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A REVIEW ON MICROEMULSION FOR DRUG DELIVERY SYSTEM

Sagar R. Wagh, Mayur B. Patil, Aparna S. Musale, Harshal D. Mahajan, Rajendra D. Wagh

DCS's A.R.A. College of Pharmacy, Dhule, Maharashtra 424005.

***Corresponding Author: Sagar R. Wagh**

DCS's A.R.A. College of Pharmacy, Dhule, Maharashtra 424005.

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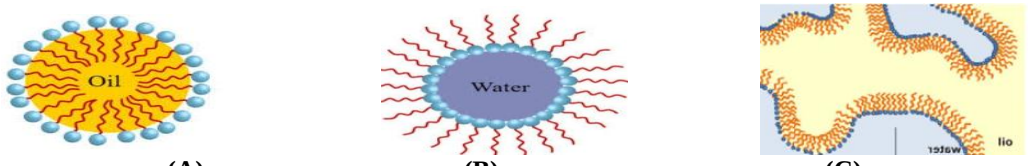
ABSTRACT

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.In addition, the size of the droplets in such microemulsions remains constant and ranges from 100-1000 A0(10-100 nm), and has very low oil/water interfacial tension. Because the droplet size is less than 25% of the wavelength of visible light,microemulsions are transparent.[1,2]

KEYWORDS: Microemulsion, Surfactants, Co-surfactants, oils, Bioavailability.

Three distinct microemulsion solubilization systems that can be used for drugs are as follows:

1) Oil in water Microemulsion where in oil droplets aredispersed in the continuous aqueous phase,
2) Water in oil microemulsions where in water droplets are dispersed in the continuous oil phase,
3) Bi-continuous microemulsions where in microdomains of oil and water are interspersed within the systems.



(A) **(B)** **(C)**

Fig. 1: (A) oil-in-water microemulsion (B) water-in-oil microemulsion (C) Bi-continuous microemulsions.[4]

All three types of microemulsions, the intebilized by an appropriate combination of surfactants and/or co-surfactants.[3]

Definition of Micro-Emulsion

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

INTRODUCTION

Microemulsions are clear, stable, isotropic liquid mixtures of oil, water and surfactant, frequently in combination with a co-surfactant. 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 two basic types of microemulsions are direct (oil dispersed in water, o/w) and reversed (water dispersed in oil, w/o).[5-6] The microemulsion concept was introduced in 1940s by Hoar and Schulman who generated a clear single-phase solution by triturating a milky emulsion with hexanol [7]. They prepared the first microemulsion by dispersing oil in an aqueous surfactants solution and adding an alcohol as a co-surfactant, leading to transparent stable formulation. Microemulsion is defined as microemulsion are clear, transparent, thermodynamically stable dispersions of oil and water, stabilized by an interfacial film of surfactant frequently in combination with a co-surfactant [2].Alternative names for these systems are often used, such as swollen micelle, transparent emulsion, solubilized oil and micellar solution. Microemulsions are

bi-continuous systems that are essentially composed of bulk phases of water and oil separated by a surfactant/co-surfactant rich interfacial region.[8] The term of micro emulsion applies to a mixture with at least three components; an oily phase, an aqueous phase and a surface active species, so called surfactants. Sometimes the forth component i.e., co-surfactant can/must be present. Depending on the ratios between the components, in the two extremes the microstructure of the micro emulsions vary microstructure of the micro emulsions vary from a very tiny water droplets dispersed in oil phase (w/o micro emulsion) to a oil droplets dispersed in water phase (o/w micro emulsion).

Advantages of Microemulsion system.[9-12]

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.
3. They may become unstable at low or high temperature but when the temperature returns to the stability range, the microemulsion reforms.
4. Microemulsions are thermodynamically stable system and allows self-emulsification of the system.
5. Microemulsions have low viscosity compared to emulsions.
6. Microemulsions act as super solvents for drug, can solubilize both hydrophilic and lipophilic drugs including drugs that are insoluble in both aqueous and hydrophobic solvents.
7. Having the ability to carry both lipophilic and hydrophilic drugs.
8. The dispersed phase, lipophilic or hydrophilic (O/W, or W/O microemulsions) can act as a potential reservoir of lipophilic or hydrophilic drugs, respectively.
9. 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[9-11]

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.

Types of Microemulsions[13-16]

Microemulsions are thermodynamically stable, but are only found under carefully defined conditions. According to Winsor, there are four types of microemulsion phases exists in equilibria, these phases are also referred as Winsor phases. They are,

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

Oil- in- water microemulsion or winsor I

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 microemulsions.

Water - in - oil microemulsion or winsor II

In Water-in-oil type of microemulsions droplets of water surrounded by a continuous oil phase. These are recognized as "reversemicelles", 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.

Bi-continuous microemulsion or winsor III

In bi-continuous 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 bi-continuous state. Bi-continuous microemulsion, may show non-Newtonian flow and plasticity. These properties make them especially useful for topical delivery of drugs or for intravenous administration.

Single phase homogeneous mixture or winsor IV

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

Methods of Preparation[17]

- **Dry Gum Method**: Triturate mixture of emulsifier and oil with addition of water which will form primary emulsion. Further add water to dilute and mix continuously to form emulsion.
- **Wet Gum Method:** Initially triturate oil with water and then with emulsifier to form primary emulsion. Further add water, dilute and mix to form emulsion.
- **In Situ Soap Method:** Take oil and lime water (calcium hydroxide solution). Mix with stirring to form emulsion.
- **Mechanical Method:** Take oil, water and emulsifier together, mix well and stir by machine to form emulsion.

Comparison between Microemulsion & Emulsion

Sr.	Emulsion	Micro-emulsion
1.	Emulsion is Biphasic	Micro-emulsion is Monophasic
2.	Stability is Thermodynamically unstable but Kinetically stable	Stability is Thermodynamically stable but Kinetically unstable
3.	Droplet size about >500 nm	Droplet size about 20-200 nm
4.	Structure of micro-emulsion Static in nature	Structure of micro-emulsion Dynamic in nature
5.	Interfacial tension is High	Interfacial tension is low
6.	Appearance of emulsion is cloudy	Appearance of emulsion is transparent

Composition

The major components of micro emulsion system are:
1) Oil phase
2) Surfactant (Primary surfactant)
3) Co-surfactant (Secondary surfactant)
4) Co-Solvent

Oil phase

Oil phase is second most important vehicle after water due to its properties to solubilize lipophilic drug molecules and improve absorption through lipid layer present in body[18]. Oil has unique property of penetrating cell wall and hence very useful for lipophilic active drug delivery. Swelling of tail group region of the surfactant is influence by oil phase. Such penetration is to greater extent in case of short chain alkanes as compared to long chain alkanes.[19].
Example;

Saturated fatty acids: lauric, myristic and capric acid
Unsaturated fatty acids: oleic acid, linoleic acid and linolenic acid
Fatty acid esters: ethyl or methyl esters of lauric, myristic and oleic acid

Surfactants

During the preparation of the microemulsion, surfactant must be able to reduce the interfacial tension nearest to zero to facilitate dispersion of all components. These surfactants can be:
Non-ionic
Anionic
Cationic
Zwitterionic,
Nature of surfactants helps in deciding stability of microemulsion. Dipole and hydrogen bond interactions stabilizes non-ionic surfactant and electrical double layer stabilizes ionic surfactants. Ionic surfactants are also affected by salt concentration.

Examples of non-ionic surfactants

Polyoxyl 35 castor oil (Cremophor EL)
Polyoxyl 40 hydrogenated castor oil (Cremophor RH 40)
Polysorbate20(Tween20)
Polysorbate80(Tween80)
d-α-tocopherolpolyethylene glycol1000succinate(TPGS)
SolutolHS-15
Sorbitanmonooleate(Span80)
Polyoxyl40 stearate etc.

Co-surfactants

It is studied that high concentrations of single-chain surfactants are required to reduce the O/W interfacial tension to a level to enable a spontaneous formation of a microemulsion. However, if co-surfactants are added then with minimum concentration of surfactants different curvatures of interfacial film can be formed to generate stable micro emulsion composition.[20-25] Co surfactants raises the fluidity of the interface due to presence of fluidizing groups like unsaturated bonds, then demolishes liquid crystalline or gel structure and alters the HLB value in such way to cause spontaneous formation of micro emulsion.

Example

Short chain alcohols like ethanol to butanol
Short chain glycols like propylene glycol
Medium chain alcohols like amines or acids

Co-solvents

Co-solvents are organic solvents like ethanol, propylene glycol (PG), and polyethylene glycol (PEG) which helps to dissolve relatively high concentrations of surfactants as well as lipid soluble drugs. Hence co-solvents are also considered as co-surfactants.

Theories of Micro Emulsion Formation[26,27]

Historically, three approaches have been used to explain micro emulsion formation and stability. They are as follows-
1- Interfacial or mixed film theories.
2- Solubilization theories
3- 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,

$$Gf = \gamma a - T S$$

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 micro emulsion is formed the change in A is very large due to the large number of very small droplets

formed. In order for a micro emulsion to be formed (transient) negative value was required, it is recognized that while value of A 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, micro emulsion is spontaneous and the resulting dispersion is thermodynamically stable.

Limitations

Some factors limit the use of microemulsion in pharmaceutical applications.

1. The need of pharmaceutically acceptable ingredients limits the choice of microemulsion components (e.g., oil, surfactant and co-surfactants) leading to difficulties in formulation.
2. The concentration of surfactants and co-surfactants used must be kept low for toxicological reasons.
3. Microemulsion also suffers from limitations of phase separation.
4. For intravenous use, the demand of toxicity on the formulation is rigorous and very few studies have been reported so far.
5. The major limitation is the toxicity of excipients i.e. surfactant/ co-surfactants. Exploration of safe excipients and evaluation of the toxicity parameters of available excipients may help in further expansion of research in this field.

Identification Tests for Microemulsion

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 Microemulsions 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.

Factors Affecting Microemulsions[28,29,30]

Factor affecting the micro-emulsion are as follows

a) Packing ratio
b) Property of surfactant
c) Property of oil phase
d) Temperature
e) Chain length
f) Nature of co-surfactant

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 here in.

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 solubilization 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 lipophilic and 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 co-surfactants, 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 target ability 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 muco-adhesive 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.

CONCLUSION

Microemulsion is drug delivery systems for the delivery of more than one medicament simultaneously. Microemulsion protect labile drug, control drug release, increase drug solubility, increase bioavailability and reduce patient variability also it has proven possible to formulate preparations suitable for most routes of administration. 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. The drug delivery through the microemulsion is a promising area for the continued research with the aim of achieving the controlled release with enhanced bioavailability and for drug targeting to various sites of the body.

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