International Standard Serial Number (ISSN): 2319-8141
International Journal of Universal Pharmacy and Bio Sciences 3(2): March-April 2014
INTERNATIONAL JOURNAL OF UNIVERSAL PHARMACY AND BIO SCIENCES
*IMPACT FACTOR 1.89****
*ICV 5.13****
Pharmaceutical Sciences **REVIEW ARTICLE……!!!**

MICROEMULSIONS: NOVEL DRUG DELIVERY SYSTEMS

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KEYWORDS:
Microemulsion, drug delivery, ternary phase diagram.

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ABSTRACT

Microemulsions are isotropic, thermodynamically stable, transparent (or translucent) systems prepared of oil, water and surfactant, frequently in combination with a co surfactant. Droplet size of microemulsion usually in the range of 20-200 nm. Microemulsions can be classified as oil-in-water (o/w), water-in-oil (w/o). These systems provide protection against, enzymatic hydrolysis and improve the solubilization of lipophilic drugs to enhance their bioavailability. In addition to oral and intravenous drug delivery they are widely used for sustained and targeted drug delivery through ophthalmic, nasal and transdermal use.

INTRODUCTION:

Recently, there has been an increased interest for the microemulsions, for the delivery of hydrophilic and lipophilic drug as drug carriers because of its improved drug solubilization, longer shelf life, ease of preparation and improvement of bioavailability of poorly soluble drugs [1]. A microemulsion system generally consists of four components, a lipophilic phase, a hydrophilic phase, surfactant and co-surfactant. The nature of the components of the system like oil, surfactant, co-surfactant and water, also temperature and pressure which affect the microemulsion systems are known as the formulation variables [2]. Interest in this field is increasing and their applications have been diversified to various administration routes in addition to the conventional oral route. Microemulsion has drawn attention for their use as novel vehicles for drug delivery. Microemulsion systems are also now being widely used for transdermal, ocular, nasal, and intravenous drug delivery [3].

Advantages of Microemulsion:

1. Microemulsions are thermodynamically stable system and the stability allows self-emulsification of the system whose properties are not dependent on the process used for manufacturing.
2. The dispersed phase lipophilic or hydrophilic (oil in water or water in oil microemulsions) behaves as a potential reservoir of lipophilic or hydrophilic drug,. Drug partitions between two phases, and when the system comes in contact with a semi permeable membrane, can be transported through the membrane effectively. Some microemulsions can carry both lipophilic and hydrophilic drugs.
3. Because of thermodynamic stability, microemulsions are easy to prepare. Microemulsions have low viscosity as compared to emulsions.
4. The use of microemulsion drug delivery systems can improve the efficacy of a drug [4].

Disadvantages of Microemulsion:

Use of a large amount of surfactant and co-surfactant required for stabilizing the droplets.

1. Limited solubilizing capacity for high-melting substances.
2. The surfactant must be nontoxic for using in pharmaceutical formulations.
3. Microemulsion stability is influenced by environmental parameters such as temperature and pH [5].

Table 1: Difference between Emulsion and Microemulsion

Sr. No	Characters	Emulsion	Microemulsion
1.	Appearance	Cloudy	Transparent (or translucent)
2.	Optical isotropy	Anisotropic	Isotropic
3.	Interfacial tension	High	Ultra low
4.	Microstructure	Static	Dynamic
5.	Droplet size	>500 nm	20-200 nm
6.	Stability	Thermodynamically unstable	Thermodynamically stable
7.	Phases	Biphasic	Monophasic
8.	Cost	Higher cost	Lower cost
9.	Viscosity	High viscosity	Low viscosity

Components of Microemulsion system:

The main components of microemulsion formulation are:

1) Oil phase

2) Surfactant

3) Secondary surfactant (co-surfactant)

1) Oil phase:

The oil represents most important excipients in the formulation because of it solubilizes the required dose of lipophilic drug that can increase the fraction of lipophilic system thereby increasing absorption from GIT depending upon the molecular weight of triglycerides. The oil component influences structure by its ability to penetrate and hence swell the tail group region of the surfactant monolayer. Short chain oils penetrate the tail region to a greater extent than long chain alkenes.

Table 2: Examples of commonly used oil phases

Vegetable Oils	Corn oil, Soyabean oil, Olive oil
Medium Chain Triglycerides	Glyceryl tricaprylate/caprate: captex 355
Mono/ Diglycerides	Glyceryl caprylate/caprate: Capmul MCM
Fatty acids	Oleic acid
Propylene glycol esters	Capmul PG 8, Propylene glycol monolaurate

2) Surfactants:

The surfactants must be able to lower the interfacial tension to a very small value which enhances dispersion process during the preparation of the microemulsion and provide a flexible film that can readily deform around the droplets and be of the appropriate lipophilic character to provide the correct curvature at the interfacial region.

Surfactants used in microemulsion system can be:

(i) Non-ionic,

(ii) Zwitterionic

(iii) Cationic, or

(iv) Anionic surfactants.

The surfactant used in microemulsion formation could be ionic or nonionic, which enhances the stabilization of the hydrophilic end of the surfactant with the aqueous phase. A nonionic surfactant is stabilized by dipole and hydrogen bond interactions with the hydration layer of water on its hydrophilic surface, an ionic surfactant is also can stabilized by the electrical double layer.

Table 3: Examples of commonly used surfactants

HLB < 10	Phosphatidylcholine, Span 80, Span 40, Labrafil M 2125
HLB > 10	Tween 80, Tween 20, Cremophor RH 40, Labrasol, Cremophor EL

3) **Co- Surfactants:**

In most cases, single-chain surfactants alone are unable to reduce the o/w interfacial tension sufficiently to form a microemulsion. The presence of co-surfactants contributes the interfacial film sufficient flexibility to take up different curvatures required to form microemulsion over a wide range of composition. Short to medium chain length alcohols (C3-C8) are commonly added as co surfactants which further reduce the interfacial tension and increase the fluidity of the interface. Typical co-surfactants are short chain alcohols (ethanol to butanol), glycols such as propylene glycol, polyethylene glycol, acids, amines, and medium chain alcohols.

The role of co-surfactants:

1) Increase the fluidity of the interface.

2) Destroy liquid crystalline or gel structure which would prevent the formation of microemulsion.

3) Adjust HLB value and curvature of the interface by

Changing partitioning characteristic [6].

Methods of Microemulsion preparation:

1) Phase Titration Method (Water 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 needful approach to study the complex series of interactions that can occur when different components are incorporated in a system. Microemulsion formulation goes along with various association structures (emulsion, micelles, hexagonal, lamellar, cubic, and gel and oily dispersions) depending on the chemical composition and concentration of each component.

The understanding of their phase equilibria and demarcation of the phase boundaries are essential aspects of the study. Pseudo ternary phase diagram is often constructed to find the different zones including microemulsion region, in which each corner of the triangle represents 100% of the one particular component. The region can be separated into o/w or w/o microemulsion by simply considering the composition that is whether it is water rich or oil rich. Observations must be made carefully so that the metastable systems are not included.

2) Phase inversion method:

Phase inversion of microemulsion occurs on addition of dispersed phase or in response to temperature. During phase inversion physical changes occurs including particle size change that can affect drug release *in vivo* and in *vitro*. These methods make use of changing the curvature of the surfactant. For non-ionic

surfactants, this can be done by changing the temperature of the system by forcing a transition from o/w microemulsions at low temperatures to w/o microemulsions at higher temperatures (transitional phase inversion). At the time of cooling, the system reaches a point of zero curvature and minimal surface tension, promoting the formation of fine oil droplets which are dispersed. This method is also known as phase inversion temperature (PIT) method. Other parameters such as salt concentration or pH value may be considered as well instead of the temperature alone. Also, a transition in the spontaneous radius of curvature can be obtained by changing the water fraction. By adding water into oil phase, initially water droplets are formed in a continuous oil phase. Increasing the water fraction changes the spontaneous curvature of the surfactant from initially stabilizing a w/o microemulsion to an o/w microemulsion at the inversion point. Short-chain surfactants form monolayers at the o/w interface resulting in a bicontinuous microemulsion at the inversion point [6].

Phase diagram for microemulsion:

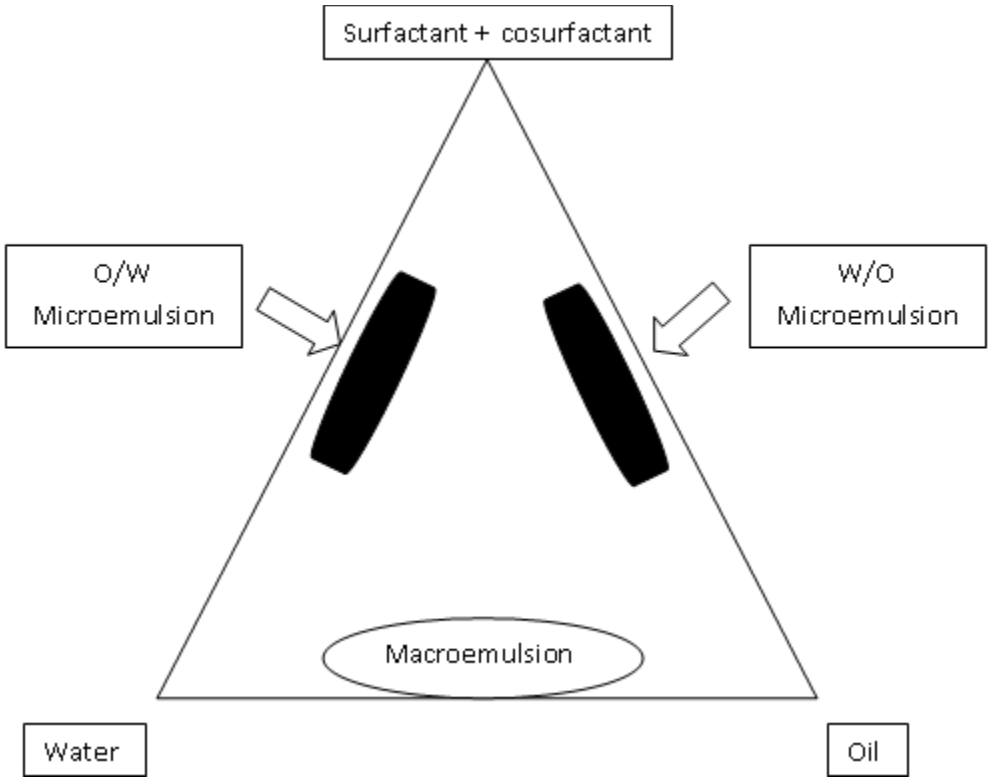

Figure 1: Ternary phase diagram for microemulsion system

From above figure, we can see that,

- When oil concentration is high, surfactant forms an reverse micelles capable of solubilizing water molecules in their hydrophilic interior.

- Continuous addition of water in this system may sometime result in the formation of W/O microemulsion in which water exists as droplets surrounded and stabilized by interfacial layer of the surfactant / co-surfactant mixture.
- At a limiting water, the isotropic clear region changes to a turbid, birefringent one.
- On further dilution with water, a liquid crystalline region may be formed in which the water is sandwiched between surfactant double layers.
- Finally, as concentration of water increases, the lamellar structure breaks down and water forms a continuous phase containing droplets of oil stabilized by a surfactant / co-surfactant (O/W microemulsions) [5].

Characterization of Microemulsion:

1) Thermodynamic stability studies:

To overcome the problem of metastable formulation, thermodynamic stability tests are performed. Formulations are centrifuged at 3000 rpm for 30 min. Those formulations which does not show any phase separation are taken for the heating and cooling cycle at temperature of 4°C and 45°C for 48 h. The formulations are then observed for phase separation. The formulations which found stable at these temperatures, survived thermodynamic stability are selected for further studies [2, 6].

2) Viscosity Measurements:

Viscosity measurements can show the presence of rod-like or worm-like reverse micelle. Viscosity measurements being a function of volume fraction used to determine the hydrodynamic radius of droplets, and interaction between droplets and deviations from spherical shape by fitting the results to appropriate models (e.g. for micro emulsions showing Newtonian behavior, Einstein's equation for the relative viscosity can be used to calculate the hydrodynamic volume of the particles) [6].

3) Conductance Measurement:

O/W microemulsion where the external phase is water are highly suitable for conduction whereas W/O are not, since water is the internal phase. To determine the nature of continuous phase and to identify phase inversion phenomena, the electrical conductivity measurement proves highly useful. Dielectric measurements are a powerful means of probing both structural and dynamic features of microemulsion systems [6].

4) Electron Microscope Characterization: Transmission Electron Microscopy (TEM) is the most important technique for the study of microstructures of micro emulsions because it directly produces images at high resolution and it can capture any co-existent structure and micro-structural transitions.

There are two variations of the TEM technique for fluid samples.

1. The cryo-TEM analyses in which samples are directly visualized after fast freeze and freeze fructose in the cold microscope.

2. The Freeze Fracture TEM technique in which a replica of the specimen is images under RT conditions [6].

5) Scattering Techniques for Microemulsions Characterization:

Small-angle X-ray scattering (SAXS), small-angle neutron scattering (SANS), and static as well as dynamic light scattering are widely applied techniques in the study of microemulsions. These methods are very valuable for getting quantitative information regarding the size, shape and dynamics of the components. Static light scattering techniques have also been widely used to determine microemulsion droplet shape and size. In this the intensity of scattered light is generally measured at various angles and for different concentrations of microemulsion droplet. Dynamic light scattering, which is also referred to as photon correlation spectroscopy (PCS), is used to analyze the fluctuations in the intensity of scattering by the droplets due to Brownian motion. The self-correlation is measured which gives information on dynamics of the system [6].

Stability Studies:

The stability of the microemulsion has been assessed by conducting long term stability study and accelerated stability studies. In long term stability studies, the system is kept at room temperature, refrigeration temperature (4-8 ˚C) and elevated temperature (50±2 ˚C). Over the time period, microemulsion systems are evaluated for their size, assay, pH, viscosity and conductivity measurements. In long term studies, the activation energy for the system and shelf life of the system may be calculated as like other conventional delivery system. Accelerated

Stability studies are the essential tools to study the stability of microemulsions. It can be performed by centrifugation, heating and cooling cycle or freeze and thaw cycles [6].

Microemulsions in Drug Delivery:

During the last two decades, microemulsions have been extensively researched because of their tremendous potential in many applications. The importance of microemulsions in drug delivery is discussed comprehensively herein [3]**.**

1. Oral Delivery:

The development of the effective oral delivery systems has always been the main goal because drug efficacy can be severely limited by instability or poor solubility in the gastrointestinal fluid.

Microemulsions have the potential to enhance the solubilization of the poorly soluble drugs and overcome the dissolution related bioavailability problem. This is mainly important for the BCS class II or class IV drugs. Microemulsions act as solvent of these drugs and can be optimized to ensure consistent bioavailability [3].

2. Parenteral Delivery:

The formulation of lipophilic and hydrophobic drugs into parenteral dosage forms has proven difficult. O/w microemulsions are found useful in parenteral delivery of sparingly soluble drugs where the administration of suspension is not suitable. They provide a relatively high concentration of drugs which usually requires frequent administration. Other advantages are they possess a higher physical stability in plasma than liposomes or other vesicles and the internal oil phase is more resistant against drug leaching out. Sparingly soluble drugs can be formulated into o/w microemulsion for parenteral delivery. Microemulsions can also be used as intravenous delivery systems for the fat soluble vitamins and lipids in parenteral nutrition [3].

3. Topical Delivery:

Microemulsions are known to enhance the transdermal permeation of drugs significantly compared to conventional formulations such as solutions, gels or creams or emulsions. They are capable to incorporate both hydrophilic (apomorphine hydrochloride, 5-fluorouracil, tetracaine hydrochloride, methotrexate, diphenhydramine hydrochloride) and lipophilic drugs (felodipine, triptolide, estradiol, finasteride, ketoprofen, meloxicam) and enhance their permeation. A large amount of drug can be incorporated in the formulation due to the high solubilizing capacity that might increase thermodynamic activity on the skin. The surfactant and co surfactant in microemulsions may reduce the diffusion barrier of the stratum corneum by acting as penetration enhancers. Due to the small droplet size and large amount of inner phase in microemulsion, the density and surface area of droplets are assumed to be high. Therefore, droplets settle down close in contact with the skin providing high concentration gradient and enhanced drug permeation. Low surface tension promotes good contact to the skin. The dispersed phase can also act as a reservoir making it possible to maintain an almost constant concentration gradient over the skin for a long time [3].

4. Ophthalmic Delivery:

In conventional ophthalmic dosage forms, like drops, solutions, water soluble drugs are delivered in aqueous solution while water insoluble drugs are formulated as suspensions or ointments. Minimum corneal bioavailability and lack of efficiency in the posterior segment of ocular tissue are drawbacks of these systems. Recent research efforts therefore have to be focused on the development of novel and more

effective delivery systems. Microemulsions have been introduced as a promising dosage form for ocular use [3].

5. Nasal Delivery:

Microemulsions are now being studied as a delivery system to enhance uptake across nasal mucosa. Incorporation of a mucoadhesive polymer helps in prolonging the residence time on the nasal mucosa. Nasal route of administration for diazepam might be a useful approach for the rapid onset of action during the treatment of status epilepticus. For this microemulsion was formulated composing of ethyl laurate (15%), Tween 80: propylene glycol: ethanol at 1:1:1

Weight ratio (70%) and water (15%). The nasal absorption of diazepam was found to be fairly rapid at 2 mg kg-1 dose with maximum drug plasma concentration reached within 2-3 min. The bioavailability (0-2 h) after nasal spray compared to i.v. injection was about 50% high [3].

Table 4: Marketed formulations of microemulsion

Drug	**Product**	**Components**
Ritonavir	Norvir	Ethanol, oleic acid, Cremophor EL, BHT
Ritonavir	Kaletra	Oleic acid, Cremophor EL, Propylene glycol,
Cyclosporine	Sandimunne	Corn oil, Labrafil, Ethanol, Glycerol
Progesterone	Prometrine	Peanut oil, Glycerin, Lecithin

References:

1. Ghosh P K, Murthy R S R, Microemulsion: Potential Drug Delivery System, Current Drug Delivery. , 2006, 3, 167-180.
2. Sejal Kumar Jha, Roop Karki, Venkatesh D. P. , Geethalakshmi A. , Formulation Development and Characterization of Microemulsion Drug Delivery System containing antiulcer drug.

International journal of drug development and research October-December 2011, volume 3, issue 4, ISSN 0975- 9344, 336-343.

3. Sushma talegaonkar, Adnan Azeem, Farhan J. Ahmad, Roop K. Khar, Shadab A pathan and Zeenat I. Khan. Microemulsion: A novel approach to enhanced drug delivery, Recent Patents on Drug Delivery and Formulation 2008, 2, 238-257.
4. Vyas S.P. , Khar R.K. Submicron emulsion in targeted and controlled drug delivery, Novel Carrier Systems; CBS Publishers and Distributers, New Delhi 2002, 282-307.
5. Shaji J., Reddy M. S. Microemulsion as Drug Delivery Systems, Pharma times 2004, 36 (7); 17-24.
6. Sarkhejiya Naimish A, Nakum Mayur A., Patel Vipul P., Atara Samir A., Desai Thusabindu R., Emerging trends of microemulsion in formulation and research. International Bulletin of Drug Research, 2012, vol. 1 issue 2: 54-83.