International Research Journal of Pharmaceutical and Applied Sciences (IRJPAS)
Available online at **www.irjpas.com**
Int. Res J Pharm. App Sci., 2013; 3(1): 109-116

Review Article

MICRO EMULSION: A PROMISING APPROACH FOR CONTROLLED DRUG RELEASE

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(Received: 12 February, 2013; Accepted: 20 February, 2013; Published: 25 February, 2013)
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Abstract: Microemulsions are class of micro heterogeneous systems having unique features of stability, solubilization capacity, Structural morphology, physical properties and applicability. Microemulsion are stable, clear, isotropic liquid mixtures of oil, water with surfactant, frequently in combination with a cosurfactant. They offer the advantage of easy 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 and the potential uses and limitations of the microemulsion system. While microemulsion is used in several fields, in this review the pharmaceutical applications are emphasized. Several references are cited, but the list is by no means exhaustive.
Key**words:** Micro Emulsion, Solubilization, Thermodynamic Stability.

INTRODUCTION

Microemulsions were first introduced by Hoar and Schulman in 1943. It is well established that large amounts of two immiscible liquids (e.g. water and oil) can be brought into a single phase (macroscopically homogeneous but microscopically heterogeneous) by addition of an appropriate surfactant or a surfactant mixture. This unique class of optically clear, thermodynamically stable and usually low viscous solutions, called 'microemulsions', have been the subject of extensive research over the last two decades primarily because of their scientific and technological importance[1].microemulsion are isotropically clear, and thermodynamically stable dispersions of two immiscible liquids such as oil and water, stabilized by relatively large amount of surfactant and usually in conjugation with a co-surfactant, typically a short to medium chain alcohols[2]. Microemulsions are isotropic, thermodynamically stable solutions in which substantial amounts of two immiscible liquids (i.e., water and oil) are brought into a single phase by means of an appropriate surfactant or surfactant mixture. Although microemulsions are macroscopically homogeneous on a microscopic level they are heterogenous, because a surfactant monolayer separates water- and oil-rich domains. The two basic types of microemulsions are direct (oil dispersed in water, o/w) and reversed (water dispersed in oil, w/o)[3].

In ternary systems such as microemulsions, where two immiscible phases (water and 'oil') are present with a surfactant, the surfactant molecules may form a monolayer at the interface between the oil and water, with the hydrophobic tails of the surfactant molecules dissolved in the oil phase and the hydrophilic head groups in the aqueous phase. As in the binary systems (water/surfactant or oil/surfactant), self-assembled structures of different types can be formed, ranging, for example, from (inverted) spherical and cylindrical micelles to lamellar phases and bi-continuous microemulsions, which may coexist with predominantly oil or aqueous phases. In principle, microemulsions can be used to deliver drugs to the patients via several routes, but the topical application of microemulsions has gained increasing interest. The three main factors determining the transdermal permeation of drugs are the mobility of drug in the vehicle, release of drug from the vehicle, and permeation of drug into the skin. These factors affect either the thermodynamic activity that drives the drug into the skin or the permeability of drug in the skin, particularly stratum corneum. Microemulsions improve the transdermal delivery of several drugs over the conventional topical preparations such as emulsions [4], and gels. Mobility of drugs in microemulsions is more facile 8, as compared to the microemulsion with gel former which will increase its viscosity and further decrease the permeation in the skin[5].The superior transdermal flux from microemulsions has been shown to be mainly due to their high solubilization potential for lipophilic and hydrophilic drugs. This generates an increased thermodynamic activity towards the skin. Microemulsions may affect the permeability of drug in the skin. In this case, the components of microemulsions serve as permeation enhancers[6]. Several compounds used in microemulsions have been reported to improve the transdermal permeation by altering the structure of the stratum corneum[7]. For example, short chain alkanols are widely used as permeation enhancers[8]. It is known that oleic acid, a fatty acid with one double bond in the chain structure, perturbs the lipid barrier in the stratum corneum by forming separate domains which interfere with the continuity of the multilamellar stratum corneum and may induce highly permeable pathways in the stratum corneum.

Isopropyl myristate (IPM) is used as a permeation enhancer in transdermal formulations, but the mechanism of its action is poorly understood. Nonionic surfactants are widely used in topical formulations as solubilizing agents but some recent results indicate that they may affect also the skin barrier function[9]. It is of interest to explore the effects of

these components in the organized microemulsion structures. The aim of the present study was to investigate the potential of several microemulsion formulations in transdermal delivery of lipophilic drugs. A unique attempt was made to emulsify coconut oil with the help of polyoxyethylene 2-cetyl ether (Brij 52) and isopropanol or ethanol, forming stable isotropic dispersion thus paving way for use of plant and vegetable oil to be used as oil phase in microemulsion[10].

Theory: Various theories concerning microemulsion formation, stability and phase behavior have been proposed over the years. For example, one explanation for their thermodynamic stability is that the oil/water dispersion is stabilized by the surfactant present and their formation involves the elastic properties of the surfactant film at the oil/water interface, which involves as parameters, the curvature and the rigidity of the film. These parameters may have an assumed or measured pressure and/or temperature dependence (and/or the salinity of the aqueous phase), which may be used to infer the region of stability of the microemulsion, or to delineate the region where three coexisting phases occur, for example. Calculations of the interfacial tension of the microemulsion with a coexisting oil or aqueous phase are also often of special focus and may sometimes be used to guide their formulation.

Historical Background: The combination of water and oil, made into a single-phase system with the aid of a third component (surfactant), was patented in mid 1930's[11]. However, it was not until 1943 when the first academic studies were performed [12]. Hoar and Schulman showed, with the help of a strong surface-active agent, it is possible to induce spontaneous emulsification. This is now attributed to microemulsion formation, owing to very low interfacial tensions promoted by the surfactants. Five years later, Winsor studied the phase behaviour of water-oil-surfactant mixtures in the presence of different additives and classified four types of phase equilibria[13]:

Type I: Surfactant-rich water phase (lower phase) coexists with surfactant-poor oil phase (Winsor I).
Type II: Surfactant-rich oil phase (the upper phase) coexists with surfactant-poor water phase (Winsor II).
Type III: Surfactant rich middle-phase coexists with both water (lower) and oil (upper) surfactant-poor phases (Winsor III).
Type IV: Single phase homogeneous mixture. In 1959, Schulman et al., [14] titrated a multiphase system (consisting of water, oil and surfactant) with alcohol and obtained a transparent solution which they termed 'a microemulsion'. At that early stage some researchers preferred to identify these systems with 'swollen micelles'[15] others used the term 'micellar emulsion'[16]. Nevertheless, the term 'microemulsion' is a commonly used name nowadays. A detailed historical background of microemulsions can be found elsewhere[17].

The key differences between ordinary emulsions (macro emulsions) and microemulsionsare shown in Table 1**.(2)**

Table 1: Emulsion Vs Microemulsion

Property	Emulsion	Microemulsion
Composition	Water, oil and emulsifier	Water, oil, emulsifier and co-surfactant
Appearance	Semi transparent to cloudy	Transparent homogenous liquid
Viscosity	Viscous liquid	Less viscous
Particle size	1-20 um	10-100 nm
Interfacial tension	5-50 dynes/cm	10-2 - 10-3 dyne/cm
Interfacial film	Tough	Highly flexible
Manufacturing	Tedious, high sheer needed	Easy and spontaneous
Free energy	More	Zero or negative
Stability	Thermodynamically unstable	Thermodynamically stable

The use of a microemulsion gel as vehicle may enhance transdermal penetration by various mechanism, many molecules or solubilised in microemulsion in addition microemulsion induce a change in the thermodynamic activity of the drug they contain, modifying their partition coefficient and thus favour penetration of the stratum corneum. Furthermore, their component surfactant reduces the functional barrier of stratum corneum[18].

ADVANTAGES OF MICROEMULSIONS:

1. Ease of manufacturing and scale-up.
2. Wide applications in colloidal drug delivery systems for the purpose of drug targeting and controlled release.
3. Helps in solubilization of lipophillic drug hence Increase the rate of absorption and bioavailability of drugs.
4. Eliminates variability in absorption.
5. Provides an aqueous dosage form for water insoluble drugs.
6. Various routes like tropical, oral and intravenous can be used to deliver the drug[19].
7. Rapid and efficient penetration of the drug moiety.
8. Helpful in taste masking.
9. Same microemulsions can carry both lipophilic and hydrophilic drugs.
10. Provides protection from hydrolysis and oxidation as drug in oil phase in O/W microemulsion is not exposed to attack by water and air.
11. Liquid dosage form increases patient compliance.
12. Less amount of energy requirement.
13. Microemulsion lower the skin irritation: alcohol-free microemulsions have been reported with much lower irritation potential.
14. Long shelf life as compared to other colloidal drug delivery system.

15. High drug loading[20].

DISADVANTAGES OF MICROEMULSIONS

1. In many cases high concentration of surfactant and co-surfactants is required to formulate a stable microemulsion.
2. A relatively small number of pharmaceutically acceptable excepients are available to be used in microemulsion formulation[21]

Method of Preparation:

1. Phase 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 useful approach to study the complex series of interactions that can occur when different components are mixed. Microemulsions are formed along with various association structures (including emulsion, micelles, lamellar, hexagonal, cubic, and various gels and oily dispersion) 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. As quaternary phase diagram (four component system) is time consuming and difficult to interpret, pseudo ternary phase diagram is often constructed to find the different zones including microemulsion zone, in which each corner of the diagram represents 100% of the particular component. 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.

2. 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. 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). 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. Additionally, a transition in the spontaneous radius of curvature can be obtained by changing the water volume fraction. By successively adding water into oil, initially water droplets are formed in a continuous oil phase. 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. Microemulsions can be prepared by controlled addition of lower alkanols (butanol, pentanol and hexanol) to milky emulsions to produce transparent solutions comprising dispersions of either water-in-oil (w/o) or oil-in-water (o/w) in nanometer or colloidal dispersions (~ 100 nm). The lower alkanols are called cosurfactants, they lower the interfacial tension between oil and water sufficiently low for almost spontaneous formation. The miscibility of oil, water and amphiphile (surfactant plus cosurfactant) depends on the overall composition which is system specific. When English chemist J.H. Schulman introduced the term "microemulsion" in 1943 he described the transition from a stable oil-rich mixture to a stable water-rich mixture. Microemulsions contain a polar component, water, and a non polar component, oil, which makes them capable of solubilizing a wide spectrum of substances. They measure in size from 3 to 300 nanometers in droplet diameter, are transparent and thermodynamically stable. Due to these special properties microemulsions offer a high potential for numerous practical applications. Consequently, microemulsions may be used for enhanced oil recovery, cosmetic formulations, edible coatings for food, and for drug delivery systems as both transdermal or oral administrative vehicles for the controlled release of dosages. Microemulsions also have industrial applications, one of them being the synthesis of polymers. Microemulsion polymerization is a complex heterogeneous process where transport of monomers, free radicals and other species (such as chain transfer agent, co-surfactant and inhibitors) between the aqueous and organic phases, takes place.[22] Compared with other heterogeneous polymerization processes (suspension or emulsion) microemulsion polymerization is a more complicated system. Polymerization rate is controlled by monomer partitioning between the phases, particle nucleation, and adsorption and desorption of radicals. Particle stability is affected by the amount and type of surfactant and pH of dispersing medium. Several authors have reported preparation of microemulsions using alcohols of short or medium length chains (e.g., butanol, heptanol or pentanol) as co-surfactants[23]. These substances limit the potential application of microemulsion due to their toxic and irritant properties. A selection of components for microemulsions suitable for pharmaceutical use involves a consideration of their toxicity and, if the systems are to be used topically, their irritation and sensitivity properties[24]. The ionic surfactants are generally too toxic to be used for preparation of lipid emulsions; therefore, non ionic surfactants, such as the poloxamers, polysorbates, polyethylene glycol are preferred. Polysorbate 80 is widely applied to pharmaceutical preparations, including ophthalmic preparations, due to its history of usefulness and safety, and it is listed in the United States Pharmacopoeia- National Formulary, the European Pharmacopoeia and the Japanese Pharmacopoeia[25]. With the recent improvements in aseptic processing and the availability of new well-tolerated emulsifieres (polysorbate 80), emulsion technology is currently under evaluation for topical cyclosporine A delivery. Ding developed a castor oil in water microemulsion[26]. This microemulsion is stabilized by polysorbate 80 where the active substance cyclosporine A remains stable over 9 months and causes only mild discomfort and slight hyperemia on the rabbit eyes applied 8 times per day during 7 days. This encouraging result allowed the formulations to undergo clinical trials of phase II and III in dry eye disease. The II phase trial performed on 162 patients demonstrated good tolerance of the emulsion[27]

Ternary and quaternary phase diagrams:

The knowledge on the phase manifestations of the pseudoternary (water/amphiphile/oil) or explicitly quaternary (water/surfactant/cosurfactant/oil) mixtures has been systematized. At low surfactant concentration, there is a sequence of equilibria between phases, commonly referred to as Winsor phases[28], they are

Winsor I: with two phases, the lower (oil/water, o/w) microemulsion phases in equilibrium with the upper excess oil;

Winsor II: with two phases, the upper microemulsion phase (water/oil, w/o) in equilibrium with excess water;

Winsor III: with three phases, middle microemulsion phase (o/w plus w/o, called bicontinuous) in equilibriumwith upper excess oil and lower excess water;

Winsor IV: in single phase, with oil, water and surfactant homogeneously mixed.

Inter-conversion among the above-mentioned phases can be achieved by adjusting proportions of the constituents. Simultaneous presenceof two microemulsion phases, one in contact with water and the other in contact with oil is also possible[29]. This may be considered as an extension of Winsor's classification forming the fifth category. A microemulsion forming systems is shown in figure 1. Another important consideration in the formation of microemulsions is related to the packing parameter, which is important for structures with high curvatures (Fig. 2). Surfactants must have the proper molecular volume dimensions and proportions to effectively pack into a micellar structure. Oil phases with high molecular volume fractions (such as triglycerides) will pack less efficiently and will have difficulties in entering between the surfactant tails. This is also reflected in the isotropic regions of a phase diagram. It should be stressed that the o/w microemulsion droplets generally have a larger effective interaction volume than w/o droplets. Also, whereas emulsions consist of roughly spherical droplets of one phase dispersed into the other, microemulsions constantly evolve into various structures ranging from "droplet-like" swollen micelles to bicontinuous structures, frequently making the usual o/w and w/o distinctions irrelevant. Because the size of the particles is much smaller than the wavelength of visible light, microemulsions are transparent and their structure cannot be observed through an optical microscope.

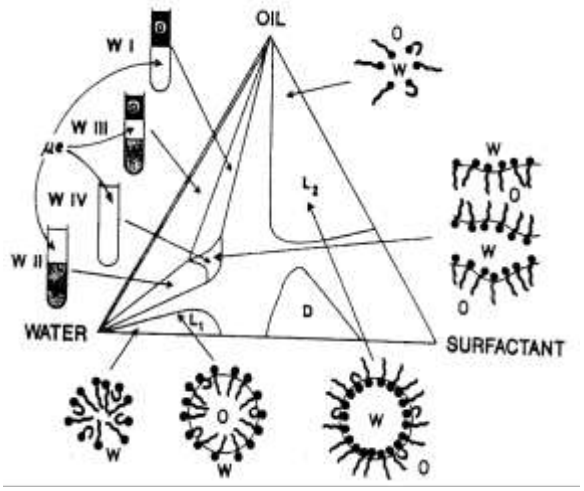

Fig.1: Microemulsion forming system

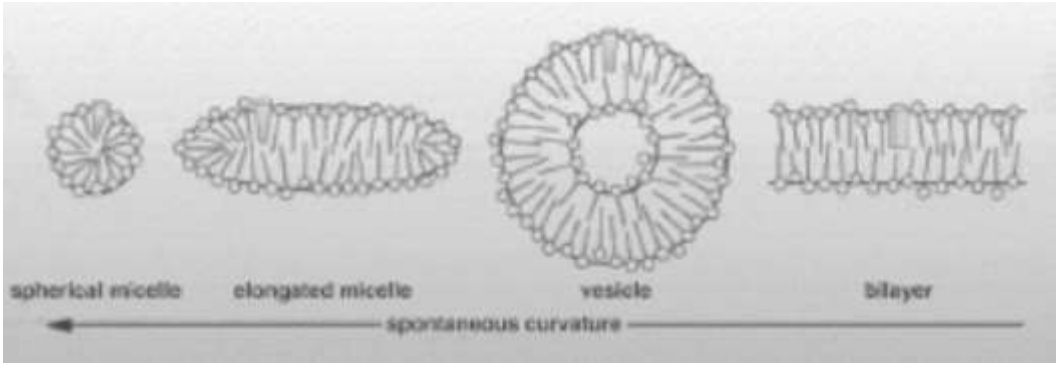

Fig 2: Schematic representation of micro emulsion microstructure

The extents of formation of w/o, o/w and bicontinuous microemulsions can be understood from the phase equilibrium studies. Such studies may often become complex with the appearance of tiny or extended additional zones of viscous gel and liquid crystalline phases[30],the establishment of their boundary demarcations is time consuming and laborious. Most commonly used methods and techniques to acquire information on the particle dimension and shape, their diffusion coefficient and polydispersity, aggregation and dynamics of coalescence, state of the water pool, thermodynamics of formation, etc. of the compartmentalized systems of microemulsion are related to conductance viscosity, ultrasound, static and dynamic light scattering, neutron and low angle X-ray scattering, nuclear magnetic resonance, dielectric relaxation, time

resolved fluorescence quenching, transmission electron microscopy, calorimetry, etc.

Differences between Emulsion & Microemulsion

In contrast to ordinary emulsions, microemulsions form upon simple mixing of the components and do not require the high shear conditions generally used in the formation of ordinary emulsions. The two basic types of microemulsions are direct (oil dispersed in water, o/w) and reversed (water dispersed in oil, w/o). The main difference between emulsions and microemulsions is in the size and shape of the droplets that are dispersed in the continuous phase, reflecting the differences in the thermodynamic stability of the two systems. Emulsions are kinetically stable but thermodynamically unstable, and after storage or aging, droplets will coalesce and the two phases separate. In contrast, microemulsions are thermodynamically stable and will not separate into the corresponding phases. It should be stressed that the term "mini-emulsions" was coined by some authors to describe emulsion droplets of submicron size with improved stabilities; other scientists may call those emulsions "nanoemulsions." While nanoemulsions do not have a long shelf life, they frequently are freshly prepared and used. It should also be stressed that in some studies, the authors neglect to test stability and consider mini- or nanoemulsions to be true microemulsions. The kinetics of microemulsion polymerization has much in common with emulsion polymerization kinetics, the most characteristic feature of which is the compartmentalization, where the radicals growing inside the particles are separated from each other, thus suppressing termination to a high extent and, as a consequence, providing high rates of polymerization. Microemulsions can be sterilized by filtration and their production is relatively simple and inexpensive. Because of these properties, they have attracted a great interest as drug delivery vehicles[31,32]. Microemulsions can be applied as liquid membrane carriers to transport lipophilic substances through an aqueous medium or to carry hydrophilic substances across lipoidal medium. They are proposed for oral, topical, dermal, transdermal, parentenal and pulmonary administration of drugs[33]. Although microemulsions have been known for a long period, their potential as vehicles for topical ocular drug delivery has been investigated only within the last decade[34].

The main problem in a microemulsion application is a high concentration and a narrow range of physiologically acceptable surfactants and co-surfactants.On the other hand, the large surfactant concentration determines their stability[35].

Applications of Microemulsions:

Pharmaceutical Applications

1. Parenteral delivery.
2. Oral drug delivery.
3. Topical drug delivery.
4. Ocular and pulmonary delivery.
5. Microemulsions in biotechnology.

Parenteral Delivery: Parenteral administration (especially via the intravenous route) of drugs with limited solubility is a major problem in industry because of the extremely low amount of drug actually delivered to a targeted site. Microemulsion formulations have distinct advantages over macroemulsion systems when delivered parenterally because of the fine particle microemulsion is cleared more slowly than the coarse particle emulsion and, therefore, have a longer residence time in the body. Both o/w and w/o microemulsion are used for parenteral delivery. The literature contains the details of the many microemulsion systems, few of these can be used for the parenteral delivery because the toxicity of the surfactant and parenteral use. An alternative approach was taken by Von Corsewant and Thoren[36] in which C3-C4 alcohols were replaced with parenterally acceptable co-surfactants, 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. The middle phase structure was preferred in this application, because it has been able to incorporate large volumes of oil and water with a minimal concentration of surfactant.

Oral Delivery: Microemulsion formulations offer the several benefits over conventional oral formulation for oral administration including increased absorption, improved clinical potency and decreased drug toxicity[37]. Therefore, microemulsion has been reported to be ideal delivery of drugs such as steroids, hormones, diuretic and antibiotics. Pharmaceutical drugs of peptides and proteins are highly potent and specific in their physiological functions. However, most are difficult to administer orally. With on oral bioavailability in conventional (i.e. non-microemulsion based) formulation of less than 10%, they are usually not therapeutically active by oral administration. Because of their low oral bioavailability, most protein drugs are only available as parenteral formulations. However, peptide drugs have an extremely short biological half life when administered parenterally, so require multiple dosing. A microemulsion formulation of cyclosporine, named Neoral® has been introduced to replace Sandimmune®, a crude oil-in-water emulsion of cyclosporine formulation. Neoral® is formulated with a finer dispersion, giving it a more rapid and predictable absorption and less inter and intra patient variability[38].

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. Second is the direct delivery and targetability of the drug to affected area of the skin or eyes. Both O/W and W/O microemulsions have been evaluated in a hairless mouse model for the delivery of prostaglandin E1[39].The microemulsions were based on oleic acid or Gelucire 44/14 as the oil phase and were stabilized by a mixture of Labrasol (C8 and C10 polyglycolysed glycerides) and Plurol Oleique CC 497 as surfactant. Although enhanced delivery rates were observed in the case of the o/w microemulsion, the authors concluded that the penetration rates were inadequate for practical use from either system. The use of lecithin/IPP/water microemulsion for the transdermal transport of indomethacin and diclofenac has also been reported. Fourier transform infra red (FTIR) spectroscopy and differential scanning calorimetry (DSC) showed the IPP organogel had disrupted the lipid organisation in human stratum corneum after a 1 day

incubation[40]. The transdermal delivery of the hydrophilic drug diphenhydramine hydrochloride from a w/o microemulsion through the excised human skin has also been investigated. The formulation was based on combinations of Tween 80 and Span 20 (surfactants) with IPM. However two additional formulations were tested containing cholesterol and oleic acid, respectively. Cholesterol increased drug penetration whereas oleic acid had no measurable effect, but the authors clearly demonstrated that penetration characteristics can be modulated by compositional selection [41].

Ocular and Pulmonary Delivery: For the treatment of eye diseases, drugs are essentially delivered topically. O/W microemulsions have been investigated for ocular administration, to dissolve poorly soluble drugs, to increase absorption and to attain prolong release profile. The microemulsions containing pilocarpine were formulated using lecithin, propylene glycol and PEG 200 as co-surfactant and IPM as the oil phase. The formulations were of low viscosity with a refractive index lending to ophthalmologic applications[42]. The formation of a water-in-HFA propellant microemulsion stabilized by fluorocarbon non-ionic surfactant and intended for pulmonary delivery has been described.

Microemulsions in Biotechnology: Many enzymatic and bio-catalytic reactions are conducted in pure organic or aqua-organic media. Biphasic media are also used for these types of reactions. The use of pure apolar media causes the denaturation of biocatalysts. The use of water-proof media is relatively advantageous. Enzymes in low water content display and have;

1. Increased solubility in non-polar reactants
2. Possibility of shifting thermodynamic equilibrium in favor of condensations
3. Improvement of thermal stability of the enzymes, enabling reactions to be carried out at higher temperatures.

Many enzymes, including lipases, esterases, dehydrogenases and oxidases often function in the cells in microenvironments that are hydrophobic in nature. In biological systems many enzymes operate at the interface between hydrophobic and hydrophilic domains and these usually interfaces are stabilized by polar lipids and other natural amphiphiles. Enzymatic catalysis in microemulsions has been used for a variety of reactions, such as synthesis of esters, peptides and sugar acetals transesterification; various hydrolysis reactions and steroid transformation. The most widely used class of enzymes in microemulsion-based reactions is of lipases.

Factors Affecting the Microemulsion

The formation of microemulsion will depend on the following factors:

Packing ratio:

The HLB of surfactant determines the type of microemulsion through its influence on molecular packing and film curvature. The analysis of film curvature for surfactant association's leadings to the formation of microemulsion.

b. Property of surfactant, oil phase and temperature:

The type of microemulsion depends on the nature of surfactant. Surfactant contains hydrophilic head group and lipophilic tail group. The areas of this group, which are a measure of the differential tendency of water to swell head group and oil to swell the tail area, are important for specific formulation when estimating the surfactant HLB in a particular system. When a high concentration of the surfactant is used or when the surfactant is in presence of salt, degree of dissociation of polar groups becomes lesser and resulting system may be w/o type. Diluting with water may increase dissociation and leads to an o/w system. Ionic surfactants are strongly influenced by temperature. It mainly causes increased surfactant counterion dissociation. The oil component also influences curvature by its ability to penetrate and hence swell the tail group region of the surfactant monolayer. Short chains oils penetrate the lipophilic group region to a great extent and results in increased negative curvature. Temperature is extremely important in determining the effective head group size of nonionic surfactants. At low temperature, they are hydrophilic and form normal o/w system. At higher temperature, they are lipophilic and form w/o systems. At an intermediate temperature, microemulsion coexists with excess water and oil phases and forms bicontinuous structure. The chain length, type and nature of cosurfactant: Alcohols are widely used as a cosurfactant in microemulsions. Addition of shorter chain cosurfactant gives positive curvature effect as alcohol swells the head region more than tail region so, it becomes more hydrophilic and o/w type is favoured, while longer chain cosurfactant favours w/o type w/o type by alcohol swelling more in chain region than head region.

Evaluation:

The microemulsions are evaluated by the following techniques. They are

(I) Phase behavior studies: visual observations, phase contrast microscopy and freeze fracture transmission electron microscopy can be used to differentiate microemulsions and coarse emulsions. Clear isotropic one-phase systems are identified as microemulsions whereas opaque systems showing bifringence when viewed by cross polarized light microscopy may be taken as liquid crystalline system.

(II) Scattering Techniques: Scattering techniques such as small angle neutron scattering, small angle X-ray scattering and light scattering have found applications in studies of microemulsion structure, particularly in case of dilute monodisperese spheres, when polydisperse and/or concentrated systems such as those frequently seen in microemulsions.

(III) Transmittance test

Stability of the optimized microemulsion formulation with respect to dilution was checked by measuring transmittance at a specific wavelength with a UV spectrophotometer.

(IV) Globule size and zeta potential measurements

The globule size and zeta potential of themicroemulsion can be determined by dynamic light scattering, using a Zetasizer HSA 3000.

(V) Viscosity measurements

Rheological behavior of the formulation can be observed by using a Brookfield LVDV III+ cone and plate (CP) viscometer (Mfg: Brookfield, USA) using rheocal software at a temperature. Change in the rheological characteristics help in determining the microemulsion region and its separation from other region. Bicontinuous microemulsion are dynamic structures with continuous fluctuations occurring between the bicontinuous structure, swollen reverse micelle, and swollen micelles

(VI) Electrical conductivity

The water phase was added drop wise to a mixture of oil, surfactant and co-surfactant and the electrical conductivity of formulated samples can be measured using a conductometer (CM 180 conductivity meter, Elico, India) at ambient temperature and at a constant frequency of 1 Hz.

(VII) Drug stability

The optimized microemulsion was kept under cold condition (4-8 o C), room temperature and at elevated temperature (50 ± 2 o C). After every 2 months the microemulsion can be analyzed for phase separation, % transmittance, globule size and % assay.

(VIII) Drug solubility

Drug was added in excess to the optimized microemulsion formulation as well as each individual ingredient of the formulation. After continuous stirring for 24 h at room temperature, samples were withdrawn and centrifuged at 6000 rpm for 10 min. The amount of soluble drug in the optimized formulation as well as each individual ingredient of the formulation was calculated by subtracting the drug present in the sediment from the total amount of drug added. The solubility of drug in microemulsion was compared with respect to its individual ingredients.

(IX)Drug release studies

(A) In-vitro drug release

The diffusion study can be carried out on a modified Franz diffusion cell, within volume of 20mL. The receptor compartment was filled with of buffer .The donor compartment was fixed with cellophane membrane, containing the microemulsion formulation and the plain drug solution, separately. At predetermined time intervals samples were withdrawn from the receptor compartment and analyzed for drug content, using a UV spectrophotometer at specific wavelength.

(B) Ex-vivo drug release

Ex -vivo drug release into buffer was studied using intestinal membrane within a Franz diffusion cell. Microemulsion formulation and plain drug solution were placed in the donor compartment of two separate diffusion cells and the temperature of each cell was maintained at 37 ±2°C. The amount of drug released from the microemulsion formulation can be estimated spectro photometrically at specific wavelength, by withdrawing samples from the receptor compartment at predetermined time intervals[44].

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