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Microemulsions: Platform for Improvement of Solubility and Dissolution of Poorly Soluble Drugs

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ABSTRACT

This study reviews the impact of microemulsion on the improvement of solubilization and dissolution of lipophilic drug. The drugs which are of poorly soluble and low absorption are considered as ideal candidates for micro emulsions. Microemulsion are thermodynamically stable, having of three components oil phase, surfactants, and co-surfactants. It is having low particle or droplet size range from 5-200 nm and have of low oil/water interfacial tension. These are transparent preparations with no involvement of energy. These preparations improved oral bioavailability and protects the drug from against enzymatic hydrolysis. These drugs are have of high permeability capacity because of low interfacial tension. This review focuses on the basic concept such as formulation, characterization, component and structure of microemulsion.

Keywords: Microemulsion, Lipophilicity, Solubilization, Bioavailability, Phase- behaviour, Thermodynamically stable.

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Introduction:

Oral drug delivery system is the most preferred and convenient option as the oral route provides maximum effective surface area among all other drug delivery system for administration of various drugs. The attractiveness of those dosage form is due to awareness of toxicity and ineffectiveness of drugs when administered by oral conventional method in the form of tablets and capsules.

Usually conventional dosage form produces wide range of fluctuation in bloodstream and tissue with having frequency of undesirable toxicity and poor efficiency. The maintenance of concentration of drug in plasma with the therapeutic index is very critical treatment. Till now a date today also the researchers on going the method to develop system of drug carrier for transport of active molecules into the organs or tissue to show in greater therapeutic efficacy which relies on bioavailability of molecules. Bioavailability is defined as the rate and extent to which drug is absorbed and form a dosage form and become available at site of action. It has an important clinical application both in pharmacology and toxic effects. These depend on several factors and the important among them is solubility in aqueous environment and permeability through lipophilic membranes.

Solubility of drugs depends on the physical form of the solid, the nature and composition of solvent medium as well as temperature and pressure of system and also on the followings parameters.[5]

1. Particle size
2. Temperature
3. Pressure
4. Nature of the solute solvent
5. Molecular size
6. Polarity
7. Polymorphs

Modifications of the physiochemical properties such as salt formation, and particle size reduction improve dissolution rate. To overcome solubility and permeability limitations various other formulation strategies have been attempted such as use of cyclodextrins, nanoparticles, solid dispersion and permeation enhancers.

Microemulsion enhance the bioavailability of poorly soluble drugs. Microemulsion are clear, thermodynamically stable, isotropic liquid mixture of oil, water and surfactant frequently in combination of co-surfactant. Microemulsion is of small particle size having low surface tension and small droplet size which have high permeability and bioavailability.

Nowadays, microemulsion are used in various routes of administration of drug such as transdermal, oral, vaginal, rectal and intravenous drug delivery. Microemulsion shows great impact in Novel drug delivery systems (NDDS).

Definition of Micro-Emulsion and Macro-Emulsion:

Microemulsion are clear and translucent but their method of preparation is different because emulsion which requires a large input of energy while microemulsion does not require. This microemulsion is of thermodynamically stable, isotropic liquid mixture of oil, water and surfactant along with frequently used co-surfactants. Macroemulsions are homogenous transparent thermodynamically unstable and of particle size differs in size ranging up to 5-140 nm. Macroemulsion get scattered and therefore appear milky because the droplets are of greater size than a wavelength of light. It can be stabilized for period of time with applications of Kinetic energy.

Table 1: Difference between Microemulsion and Macroemulsion:[2]

Property	Microemulsion	Macroemulsion (emulsion)
Appearance	transparent	cloudy
Optical isotropy	isotropic	Anisotropic
Interfacial tension	Ultra-low	High
Microstructure	Dynamic	Static
Droplet size	20-200 nm	>500 nm
Stability	Thermodynamically stable and long shelf life	Thermodynamically unstable
Phases	Monophasic	Biphasic
Preparation	Facile preparation	Require large input energy
Viscosity	Low viscosity with Newtonian behaviour	High viscosity
Turbidity	Transparent	Turbid
Co-surfactant	Yes	No
Surface concentration	<0.1micron	<0.5-5 micron
Molecular packing	Efficient	Inefficient

Structure of microemulsion:

Microemulsions are of dynamic structure and their interface is continuously changing. Microemulsion possesses a definite portion of 3 parts namely; oil, water and mixture of surfactant and co- surfactant. Structurally they are divided into oil-in-water (O/W), water-in oil (W/O) and bi-continuous microemulsions by adding of water into the hydrophilic core, if results in the formation of O/W microemulsion where water exist as a dispersed phase droplets are stabilized by interfacial layer of the surfactant/ co-surfactant mixture. In case of O/W microemulsion, where oil droplets are dispersed into continuous aqueous phase. The flexibility of surfactant film is important in this regard while preparing microemulsion. Clear isotropic one- phase systems are identified as microemulsions.

Small-angle X ray scattering (SAXS), static as well as dynamic light scattering (DLS), transmission electron microscopy (TEM) and nuclear magnetic resonance (NMR) spectroscopic methods are the most relevant techniques to characterize microstructure of microemulsion.

Components of Microemulsions:

A large proportion of oil and surfactants are used in the microemulsion preparation system but they are having a chance of high toxic, irritable and potential in use. So materials which are bio compatible and non-toxic to use and administer into the body by using of safe excipients should be used.

The main components of microemulsion are

1. Oil phase
2. Surfactant
3. Co-surfactant

Oil phase: Oil phase is of important component in microemulsion. Oils are of essential oil derived from plant sources, regarded as safe and bio-compatible. Chemically, oils are of unsaturated fatty acid derivatives or polyglyceride fatty acids ester but all are existing in liquid state. The oil phase must be of safe when it is used in topical purpose and also it in should be non-toxic, less irritant, having smoothing effect and exerts emollient action. The oil must be chosen carefully which should be free from rancidity.

Oil is one of the most important components in microemulsion for solubilising of lipophilic drug and it increases the fraction of lipophilic drug transport in the intestinal lymphatic system. Oil is having low polarity and low miscibility with water. Examples of oil used in microemulsion are cyclohexane, mineral oil, toluene and vegetable oils.

Surfactants: Surfactants are called as surface-active agents which enhances and increases the drug solubilisation at a greater speed. Smaller particle size, greater is the surface area which increases the absorption. This surfactant also promotes the bioavailability of the drug. To stabilize microemulsion system, The following surfactants are used

A. Non-ionic
B. Zwitter ionic
C. Cationic
D. Anionic surfactants

Higher amount of surfactant in microemulsion produce lower droplet size of dispersed phase. Selection of surfactant is important for topical microemulsion preparation. It has affinity for polar and non-polar solvents. Surfactants molecules consist of polar head group and non-polar tail. These are among themselves by of intra and inter molecular forces as well as entropy.

Anionic surfactants: These can penetrate and tightly bind with skin. Examples dioctyl sulphosuccinate, sodium lauryl sulphate, decodecylmethylsulphoxide.[2]

Cationic surfactants: These are more irritating than anionic surfactants and not used in topical products.[2]

Non-ionic surfactant: These have less irritation. Example pluronic F 127, pluronic F 68. [2]

These are commercially available solubilized oral formulations which include polyoxyl 35 castor oil (cremophor EL), polyoxyl 40 hydrogenated castor oil (cremaphor PH 40), polysorbate 20(tween 20), polysorbate 80 (tween 80), solutol HS-15, sorbitan monooleate (span 80), polyoxyl 40 sterate and various polyglycolized glycerides including labrafil M-1944CS, Labrafil M-2125CS, Labrasol, Gellucire 44/14: etc. Low HLB (3-6) surfactants are suitable for W/O microemulsion whereas high HLB (8-18) are suitable for O/W microemulsion. [1,7]

Co-Surfactants: Surfactant are added in addition to another surfactant, for further reducing the surface tension of a liquid. In microemulsion it reduces the interfacial tension between two immiscible phases of liquid. Typical co-surfactants are short chain alcohols (ethanol to butanol), glycols such as propylene glycol (PG), medium chain alcohols, amines or acids. The role of co-surfactant is as follows

a. Increases the fluidity of the interface.
b. Destroy liquid crystalline or gel structure which prevents formulation of microemulsion.
c. Adjusts HLB value for spontaneous curvature of the interface.

Organic solvents such as ethanol, PG and polyethylene glycol (PEG) are suitable for oral delivery and act as co-surfactants in microemulsion systems.

Formulation of Microemulsion: [3,4,1]

The two methods of preparation are responsible in formulation of microemulsion

A. Phase Titration Method
B. Phase Inversion Method

Phase titration Method (water titration method):

It is prepared by spontaneous emulsification method and it can be depicted with the help of phase diagram. Microemulsions are formed along with various association structures (including emulsion, miscelles, lamellar, hexagonal, cubic) depending on the chemical composition and concentration of each component. Quaternary phase diagram (four-component system) is of time consuming and difficult to interpret and is easily constructed to figure out microemulsion zone.

Phase Inversion Method:

Phase inversion of microemulsion happens due to addition of excess dispersed phase. Phase inversion leads to physical changes as changes in particle size alter drug release. During cooling, system crosses the point of zero spontaneous curvature and minimal surface tension.

Construction of phase diagram:

Pseudo-ternary phase diagram of oil, water and co-surfactant mixtures constructed at fixed ratios Phase diagram obtained by mixing all the ingredients and are placed in glass vials to take their pre weighed and then titrated with water which are stirred at room temperature. Formation of monophasic and biphasic system leads to phase separation. Monophasic microemulsion is of clear, transparent and marked by all sides and easily visualised after stirring of samples.

Types of Microemulsion System: [2,7]

According to winsor there are four types of microemulsion phases exits in equilibria. These phases are called as Winsor phases. They are

Winsor 1: With two phases, the lower (O/W) microemulsion phase is in equilibrium with excess oil.

Winsor 2: With two phases, upper (W/O) microemulsion phase is in equilibrium with excess water.

Winsor 3: With three phases, middle microemulsion phase (O/W plus W/O, called bio-continuous) in equilibrium with upper excess oil and lower excess water.

Winsor 4: In single 'n' phases, with oil, water and surfactant homogenously mixed.

Characterization of Microemulsions: [7]

Characterization of microemulsion is very difficult because of wide variety of structures. For this several techniques are required to characterize microemulsion. Various technique such as Nuclear magnetic resonance (NMR) spectroscopy, microscopy electrical conductivity been employed to characterize these systems.

a. Microscopy: Polarizing microscopy which confirms the optical isometry but conventional optical isometry cannot be used because of small droplet whose size diameter is < 150 nm. However, the sensitivity of microemulsion structure with respect of temperature causes problem in artificial results.

b. NMR (Nuclear Magnetic Resonance) spectroscopy: Self diffusion is the random movement of molecules in the absence of any concentration gradient. Thus, it reflects the molecules are in this environment are localized. The molecules in this system are closed and thus they undergo self-diffusion. Therefore, in W/O microemulsions, self-diffusion of water molecules is slow, whereas the diffusion of O/W is high. This structure is obtained by proton -Fourier transform pulse gradient spin – echo NMR (PGSE-NMR).

c. Conductivity and viscosity: The nature of microemulsion and phase inversion which fall under the rheological properties. If viscosity of the microemulsion system is more than it is of good in nature in stability and also drug release. Where as in conductivity the water phase of emulsion conducts electricity whereas oil phase does not conduct electricity.

Advantages of Microemulsion based System: [2,1]

Microemulsions have the following advantages.

A. Microemulsion solubilizes the hydrophilic drugs and lipophilic drugs relatively which are insoluble in aqueous and hydrophobic solvents.

B. These are thermodynamically stable and require less energy in formation.

C. Microemulsion based systems have long shelf life.

D. Microemulsion helps in improvement of oral bioavailability. Bioavailability of lipophilic drugs.

E. 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.

F. Microemulsions minimise first pass metabolism.

G. 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.

Conclusion:

Microemulsions are of very much importance in novel drug delivery systems and it has been effective and attractive area of research and industrial processes. The main role in microemulsion is to overcome the problems of poor aqueous solubility of highly lipophilic drug and make it more bioavailable. In, microemulsion one can design the interface of nanometre size droplet as to improve the drug stability in humans from a few milliseconds to minutes. It plays key roll to cells and tissue. However, the toxicological evaluations of the prepared microemulsion are in research area in future.

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