential of microemulsion will be determined using particle size analyzer.

i) Refractive index

Refractive index of microemulsion is measured by digital Abbe Refractometer.

j) Osmolarity determination:

Osmolarity of microemulsion is measured by following aguation:

mOsm/L = [concentration (g/L)/ molecular weight]x 100. [16]

13. CONCLUSION

Microemulsions are clear, thermodynamically stable, isotropic liquid mixture of oil, water and surfactant, frequently in combination with a cosurfactant. The role of microemulsion in providing novel solutions to overcome the problems of poor aqueous solubility of highly lipophilic drug compounds and provide high, more consistent and reproducible bioavailability. Microemulsions have more advantages, but have some disadvantages and limitations. It has the ability to protect labile drug, control drug release, increase drug solubility, increase bioavailability and reduce patient variability. Microemulsion evaluated by various parameters.

14. ACKNOLEDGEMENT

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