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Review Article

Futuristic Drug Delivery System Microemulsions: A Review

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ABSTRACT

Recently microemulsions have attracted great attention as they help to optimize efficiency of wide range of products and processes. Microemulsion is isotropic, thermodynamically stable multicomponent fluids which is composed of water, oil, surfactant or cosurfactant where the diameter of the droplet of the microemulsion is in the range of 100A° TO 1000A°. Microemulsion are unique class of optically transparent (translucent) solution which comprises of the colloidal system that are attracting many scientific and technological interest past few decades. This interest is due to their properties like ultra low interfacial tension, large interfacial tension and solubilization capacity of both oil and water soluble drugs.

KEYWORDS: Composition, Method of preparation, Applications.

INTRODUCTION

Emulsion is heterogeneous system where immiscible liquids are dispersed as droplet form in liquid system. They are thermodynamically unstable systems which are stabilized with the component which exhibit emulsifying properties thus making it kinetically stable. There has been a revolution in the last two decades in the utilization of microemulsion systems in a variety of chemical and industrial processes. Microemulsions have shown a wide range of applications starting with enhanced oil recovery in the 70's, expanding to a wide range of chemicals and entering the pharmaceutical and cosmetic formulation area a decade ago.[1] Microemulsions have been widely studied to enhance the bioavailability of the poorly soluble drugs. They offer a cost effective approach. Microemulsions have very low surface tension and small droplet size which results in high absorption and permeation. Microemulsions have the ability to deliver larger amounts of water and topically applied agents into the skin than water alone or other traditional vehicles such as lotions or creams because they act as a better reservoir for a poorly soluble drug through their capacity for enhanced solubilization [2] The main difference between macroemulsions and microemulsions lies in the size and shape of the particles dispersed in the continuous phase: these are at least an order of magnitude smaller in the case of microemulsions (10-200 nm) than those of conventional emulsions (1-20 m). Macroemulsions consist of roughly spherical droplets of one phase dispersed into the other whereas microemulsions constantly evolve between various structures ranging from droplet-like swollen micelles to bicontinuous structures, making the usual “oil in water” and “water in oil” distinction sometimes irrelevant.[3] The key differences between ordinary emulsions (macro emulsions) and microemulsions are shown in Table 1.

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Table 1. Comparison of Microemulsion with Conventional Emulsion

S. No	Property	Microemulsion	Emulsion
1	Appearance	Transparent (or translucent)	Cloudy
2	Optical Isotropy	Isotropic	Anisotropic
3	Interfacial Tension	Ultra low	High
4	Microstructure	Dynamic(interface is continuously and spontaneously fluctuating)	Static
5	Droplet Size	20-200 nm	> 500 nm
6	Stability	Thermodynamically stable	long shelf-life Thermodynamically unstable (kinetically will eventually phase separate
7	Phases	Monophasic	Biphasic
8	Preparation	Facile preparation, relatively lower cost for commercial production	Require a large input of energy, higher
9	Viscosity	Low viscosity with Newtonian behaviour	Higher viscosity

Self – microemulsifying drug delivery systems (SMEDDS) are not exactly microemulsions but are related with each other. It is composed of oil, surfactant and cosurfactant and has the ability to form o/w microemulsion when dispersed in aqueous phase under gentle agitation. The agitation required for the self-emulsification comes from stomach and intestinal motility [4,5].

COMPOSITION

Today, a variety of oil and surfactants are available which can be utilized for the formulation of microemulsion but their toxicity, irritation potential and unclear mechanism of action limit their use. It is essential to select material that are biocompatible, non-toxic, clinically acceptable and use emulsifiers in appropriate concentration range which will result in mild and non – aggressive microemulsions. Thus importance is given on the use of generally regarded as safe (GRAS) excipients.

Oil Phase

The oil has the ability to penetrate thereby swelling the tail group region of the surfactant monolayer and thus influencing curvature. Short chain oils penetrate the tailgroup region to a greater extent than long chain alkanes, and hence swell this region to a greater extent, resulting in increased negative curvature (and reduced effective HLB) [6]. Saturated (for example, lauric, myristic and capric acid) and unsaturated fatty acids (for example, oleic acid, linoleic acid and linolenic acid) have penetration enhancing property of their own and they have been studied since a long time. Fatty acid esters such as ethyl or methyl esters of lauric, myristic and oleic acid have also been employed as the oil phase.

Surfactants

The surfactant chosen must be able to lower the interfacial tension to a very small value which facilitates 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. It is generally accepted

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that low HLB surfactants are favoured for the formulation of w/o microemulsion, whereas surfactants with high HLB (>12) are preferred for the formation of o/w microemulsion. Surfactants having HLB greater than 20 often require the presence of cosurfactants to reduce their effective HLB to a value within the range required for microemulsion formation [7]

Cosurfactants

In most cases, single-chain surfactants alone are unable to reduce the o/w interfacial tension sufficiently to enable a microemulsion to form [8-11]. The presence of cosurfactants allows the interfacial film sufficient flexibility to take up different curvatures required to form microemulsion over a wide range of composition [12-14].

METHOD OF PREPARATION

Phase Titration Method

Microemulsion can be prepared by phase titration method (spontaneous emulsification methods) and can be depicted with the help of phase diagram. The phase diagram is useful in understanding the complex series of interactions that can occur when different components are mixed. Depending upon the chemical composition and concentration microemulsions are formed with various association structures (including emulsion, micelles, lamellar, hexagonal, cubic, and various gels and oily dispersion). A quaternary phase diagram is difficult and time consuming compared to pseudo ternary phase diagram. The region can be separated into w/o or o/w microemulsion 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. The methodology has been comprehensively discussed by Shafiq-un-Nabi et al. [15].Fig. (1).depicts the pseudoternary phase diagram of oil, water and surfactant showing microemulsion region.

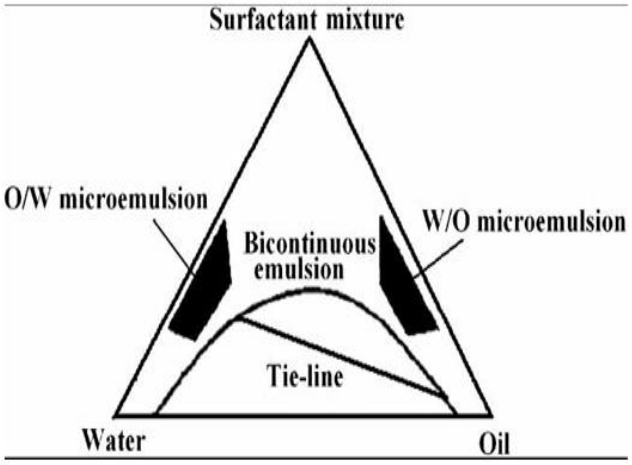

Fig. (1). Pseudoternary phase diagram of oil, water and surfactant showing microemulsion region.

Phase Inversion Method

Phase inversion of microemulsions occurs upon addition of excess of the dispersed phase or in response to temperature. During phase inversion drastic physical changes occur including changes in particle size that can affect drug release both in vivo and in vitro. These methods make use of changing the spontaneous curvature of the surfactant [7]. For non-ionic surfactants, this can be achieved by changing the temperature of the system, forcing a transition from an o/w microemulsion at low temperatures to a w/o microemulsion at higher temperatures (transitional phase inversion)[7]. During cooling, the system crosses a point of zero spontaneous curvature and minimal surface tension, promoting the formation of finely dispersed oil droplets. This method is referred to as phase inversion temperature (PIT) method. Instead of the temperature, other parameters such as salt concentration or pH value may be considered as well instead of the temperature alone.[7]

CHARACTERISATION

The characterization of these systems is highly challenging due to small size with fluctuating boundaries and complex structure.

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Physicochemical characterization of microemulsion systems are:

1. Phase stability and phase behavior,
2. Microstructure, dimension (size and size distribution), shape and surface features (specific area, charge, and distribution),
3. Local molecular arrangements, interactions and dynamics.

Among these properties, particle size, interactions, and dynamics are of great importance as they help in controlling various properties of microemulsions. In particular, the size distributions of microemulsions give essential information for a reasonable understanding of the mechanism governing both the stability and penetration into the membrane [16, 17]. Many technologies like dynamic light scattering (DLS) [18, 19], small angle neutron scattering (SANS) [20-22] and small angle X-ray scattering (SAXS) [23-28] have been in growing use in particle size characterization. Other methods include electrokinetic chromatography, conductance, viscosity, electrical birefringence, infrared spectroscopy and calorimetry.

APPLICATIONS

Some of the application of microemulsion in pharmaceutical industries are:

Oral Drug Delivery System

Large amount of proteins and peptides are being synthesized due to advancement in pharmaceutical and biotechnology area. Conformation on stability, biodegradability and short half life cause difficulty in their formulation for oral administration. Therefore microemulsions are studied for protection of biodegradable drugs. Microemulsions help to enhance the solubilization of the poorly soluble drugs and overcome the bioavailability problems. This is particularly important for the BCS class II or class IV drugs. Microemulsions behave as solvent for these drugs and can be optimized to ensure consistent bioavailability. They can be used for the delivery of hydrophilic drugs e.g proteins and peptides. Moreover, these systems have been reported to protect the incorporated drugs against oxidation, enzymatic degradation [29] and enhance the membrane permeability [30]. Presently, Sandimmune Neoral® (Cyclosporine A), Fortovase® (Saquinavir), Norvir® (Ritonavir), etc. are the commercially available SMEDDS formulations.

Topical Drug Delivery System

Administration of drug via skin has been extensively studied and found the drug transport due to the administration of microemulsion was better than ointment, gels and creams. Microemulsion is multicomponent system. The skin irritation aspect must be considered if applying for longer duration of time. There are several advantages of incorporating microemulsion in transdermal drug delivery system. Some of them are listed below:

1. The permeation rate of the drug from microemulsion may be increased, since the affinity of a drug to the internal phase in microemulsion can be easily modified to favour partitioning into stratum corneum, using different internal phase, changing its portion in microemulsion [31].
2. The surfactant and co surfactant in the microemulsion may reduce the diffusional barrier of the stratum corneum by acting as penetration enhancers [32].
3. The percutaneous absorption of drug will also increase due to hydration effect of the stratum corneum if the water content in microemulsion is high enough [33].
4. A large amount of drug can be incorporated in the formulation due to the high solubilizing capacity that might increase thermodynamic activity towards the skin [34].

Surface area is assumed to be high due to small droplet size. Therefore, droplets settle down to close contact with the skin providing high concentration gradient and improved drug

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permeation. Moreover, low surface tension ensures good contact to the skin. Also, the dispersed phase can act as a reservoir making it possible to maintain an almost constant concentration gradient over the skin for a long time [35]. The liquid, transparent, multicomponent systems according to the invention of Muller et al. contained the active agents in a solution of an oily and optionally an aqueous component in the presence of surfactants and cosurfactants[34]

Parenteral Drug Delivery System

The formulation of lipophilic and hydrophobic drugs into parenteral dosage forms has been difficult. O/w microemulsions are beneficial in the parenteral delivery of sparingly soluble drugs where the administration of suspension is not desirable. 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 liposomes or other vesicles [36]

Antifungal

Superficial mycoses usually respond to topical therapy. In the settling of eczema, topical antifungal agents such as ketoconazole are used to reduce the fungal infection caused by Pityrosporum ovale or Malassezia furfur. Antifungal agents e.g miconazole, ketoconazole, and itraconazole being lipophilic in nature have been formulated as microemulsions to impart to them the advantages like ease of preparation due to spontaneous formation, thermodynamic stability, transparent and elegant appearance, increased drug loading, enhanced penetration through the biological membranes, increased bioavailability compared to conventional dosage forms. .[37,38] Microemulsion based gels for vaginal delivery of clotrimazole and fluconazole were developed and compared with the marketed clotrimazole gel (Candid-V® gel) by in vitro methods [39]. These microemulsion based gels showed significantly higher in vitro bioadhesion, antifungal activity as compared to that of Candid-V® gel.[40]

Ocular Drug Delivery System

Eye drops account for 90% of the available ophthalmic formulations due to their simplicity and convenience. However, rapid precorneal loss caused by drainage and high tear fluid turnover is amongst the major problems associated with topical ophthalmic drug delivery. Only 5% of the applied drug in eye drops penetrates the cornea and reaches the intraocular tissues with the rest of the dose undergoing transconjunctival absorption or drainage via the nasolacrimal duct before transnasal absorption. This results in loss of drug into the systemic circulation and provides undesirable systemic side effects. Accordingly, microemulsions provided a promising alternative with improved ocular retention, increased corneal drug absorption and reduced systemic side effects whilst maintaining the simplicity and convenience of the dosage form as eye drops. [41]

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