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Microemulsions- Potential Carrier for Improved Drug Delivery

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Abstract

The novel carriers have been exploited through almost all the routes of administration. Association of drugs with carriers is normally noncovalent, based on collective strength of weak binding forces. Many newer carriers are evolving with the advent of technology and the demand of targeted delivery like microemulsions. Microemulsions are clear, stable, isotropic mixtures of oil, water and surfactant, frequently in combination with a cosurfactant. These systems are currently of interest to the pharmaceutical scientist because of their considerable potential to act as drug delivery vehicles by incorporating a wide range of drug molecules. They offer the advantage of spontaneous formation, ease of manufacturing and scale-up, thermodynamic stability, and improved drug solubilization and bioavailability. Preparing a pharmaceutically acceptable dosage form demands a clear understanding of the micro-emulsion structure, phase behavior, factors leading to its thermodynamic stability, factors influencing drug release from the formulation, requirements of ideal microemulsion excipients, and the potential uses and limitations of the microemulsion system.

Key Words: ***Microemulsions, Surfactants, Cosurfactants, Thermodynamic stability, Phase behavior, Novel carriers,***

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Introduction

In search of safe and effective therapy, the development of new drugs has been the common practice historically. However, it involved a long gestation period in terms of time, efforts, and huge cost. Later on, it was realized that the issues pertaining to efficacy and safety are largely influenced by the distribution of the drug within the biological system, as there is appreciable deviation from the desired site of action, i.e., the target site. This objective, hitherto un-accomplished gave way to an alternate approach of drug delivery, wherein the carrier systems were used to deliver the molecules to specific receptor sites without afflicting the normal tissues and organs of the body. The fundamentals lie in hosting the drug in carefully designed carriers to bring favorable change(s) in its surrounding microenvironment, and consequently, its delivery. It is the modification(s) in physicochemical characteristics of the molecules and in the barrier properties of the biological membranes at various locations, which lead to improved transportation of drugs toward the diseased locations. Further, it improves the chances of the availability of the drug at the specific receptor site and enhances drug receptor interaction through mediation of specialized composition and design of the carrier systems. All these factors tend to potentiate the degree of pharmacodynamic response, the safety and patient compliance being the immediate benefits [1]. Microemulsions are dispersions of nanometer-sized droplets of an immiscible liquid within another liquid. Droplet formation is facilitated by the addition of surfactants and often also cosurfactants. Through the years much has been written on the formation and stability of these oil-dispersed-in-water (o/w) or water-dispersed-in-oil (w/o) systems. Nevertheless, the cosmetic formulator still seeks to understand and create the most favorable cosmetically eloquent and functional products possible. Aesthetically appealing products can be formulated as trans- parent o/w or w/o dispersions called microemulsions. The possible application for these systems range from products with an extended shelf life to delivery systems for active ingredients [2]. These versatile systems are currently of great technological and scientific interest to the researchers because of their potential to incorporate a wide range of drug molecules (hydrophilic and hydrophobic) due to the presence of both lipophilic and hydrophilic domains. These adaptable delivery systems provide protection against oxidation, enzymatic hydrolysis and improve the solubilization of lipophilic drugs and hence enhance their bioavailability.

In addition to oral and intravenous delivery, they are amenable for sustained and targeted delivery through

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ophthalmic, dental, pulmonary, vaginal and topical routes. Microemulsions are experiencing a very active development as reflected by the numerous publications and patents being granted on these systems [3].

Theories of Microemulsion Formation

Historically, three approaches have been used to explain microemulsion formation and stability. They are as follows-

- Interfacial or mixed film theories.
- Solubilization theories.
- Thermodynamic treatments.

The free energy of microemulsion 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 microemulsion
S = change in entropy of the system
T = temperature
γ = surface tension of oil water interphase

It should be noted that when a microemulsion is formed the change in A is very large due to the large number of very small droplets formed. In order for a microemulsion to be formed (transient) negative value of was required, it is recognized that while value of 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, microemulsion is spontaneous and the resulting dispersion is thermodynamically stable [4-5].

Types of microemulsion systems:

According to Winsor, there are four types of microemulsion phases exists in equilibria, these phases are referred as Winsor phases [6-7]. They are,

1. **Winsor I:** With two phases, the lower (o/w) microemulsion phases in equilibrium with the upper excess oil.
2. ***Winsor II*:** With two phases, the upper microemulsion phase (w/o) microemulsion phases in equilibrium with lower excess water.
3. ***Winsor III:*** With three phases, middle microemulsion phase (o/w plus w/o, called bicontinous) in equilibrium with upper excess oil and lower excess water.
4. ***Winsor IV:*** In single phase, with oil, water and surfactant homogenously mixed.

Advantages of microemulsion over other dosage forms

- Increases the rate of absorption
- Eliminates variability in absorption
- Helps solublize lipophilic drug
- Provides a aqueous dosage form for water insoluble drugs
- Increases bioavailability
- Various routes like tropical, oral and intravenous can be used to deliver the product
- Rapid and efficient penetration of the drug moiety
- Helpful in taste masking
- Provides protection from hydrolysis and oxidation as drug in oil phase in o/w microemulsion is not exposed to attack by water and air.
- Liquid dosage form increases patient compliance.
- Less amount of energy requirement.

Components of Microemulsion System

A large number of oils and surfactant are available but their use in the microemulsion formulation is restricted due to their toxicity, irritation potential and unclear mechanism of action. Oils and surfactant which will be used for the formulation of microemulsion should be biocompatible, non-toxic, clinically acceptable, and use emulsifiers in an appropriate concentration range that will result in mild and non-aggressive microemulsion. The emphasis is, excipients should be generally regarded as safe (GRAS) [3].

Oil Phase

The oil component influences curvature by its ability to penetrate and swell the tail group region of the surfactant monolayer. As compare to long chain alkanes, short chain oil penetrate the tail group region to a greater extent and resulting in increased negative curvature (and reduced

effective HLB). Following are the different oils mainly used for the formulation of microemulsion:

- 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, myristic and oleic acid.

The main criterion for the selection of oil is that the drug should have high solubility in it. This will minimize the volume of the formulation to deliver the therapeutic dose of the drug in an encapsulated form.

Surfactants

The role of surfactant in the formulation of microemulsion is to lower the interfacial tension which will ultimately facilitates dispersion process during the preparation of microemulsion and provide a flexible around the droplets. The surfactant should have appropriate lipophilic character to provide the correct curvature at the interfacial region. Generally, low HLB surfactants are suitable for w/o microemulsion, whereas high HLB (>12) are suitable for o/w microemulsion. Following are the different surfactants are mainly used for microemulsion-

Polysorbate (Tween 80 and Tween 20), Lauromacrogol 300, Lecithins, Decyl polyglucoside (Labrafil M 1944 LS), Polyglyceryl-6-dioleate (Plurol Oleique), Dioctyl sodium sulfosuccinate (Aersol OT), PEG-8 caprylic/capril glyceride (Labrasol).

Cosurfactants

Cosurfactants are mainly used in microemulsion formulation for following reasons:

- They allow the interfacial film sufficient flexible to take up different curvatures required to form microemulsion over a wide range of composition.
- Short to medium chain length alcohols (C3-C8) reduce the interfacial tension and increase the fluidity of the interface.
- Surfactant having HLB greater than 20 often require the presence of cosurfactant to reduce their effective HLB to a value within the range required for microemulsion formulation.

Following are the different cosurfactant mainly used for microemulsion:

sorbitan monoleate, sorbitan monosterate, propylene glycol, propylene glycol monocaprylate (Capryol 90), 2-(2-ethoxyethoxy)ethanol (Transcutol) and ethanol.

Preparation of Microemulsion

Following are the different methods are used for the preparation of microemulsion[3]:

-Phase titration method

-Phase inversion method

Phase titration method

Microemulsions are prepared by the spontaneous emulsification method (phase titration method) and can be portrayed with the help of phase diagram. As quaternary phase diagram (four component system) is time consuming and difficult to interpret, pseudo ternary phase diagram is constructed to find out the different zones including microemulsion zone, in which each corner of the diagram represents 100% of the particular components. Pseudo-ternary phase diagrams of oil, water, and co-surfactant/surfactants mixtures are constructed at fixed cosurfactant/surfactant weight ratios. Phase diagrams are obtained by mixing of the ingredients, which shall be pre-weighed into glass vials and titrated with water and stirred well at room temperature. Formation of monophasic/ biphasic system is confirmed by visual inspection. In case turbidity appears followed by a phase separation, the samples shall be considered as biphasic. In case monophasic, clear and transparent mixtures are visualized after stirring; the samples shall be marked as points in the phase diagram. The area covered by these points is considered as the microemulsion region of existence.

Phase inversion method

Phase inversion of microemulsion is carried out 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 ultimately affect drug release both *in vitro* and *in vivo*. 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 temperature to a w/o microemulsion at higher temperatures (transitional phase inversion). During cooling, the system crosses a point zero spontaneous curvature and minimal surface tension, promoting the formation of finely

dispersed oil droplets. Apart from temperature, salt concentration or pH value may also be considered.

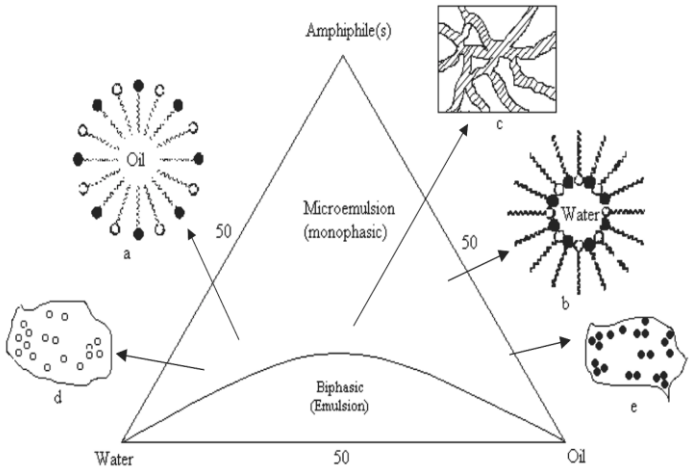

Fig. A ternary phase diagram portraying various structures a) o/w microemulsion; b) w/o microemulsion; c) bicontinuous microemulsion; d) and e) various dispersions.

A transition in the radius of curvature can be obtained by changing the water volume fraction. Initially water droplets are formed in a continuous oil phase by successively adding water into oil. Increasing the water volume fraction changes the spontaneous curvature of the surfactant from initially stabilizing a w/o microemulsion to an o/w microemulsion at the inversion locus.

Characterization of Microemulsions

The characterization of microemulsions is a difficult task due to their complexity, variety of structures and components involved in these systems, as well as the limitations associated with each technique but such knowledge is essential for their successful commercial exploitation. Phase Behavior StudiesPhase behavior studies are essential for the study of surfactant system determined by using phase diagram that provide information on the boundaries of the different phases as a function of composition variables and temperatures, and, more important, structural organization can be also inferred. Phase behaviour studies also allow comparison of the efficiency of different surfactants for a given application. In the phase behaviour studies, simple measurement and equipments are required. The boundaries of one-phase region can be assessed easily by visual observation of samples of known composition. The main drawback is long equilibrium time required for multiphase region, especially if liquid crystalline phase is involved [15].

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 obtaining quantitative information on the size, shape and dynamics of the components. The major drawback of this technique is the dilution of the sample required for the reduction of interparticular interaction. This dilution can modify the structure and the composition of the pseudophases. Nevertheless, successful determinations have been carried out using a dilution technique that maintains the identity of droplets. Small-angle X-ray scattering techniques have been used to obtain information on droplet size and shape [16].

Nuclear Magnetic Resonance Studies

The structure and dynamics of microemulsions can be studied by using nuclear magnetic resonance techniques. Self-diffusion measurements using different tracer techniques, generally radio labeling, supply information on the mobility of the components. The Fourier transform pulsed-gradient spin-echo (FT-PGSE) technique uses the magnetic gradient on the samples and it allows simultaneous and rapid determination of the self-diffusion coefficients (in the range of 10^{-9} to 10^{-12} m^2s^{-1}), of many components [17-18].

Interfacial Tension

The formation and the properties of microemulsion can be studied by measuring the interfacial tension. Ultra low values of interfacial tension are correlated with phase behaviour, particularly the existence of surfactant phase or middle-phase microemulsions in equilibrium with aqueous and oil phases. Spinning-drop apparatus can be used to measure the ultra low interfacial tension. Interfacial tensions are derived form the measurement of the shape of a drop of the low-density phase, rotating it in cylindrical capillary filled with high-density phase [19].

Viscosity Measurements

Viscosity measurements can indicate the presence of rod-like or worm-like reverse micelle.Viscosity measurements as a function of volume fraction have been used to determine the hydrodynamic radius of droplets, as

well as interaction between droplets and deviations from spherical shape by fitting the results to appropriate models (e.g. for microemulsions showing Newtonian behaviour, Einstein's equation for the relative viscosity can be used to calculate the hydrodynamic volume of the particles)[20].

Electron Microscope Characterization

Transmission Electron Microscopy (TEM) is the most important technique for the study of microstructures of microemulsions 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.

Applications of microemulsion in delivery of drug

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 herein.

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, nonpolar 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, Sandimmune 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 bioavialbility of poorly water soluble drugs by enhancing their solubility in gastrointestinal fluid [8].

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 Corsewant and Thoren[9] in which C3-C4 alcohols were replaced with parenterally acceptable cosurfactants, 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.

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 of the drug and related toxicity effects. Another is the direct delivery and targetability of the drug to affected areas of the skin or eyes. Now a day, there have been a number of studies in the area of drug penetration into the skin. They are able to incorporate both hydrophilic (5-flurouracil, apomorphine hydrochloride, diphenhydramine hydrochloride, tetracaine hydrochloride, methotrexate) and lipophilic drugs (estradiol, finasteride, ketoprofen, meloxicam, felodipine, triptolide) and enhance their permeation. Since formation of microemulsion formation requires high surfactant concentration, the skin irritation aspect must be considered especially when they are intended to be applied for a longer period [10].

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. Recent research has been focused on the development of new and more effective delivery systems. Microemulsions have emerged as a promising dosage form for ocular use.

Chloramphenicol, an antibiotic used in the treatment of trachoma and keratitis, in the common eye drops hydrolyzes easily. Lv *et al*. investigated the microemulsion composed of Span 20, Tween 20, isopropylmyristate and water as potential drug delivery systems for eye drops. Chlroamphenicol was entrapped in the o/w microemulsion free of alcohol. The authors revealed that microemulsion formulation content much lower glycol (main hydrolysis product) than that in the commercial eye drops at the end of the accelerated experiments. Thus, a remarkable increase in the chloramphenicol stability was observed in the microemulsion formulations [11].

Fialho *et al*. studied microemulsion based dexamethasone eye drops which showed better tolerability and higher bioavailability. The formulation showed greater penetration in the eye which allowed the possibility of decreasing dosing frequency and thereby improve patient compliance [12].

Nasal delivery

Recently, microemulsions are being studied as a delivery system to enhance uptake of drug through nasal mucosa. In addition with mucoadhesive 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[13].

Drug targeting

Drug targeting to the different tissues has evolved as the most desirable goal of drug delivery. By altering pharmacokinetics and biodistribution of drugs and restricting their action to the targeted tissue increased drug efficacy with concomitant reduction of their toxic effects can be achieved. Shiokawa *et al*. reported a novel microemulsion formulation for tumor targeting of lipophilic antitumor antibiotic aclainomycin A (ACM). They reported that a folate-linked microemulsion is feasible for tumour targeted ACM delivery. They also reported that folate modification with a sufficiently long PEG chain on emulsions is an effective way of targeting emulsion to tumour cells [14].

Brain Targeting

Intranasal administration confers a simple, practical, cost effective, convenient and noninvasive route of administration for rapid drug delivery to the brain. It allows a direct transport of drugs to the brain circumventing the brain barriers Vyas *et al*. prepared mucoadhesive microemulsion for an antiepileptic drug clonazepam. The aim was to provide rapid delivery to the rat brain. Brain/blood ratio at all sampling points up to 8h following intranasal administration of clonazepam mucoadhesive microemulsion compared to i.v. was found to be 2- fold higher indicating larger extent of distribution of the drug in the brain [21].

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 provide reproducible bioavailability. Industrial point of view, it can be easily scaled up with considering relative cost of commercial production. Microemulsion can also be used for cosmetic purpose and drug targeting. 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.

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