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Microemulsion: Current Trends in Novel Drug Delivery System

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ABSTRACT:
Microemulsion are thermodynamically stable, waterproof, and amphiphilic, making them ideal for novel drug delivery systems. It has long shelf life. They have emerged as new drug delivery vehicles that provide controlled or sustained release for ocular, transdermal topical, transdermal, and parenteral administration of drug. Microemulsions are easily distinguishable from regular emulsions due to their low viscosity, high transparency and especially high thermodynamic stability. Microemulsion have a wide range of uses and applications. Pharmaceuticals, agrochemicals, cutting oils, biotechnology, food, cosmetics, analytical application, environmental detoxification and more. The term "microemulsion" refers to a thermodynamically stable, isotopically transparent dispersion of two immiscible liquids, such as oil and water, stabalized by and interfacial film of surfactant molecules.

KEYWORDS:
Microemulsion, Surfactant, Novel Drug Delivery System.

I. INTRODUCTION

The concept of microemulsions was introduced by Hoar and Schulman in the 1940s. Hoar and Schulman produced clear, single-phase solutions by grinding milky emulsions with hexanol [1]. Alternate names for these systems arecommonly used: B. Swollen micelles, clear emulsions, solubilized oils and micellar solutions. A mixture of at least three components is called a microemulsion. Oil phase, water phase and surface-active species, so-called surfactants. In some cases, a fourth component, i.H. co-surfactant. The application of drug-containing formulations to the skin to directly treat skin diseases can be characterized as topical drug delivery Topical administration is generally used in cases where other routes, such as oral, sublingual, rectal, parenteral or local infections, such as fungal infections, have failed. Human skinis a remarkable organ that supports life on Earth by controlling the loss of body heat and wate and preventing the entry of harmful substances or germs. The microemulsion is a bicontinuous system and consist primarily bulk phase of water and oil and Surfactant/cosurfactant-rich interfacial region [2].

These systems have advantages over conventional emulsions in that they are thermodynamically stable liquid systems and are spontaneously formed [3]. Another important parameter that influences the main properties of microemulsions, depending on the type of surfactants used to prepare them, is the presence of electrolytes in the aqueous phase Microemulsions are thermodynamically transparent, stable, isotropic liquid mixture of oil, water, and surfactants in combination with co-surfactants . These systems also offer several advantages for oral administration, including increased absorption, improved clinical efficacy, and reduced toxicity [4].

II. HISTORY AND TERMINOLOGY

Work by Hoar and Schulman in 1943 reported spontaneous emulsions of water and oil when adding strong surfactants, but microemulsions were not really recognized. The term "microemulsion" has often been debated to characterizethese systems. Although not used systematically today, some people prefer "swollen micelles" or "micelle emulsions" [5].

Microemulsions were probably discovered much earlier than Shulman's work. At the beginning of the last century, Australian housewives mixed the liquid wax discovered by Rodwald in 1928 with water and eucalyptus oil/soap flakes/alcohol to wash wool. Interest in microemulsions grew in the

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late 1970s and early 1980s as the recognition that these systems had the potential to improve oil recovery and the price of oil made tertiary recovery processes a profitable process. It startedin earnest when I reached a certain level [6]. This is no longer the case, but 60 microemulsions have been added. B. Catalysis, submicron particle generation, solar energy conversion, and liquid-liquid extraction have been identified (minerals, proteins, etc.). This topic is important enough to keep many Scientists use it in conjunction with traditional applications in cleaning and lubrication.

Over the past two decades, our knowledge of microemulsion properties has evolved significantly from a fundamental scientific perspective. In particular, novel and powerful methods such as small-angle neutron diffusion have enabled us to study interfacial film stability and microemulsion structure in detail Thefollowing sections discuss basic microemulsion properties such as formation andstability, surfactant films, gradations, and phase behavior.

STRUCTURE OF MICRO EMULSION

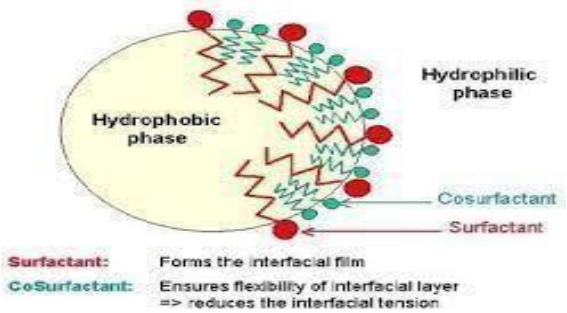

Fig.1: Structure of Microemulsion

Micro emulsions **(Fig. 1)** or Micellar emulsion are dynamic system in which the interface is continuously and spontaneously fluctuating [7]. Structurally, they are divided in to oil in water (o/w), water in oil (w/o) and bi-continuous micro emulsions. In w/o micro emulsions, water droplets are dispersed in the continuous oil phase while o/w micro emulsions are formed when oil droplets are dispersed in the continuous aqueous phase. In system where the amounts of water and oil are similar, the bi-continuous micro emulsions may result [8].

The mixture oil water and surfactants are able to form a wide variety of structure and phase depending upon the proportions of component. In a structure split into oil into water (o/w), oil water (w/o) and bilateral microemulsions. microemulsions or micellar emulsions are dynamic systems in which the interface is fluctuated constantly and spontaneously [9]. Water droplets are distributed inthe continuous oil phase in w / w of micro-emulsions during the continuous aqueous phase of the oil droplets. The two-continuous microemulsions may occur in systems with comparable quantities of water and oil [10] . The combination ofoil water and surfactants can create a broad range of phases and structures depending on the component quantities.

CHARACTERISTICS OF MICROEMULSION:

A well-defined oil-water system should be created when a surfactant with a balance of hydrophilicity and lipophilicity is used at the right concentration. Although the system remains an emulsion, it has a different function than the milk emulsion mentioned above. These are "microemulsions". There are interfacial tension between phases and energy required for formation, low viscosity for droplet size and Newtonian flow characteristics. The heat flow remains constant when exposed to a range of shear rates. Some non-Newtonian flows and plasticity may exhibit discontinuous formulations. Even at high droplet levels, micro- emulsion viscosity is near to water. This continually alters the microstructure, creating highly dynamic systems with reversible gout coalescence. A number of approaches are used to characterize distinct micro-emulsion characteristics. We employed extensively light dispersion, X-ray diffraction, UC, electrical conductivity and viscosity tests [11]

CLASSIFICATION OF MICRO EMULSION [12-14]

According to Winsor **(Fig 2),** there are four types of micro emulsion phases existsin equilibrium, these phases are referred as Winsor phases. they are:

- Winsor I (two phase system): upper oil layer exists in equilibrium with lower (o/w) micro emulsion phase
- Winsor II (two phase system): the upper (w/o) micro emulsion exists in equilibrium with lower excess water.
- Winsor III (three phase system): middle bi-continuous phase of o/w and w/o

called) exists in equilibrium with upper phase oil and lower phase water.

- Winsor IV (single phase system): it forms homogenous mixture of oil, water and surfactant.

The R-ratio is one of the characterization concepts which were first proposed by Winsor to explain the influence of amphiphiles and solvents on interfacial

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curvature. R-ratio compares the affinity for an amphiphile to disperse into oil, to its affinity to dissolve in water.

Fig. 2 : Classification of Microemulsion

TYPES OF MICROEMULSIONS [15-18] :

Microemulsions are thermodynamically stable but only found under carefully
defined conditions. According to Winsor, four types of microemulsion phases exist in equilibrium and these phases are also called his Winsor phases. They are,

1. Oil- in- water microemulsion or winsor I.
2. Water – in oil microemulsion or winsor II.
3. Bicontinuous microemulsion or winsor III.
4. Single phase homogeneous mixture or winsor IV.

1. Oil- in- water microemulsion (winsor I) :

In oil-in-water microemulsions, the oil droplets are surrounded by a surfactant film(and sometimes a co-surfactant) that forms an internal phase that disperses in the continuous phase, water. This type of microemulsion typically has a larger interaction volume than w/o microemulsions.

2. Water - in - oil microemulsion (winsor II) :

In Water-in-oil type of microemulsions droplets of water surrounded by a
continuous oil phase. These are recognized as "reverse micelles", where the polar headgroups 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 or parenterally may be destabilized by the aqueous biological system.

3. Bicontinuous microemulsion (winsor III) :

In bicontinuous microemulsion system the amount of water and oil present are similar, In this 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 ofdrugs or for intravenous administration.

4. Single phase homogeneous mixture (winsor IV):

In single phase homogeneous mixture or winsor IV the oil, water and surfactants are homogenously mixed.

ADVANTAGES OF MICROEMULSION SYSTEM [19-24]

1. Microemulsions are easy to prepare and have excellent thermodynamic stability, requiring no energy input during preparation.
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 allows self- emulsification of the system.
4. Microemulsions have low viscosity compared to emulsions.
5. Microemulsion act as super solvents for drugs and can dissolve both hydrophilic and lipophilic drugs, including drugs that are insoluble in both aqueous and hydrophobic solvents.
6. Having the ability to carry both lipophilic and hydrophilic drugs.
7. The dispersed phase, lipophilic or hydrophilic (O/W, or W/O microemulsions) can act as a potential reservoir of lipophilic or hydrophilic drugs, respectively.

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8. 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.

DISADVANTAGES OF MICROEMULSION SYSTEMS

1. Having limited solubilizing capacity for high melting substances.
2. Require large amount of Surfactants for stabilizing droplets.
3. Microemulsion stability is influenced by environmental parameters such as temperature and ph.

BASIC DIFFERENCE BETWEEN ANDMICROEMULSION [25-27]

Table 1:Difference Between Macroemulsion and Microemulsion.

Sr.	MACROEMULSION	MICROEMULSION
1.	They are lyophobic in nature	They are the boundaries between lyophilic and lyophobic.
2.	Droplet diameter 1-20 mm.	Droplet diameter 10-100 mm.
3.	Macroemulsion droplets exist as individual entities	Microemulsion droplets disappear within fraction of seconds.
4.	Emulsion droplets are roughly spherical droplets of one phase dispersed in another.	Microemulsions are a variety of droplet structures ranging from bicontinuous to swollen micelles.
5.	Macroemulsions requires quick agitation for their formation.	Microemulsions are obtained by gentle mixing of ingredients.

INGREDIENTS OF MICROEMULSION [28-30]

Various ingredients are used in the formulation and development of microemulsions. Mainly oil and surfactants are used in microemulsion they should be biocompatible, non-toxic and clinically acceptable. Main components of microemulsion are

1. Oil phase
2. Aqueous phase
3. Surfactant
4. cosolvent

1) Oil phase [31]

Oil is one of the most important components of microemulsions as it can solubilize the required dose of lipophilic drugs and increase the proportion of lipophilic drugs transported through the intestinal lymphatic system. Oils are defined as liquids with low polarity and low miscibility with water. Examples of such phases are cyclohexane, mineral oil, toluene, vegetable oil, etc.

2) Aqueous phase

Generally, the aqueous phase contains hydrophilic active ingredients and preservatives. Buffers are sometimes used as the aqueous phase.

3) Surfactant [32]

The term surfactant (surface-active-agent) denotes a substance which exhibits some superficial or interfacial activity & used to lower the surface or interface tension. It has affinity for polar & nonpolar solvents. Surfactants are the molecules that contain a polar head group and a polar tail. Surfactant molecules self-associate due to various inter- and intra-molecular forces as well as entropy considerations. For example, when surfactant is mixed with oil and water, they accumulate at the oil/water interface, because it is thermodynamically favorable.

The surfactant molecules can arrange themselves in a variety of shapes. They can form spherical micelles, a hexagonal phase, lamellar (sheet) phases, rodshaped micelles, reverse micelles, or hexagonal reverse micelles. At low concentrations of dispersed (internal) phase, spherical, isolated droplets are present in the microemulsions. The various types of surfactants that help in the progressive development of microemulsion system are

i. Cationic
ii. Anionic
iii. Non-ionic
iv. Zwitterionic surfactants.

i.Cationic

Upon contact with water, cationic surfactants transform into amphiphilic and anionic forms, mostly halogen forms. A very large proportion of this class corresponds to nitrogen compounds such as quaternary ammonium compounds and long-chain alkyl aliphatic amine salts, often derived from natural fatty acids.

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The most well-known examples from the cationic surfactant class are hexadecyl trimethylammonium bromide and didodcecyl ammonium bromide. These surfactants are in general more expensive than anionics.

ii.Anionic surfactant

When anionic Surfactants are dissociated in water in an amphiphilic anion, and a cation, which is in general an alkaline metal (Na, K) or a quaternar ammonium. These are the most commonly used surfactants. The anionic charge in these surfactants comes from the ionized carboxyl group. Anionic surfactants account for about 50 % of the world production. Alkali alkanoates, also known as soaps, are the most common anionic surfactants. This is the most well-known type of surfactant when it comes to their shape and function. The three most important anionic groups in all of these surfactants are carboxylate, sulfonate and sulfate groups.

iii.Non-ionic surfactant

Non-ionic surfactant is stabilized by dipole and hydrogen bond interactions with the hydration layer of water on its hydrophilic surface. They do not ionize in aqueous solution, because their hydrophilic group is of non-dissociable type, suchas phenol, alcohol, ester, or amide. A large proportion of these nonionic surfactants are made hydrophilic by the presence of a polyethylene glycol chain.

iv.Zwitterionic surfactant

Zwitterionic surfactants contain both positively and negatively charged groups and form microemulsions upon the addition of co-surfactants. Phospholipids, such as lecithin derived from soybeans and eggs, are common zwitterionic surfactants. Lecithin, which is based on diacylphosphatidylcholine, exhibits excellent biocompatibility, unlike other toxic ionic surfactants. Anotherimportant class of zwitterionic surfactants is the betaines, such as the alkyl and heterocyclic betaines.

4.Cosolvent [33]

It has been observed that single-chain surfactants are unable to reduce the o/w interfacial tension sufficiently to form a microemulsion. The addition of co- surfactants allows the interfacial film to be flexible to take up different curvatures required to form microemulsion over a wide range of excipients.

If a single surfactant film is desired, the lipophilic chains of the surfactant should be sufficiently short, or contain fluidizing groups (e.g. unsaturated bonds). Basic co-surfactants are short chain alcohols (ethanol to butanol), glycols such as propylene glycol, medium chain alcohols, amines or acids. The use of co- surfactant is to destroy liquid crystalline or gel structures that come in place of amicroemulsion phase.

PREPARATION METHOD OF MICRO-EMULSION [34-35]

Following are the method used for the preparation of the micro emulsion:

1) Phase titration method:
2) Phase inversion method:

1) Phase Titration Method :

Micro emulsions 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. Micro emulsions 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 micro emulsion 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 micro
emulsion by simply considering the composition that is whether it is oil rich or water rich. Observations should be made carefully so that the metastable systems are not included.

2) Phase Inversion Method:

Microemulsion phase inversion occurs as a result of the addition of excess dispersed phase or as a function of temperature. Dramatic physical changes occur during phase inversion, including changes in particle size that can affect drug release both in vivo and in vitro. These methods take advantage of the changes in the natural curvature of surfactants. The use of nonionic surfactants does this by changing the temperature of the system and forcing a transition from o/w microemulsion at low temperature to w/o microemulsion at high temperature (transitional phase inversion). It can be achieved. During cooling, the system passes through points of minimum surface tension with no spontaneous curvature, promoting the formation of finely divided oil droplets. This method is called the Phase Inversion Temperature (PIT) method. Instead of temperature, other parameters such as salt

concentration or pH can also be considered. Moreover, transitions in the spontaneous radius of curvature can be achieved by changing the volume fraction of water.

Continuous addition of water to oil initially produces water droplets in the continuous oil phase. Increasing the water volume fraction changes the spontaneous curvature of the surfactant from an initial stabilization of the w/o

microemulsion to an o/w microemulsion at the inversion site. Short-chain surfactants form flexible monolayers at the o/w interface, leading to inversion and discontinuous microemulsions.

THEORIES OF MICRO EMULSION FORMATION [36-37]

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

a) Interfacial or mixed film theories
b) Solubilization theories
c) Thermodynamic treatments

The free energy of micro emulsion 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 = γ a - T S

Where,

Gf = free energy of formation

A = change in interfacial area of micro emulsion S = change in entropy of the system

T = temperature

γ = surface tension of oil water interphase.

When the microemulsion is formed, the variation of A is very large due to the formation of many very small droplets. Although the value of A is always positive, it is known to be very small and cancled out by the entropic component,

so a (temporary) negative value was needed to form a microemulsion. The dominantfavorable entropy contribution is the very large dispersive entropy resulting from the mixing of the phase, which is in the form of numerous small

droplets, into the other phase. However, we also expect that there are favorable contributions to the entropy arising from other dynamic processes, such as surfactant diffusion at the interfacial layer and surfactant exchange between monomers and micelles.

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, micro emulsion is spontaneous and the resulting dispersion is thermodynamically stable.

FACTOR AFFECTING MICROEMULSION[38-40] :

Factor affecting the micro-emulsion are as follows Ø

- Packing ratio [41]
- Surfactant properties
- Property of oil phase
- Temperature [42]
- Chain length
- Types of co-surfactants

APPLICATION OF MICROEMULSION

The application of micro-emulsion is given as follows Ø

- Oral delivery system
- Parental delivery system
- Ophthalmic delivery system
- micro-emulsion in detergency
- micro-emulsion in cosmetics
- micro-emulsion in food .

III. CONCLUSION

Microemulsions are drug delivery systems for the simultaneous delivery of multiple drugs. Microemulsions protect labile drugs, control drug release, enhance drug solubility, enhance bioavailability, and reduce patient variability. It has also been proven that formulations suitable for most routes of administration can be formulated. The role of microemulsions in providing a new solution to overcome the problem of poor water solubility of highly lipophilic drug compounds and to provide more consistent and reproducible bioavailability. Microemulsion drug delivery is a promising area for further research aimed at achieving controlled release with improved bioavailability and targeted drug delivery to different sites in the body.

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