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Microemulsions-A review

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Abstract

Microemulsions are have appear as novel vehicles for drug delivery system, microemulsions clear, stable, isotropic mixtures of oil, water, and surfactants, frequently in combination with co-surfactants. Microemulsions acts as potential drug carrier systems for oral, topical, and parenteral administration. They are having the advantages like spontaneous formation, thermodynamically stable, ease of manufacturing and scale-up, improved drug solubilization and bioavailability, long self-life.

Key Words: Co-surfactants**,** Microemulsions, Surfactants, Thermodynamically stable.

INTRODUCTION

Microemulsions are thermodynamically stable isotopically clear dispersion of two immiscible liquids, such as oil and water, stabilized by an interfacial film of surfactants along with co-surfactants. Microemulsions are having the advantages over both colloidal systems under investigation and conventional emulsions, suspensions and micellar solutions. Microemulsions provide alternative drug carriers. Microemulsions offer the advantages of spontaneous formation, easy of manufacturing and scale-up, thermodynamic stable, improved drug solubilization of hydrophobic drugs and bioavailability [1-3].

Microemulsions are three types based on their composition:

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

In all three types of microemulsions, the interface is stabilized by an appropriate combination of surfactants and/or co-surfactants.

History

Microemulsions are introduced by Hoar and Schulman [4]. Microemulsions are defined as a transparent solution obtained by titrating a normal coarse emulsion with medium-chain alcohols. Microemulsions are thermodynamically stable isotropic systems in which two immiscible liquids (water and oil) are mixed to for a single phase by means of an appropriate surfactants and co-surfactants. The short to medium chain alcohols are generally considered as co-surfactants in the microemulsion system. Interfacial tension is reduced by using surfactant and co-surfactant. Therefore, microemulsions are formed spontaneously, with an average droplet diameter of 10 to 140 nm [5].

Objectives

- To prepare and optimise w/o microemulsions using combination of surfactants, organic and aqueous phases. These are used to characterise the resulting microemulsions along two dilution lines within the monophasic region in ternary phase diagrams.
- To incorporate a model hydrophilic guest molecule (sodium chloride) in to the water domains of oil-continuous microemulsions.
- To test the capability of selected salt-containing microemulsion compositions for salt-release using conductivity and establish the mechanism of release.

FORMULATION

The microemulsions are colloidal dispersions composition of oil phase, aqueous phase, surfactant, and co-surfactants at appropriate ratios [6].

Surfactants

Surfactants are used to stabilize the system. In the formulation of microemulsions, the surfactants are used to lower the interfacial tension they are ultimately facilitates the dispersion process and provide a microemulsions around the droplet. They are non-ionic, zwitter ion, cationic or anionic surfactants.

Co-surfactants

Co-surfactants are a chemical added to a process to enhance the effectiveness of a surfactants. These are used to increase the oil-solubilizing capacity of microemulsion surfactant system [7-13]. Co-surfactants are short to medium chain length alcohols (C3-C8) these are reducing the interfacial tension and are having the capability to increase the fluidity of the interface. They are alcohols, amines, and cholesterol.

Oils

The oil component influences curvature by its ability to penetrate the tail group region of the surfactants. As compare to long chain alkenes, short chain oil to increase the negative culture and reduce the HLB [14].

The formulation of the microemulsions different types of the oils are used they are,

- Saturated fatty acid: lauric acid, myristic acid, capric acid.
- Unsaturated fatty acid: Oleic acid, linoleic acid, linolenic acid.
- Fatty acid ester: Ethyl or methyl esters of lauric acid, myristic acid, oleic acid.

The main use of oil selectin is that the drug should have high soluble in it. The oil should be used to minimise the

volume of the formulation. The oil should be delivering the therapeutic dose of the drug in an encapsulated form.

The formulation of microemulsion must have low allergic, potential, good physiological compatibility and high biocompatibility.

The components involved the general formulation of microemulsions include:

(a) an oil phase, (b) an aqueous phase containing hydrophilic active ingredients [preservatives and buffers may be included], (c) a primary surfactant [anionic, non-ionic or amphoteric], (d) secondary surfactant or cosurfactants.

Advantages of microemulsions over other dosage forms

- The rate of absorption will be increases
- The variabilities should be eliminating in absorption process
- Lipophilic drugs will be solubilized
- Provides aqueous dosage forms for water insoluble drugs
- Bioavailability increases
- Various routes like tropical, oral and intravenous can be used to deliver the product
- The drug moiety should be rapid and effective penetration
- Helpful in taste masking
- Increases the patient compliance in liquid dosage forms
- Energy requirement is very low.

PREPARATION OF MICREMULSIONS

Preparation of microemulsions are used for two different methods they are,

Phase titration method and Phase inversion method.

Phase titration method

Microemulsions are prepared by the phase titration method. These is also called as spontaneous emulsification method. Microemulsions can be characterized by the phase diagram. As four compartment system is difficult to intercept and time-consuming process. So, in the preparation of microemulsions we are using the pseudo ternary phase diagram. These are having the different zones and microemulsion zones. These showing the 100% of the particular components.

In this phase titration method, we are using the oils, water, surfactants & mixture of co-surfactants in fixed weight ratios. This phase diagram is responsible for the mixing of ingredients. All these mixtures will be stirred at room temperature, then the monophasic/biphasic system will be confirmed by the visual inspection. In phase separation turbidity may appears, the samples should be considered as biphasic because the monophasic is visualized as clear and transparent mixtures after continuous stirring. The obtained points should be marked in phase diagram.

Phase inversion method

Phase inversion of microemulsion is carried out upon addition of excess of the dispersed phase or in response to temperature. In the process of phase inversion method, physical changes can occur, also changes in particle size, these can be ultimately affected drug release in in-vitro and in-vivo. For non-ionic surfactants can be accomplish by the changing the temperature of the system, in these processes an o/w microemulsion at low temperature changes to w/o microemulsion. This is also called as transitional phase inversion method. During the cooling, the system crosses the zero-point spontaneous shape and maintaining the surface tension, and increasing the formation of oil droplet dispersion. Apart from temperature salt concentration and pH value may also considered.

In this phase inversion method, transition in the radius can be occur by changing in the water volume fraction. Initially water droplets are formed in a continuous oil phase by addition of water in to oil. Water volume fraction can be increased, surfactants from stabilizing a w/o microemulsion to an o/w microemulsion using temperature. Figure-1.

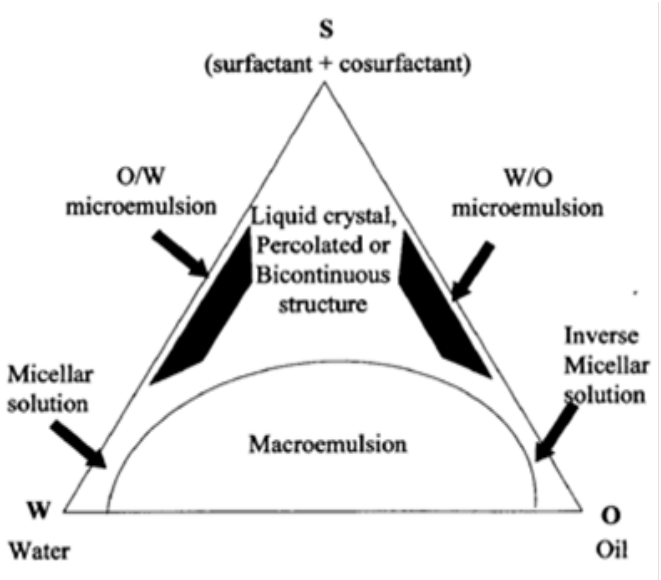

Figure 1

Hypothetical phase regions of microemulsion system of oil (O), water (W), and surfactant + cosurfactant (S)

CHARACTERIZATION OF MICROEMULSION

The droplet size, viscosity, density, turbidity, refractive index, phase separation and pH measurements shall be performed to characterize the microemulsions.

Droplet size

The light scattering technique or electron microscopy is used to determining the droplet size distribution of microemulsions. This technique has been used as the best method for predicting microemulsion stability.

- **Dynamic Light-Scattering Measurements**
  The DLS measurements are taken at 90° in a dynamic light-scattering spectrophotometer using a neon laser of wavelength 632 nm. The data is processed by the built-in computer with the instrument [15].
- **Polydispersity**
  Abbe refractometer is used to study the polydispersity.

- **Phase analysis**
  The type of microemulsion forming the phase system (o/w or w/o) is determined by measuring the electrical conductivity using a conductometer.

Viscosity Measurement

The Brookfield rotary type viscometer is used in viscosity of microemulsions. In this viscosity of microemulsions are having the several compositions is measured at different shear rates at different temperatures. The instrument should be maintained at 37 ± 0.2°C by a thermobath, and the samples for the measurement are to be immersed in it before testing [19].

Nuclear Magnetic Resonance Studies

Nuclear Magnetic Resonance technique is used to study the structure and dynamics of microemulsions. Different traces techniques are using the self-diffusion measurements, generally radio labelling, supply information on the mobility of the components. Magnetic gradient on the samples and it allows simultaneous and rapid determination of the self-diffusion coefficients using Fourier transform pulsed-gradient spin-echo (FT-PGSE) [16-17].

Interfacial Tension

The formation and the properties of microemulsion can be studied by measuring the interfacial tension. This interfacial tension is correlated with phase behaviour in low ultra-values, these low ultra-values shows the existence of surfactant phase or middle phase microemulsions in equilibrium with aqueous and oil phases. Ultra-low interfacial tension is measured by using the spinning-drop apparatus. These are derived from the measurement of the shape of a drop of the low-density phase, rotating it in cylindrical capillary filled with high density phase [18].

Electron Microscope Characterization

The study of microstructure of microemulsions Transmission Electron Microscopy (TEM) is the most important technique, because it directly produces images at high resolution, and it can capture any co-existent structure and micro structural transitions.

- The cryo-TEM are used to analyse the samples are directly visualized after fast freeze and freeze fructose in the cold microscope.
- Tn the freeze fracture TEM technique used in replica of the specimen is images under RT conditions.

APPLICATIOS OF MICROEMULSIONS

These are some applications of microemulsions in delivery of drug

During the last two decades, microemulsions are used as drug delivery system, they are offer the advantages like thermodynamic stability, optical clarity, easy of penetration.

Parenteral Delivery

The formulation of parenteral dosage form of lipophilic and hydrophilic drugs has proven to be difficult. The formulation of w/o microemulsions are beneficial in the parenteral delivery of sparingly soluble drugs where the administration of suspensions is not required. For frequent administration of drugs requires high concentration. They are existing the higher physical stability in plasma than liposomes or other vehicles and the internal oil phase is more resistant against drug leaching. Several sparingly soluble drugs have been formulated in to o/w microemulsions for parenteral delivery. Von Corsewant and Thoren was taken the alternate approach in which C3-C4 alcohols were replaced with parenterally acceptable co-surfactants, poly ethylene glycol (400)/ poly ethanol glycol (600) 12-hydroxy stearate/ ethanol will maintaining a flexible surfactant film, these are forming the spontaneous curvature near zero, in the microemulsions obtaining the almost balanced middle phase [20].

Oral Delivery

The development of effective oral delivery systems has been challenging because drug efficiency can be restricted by instability or poor solubility in gastrointestinal fluid. The solubilization of poorly soluble drugs (particularly BCS class II/class IV) are enhanced by the microemulsions. Also overcome the dissolution related bioavailability problems. The presence of polar, non-polar and interfacial domains, hydrophilic drugs are encapsulated with varying solubility of macromolecules. These systems have been protecting the incorporated drugs agonist oxidation, enzymatic degradation and enhance membrane permeability. Commercially available microemulsions for formulation of oral delivery are Sandimmune Neoral® (Cyclosporine A), Fortovase® (Saquinavir), Norvir® (Ritonavir) etc. Improving the oral bioavailability of poorly water-soluble drugs can be enhanced their solubility in gastrointestinal fluids are potential useful in the formulation of microemulsions [21-23].

Topical Delivery

Topical administration of drugs having the advantages like avoidance of hepatic first-pass metabolism of drug and related toxicity effects. These are having the direct delivery and targetability of the drug to affected areas of the skin and eyes. The area of drug penetration into the skin having the number of studies. In these drug penetration studies they are incorporate both hydrophilic (5-fluroracil, apomorphine hydrochloride, diphenhydramine hydrochloride, tetracaine hydrochloride, methotrexate) and lipophilic drugs (oestradiol, finasteride, ketoprofen, meloxicam, felodipine, triptolide) and enhance their penetration. In the formulation of microemulsions requires high surfactant concentration. Skin irritating aspects must be considered specially when they are intended to be applied for a long period [24].

Nasal Delivery

Recently, microemulsions are being studied as a delivery system to enhance uptake of drug through nasal mucosa. Mucoadhesive polymers helps in prolonging residence time on the mucosa. Lianly et al. investigating 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 [25].

Other Applications

- Skin penetration of lycopene are improved by the microemulsions.
- Microemulsion as a vehicle for transdermal permeation of nimesulide
- Oil recovery, detergency, cosmetics, agrochemicals, foods are enhanced by the microemulsions.
- Microemulsions as fuels, as lubricants, cutting oils and corrosion inhibitors, coatings and textile finishing.
- Microemulsions in microporous media synthesis (microemulsion gel technique) Microemulsions in analytical applications.
- Microemulsions as liquid/membranes Novel crystalline colloidal arrays as chemical sensor materials [26].

Recent Trends & Future Developments

During the last two decades lot of research work has been carried out on microemulsion system for providing novel solutions to overcome the problems of poor aqueous solubility of highly lipophilic drug compounds and these are providing reproducible bioavailability. Industrial point of view, it can be easily scaled up with considering relative cost of commercial production. Cosmetic purpose and drug targeting, microemulsion are used. Now a day, researcher work is focused on the production of safe, efficient and more compatible microemulsion constituents which will further enhance the utility of this novel delivery system. One hopes that our society will be able to muster the collective financial and moral courage to allow such extraordinarily powerful drug delivery carrier to be deployed for human betterment, with due regard to essential ethical considerations.

CONCLUSION

Microemulsions are commercially simple and convenient vehicle for delivery of medicaments which can enhance drug absorption with reduced systemic side effect. They can be used to optimise drug targeting without a concomitant increase in systemic absorption. Appropriate excipients selection and safety evaluation especially of the cosurfactants is crucial in the formulation of microemulsions. They can be potential drug delivery systems for the delivery of more than one medicament simultaneously.

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