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Review Article

REVIEW ON MICROEMULSION AS FUTURISTIC DRUG DELIVERY

FAIZI MUZAFFAR*, U. K. SINGH, LALIT CHAUHAN

Department of Pharmaceutics, Kharvel Subharti College of Pharmacy, Swami Vivekanand Subharti University, Meerut, 250005 UP, India.
Email: faizimuzaffar@rediffmail.com

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ABSTRACT

Since the discovery of microemulsions by Jack H. Shulman, there have been huge progresses made in applying microemulsion systems in a plethora of research and industrial processes. Microemulsions are clear, stable, isotropic mixtures of oil, water and surfactant, frequently in combination with a cosurfactant. Microemulsions are optically isotropic and thermodynamically stable liquid solutions of oil, water and amphiphile. To date microemulsions have been shown to be able to protect labile drug, control drug release, increase drug solubility, increase bioavailability and reduce patient variability. Furthermore, it has proven possible to formulate preparations suitable for most routes of administration. Since the discovery of microemulsions, they have attained increasing significance both in basic research and in industry. Due to their unique properties, namely, ultralow interfacial tension, large interfacial area, thermodynamic stability and the ability to solubilise otherwise immiscible liquids, uses and applications of microemulsions have been numerous. Microemulsions are readily distinguished from normal emulsions by their transparency, low viscosity and more fundamentally their thermodynamic stability. Microemulsions are shown to be effective dermal delivery mechanism for several active ingredients for pharmaceutical and cosmetic applications. Topical microemulsions allow rapid penetration of active molecules due to the large surface area of the internal phase, and their components reduce the barrier property of stratum corneum. Microemulsions thereby enhance dermal absorption compared with conventional formulations and are therefore a promising vehicle due to their potential for transdermal drug delivery.

Keywords: Microemulsions, Surfactant, Thermodynamically stable.

INTRODUCTION

The design and development of new drug delivery system with the intention of enhancing the efficacy of existing of drug is an ongoing process in pharmaceutical research. Since there are many types of drug delivery systems that have been developed, one in particular the colloidal drugs delivery system has great potential for achieving the goal in drug targeting. The microemulsion concept was introduced as early as the 1940s by Hoar and Schulman who generated a clear single-phase solution by titrating a milky emulsion with hexanol [1]. They prepared the first microemulsion by dispersing oil in an aqueous surfactants solution and adding an alcohol as a co-surfactant, leading to transparent stable formulation. Schulman and co-workers (1959) subsequently coined the term microemulsion [2], and it has since been defined and indeed redefined on many occasions. For the purposes of this review, however, the microemulsion definition provided by Danielsson and Lindman in 1981 will be used as the point of reference [3]. Microemulsions are thus defined as 'a system of water, oil and amphiphile which is a single optically isotropic and thermodynamically stable liquid solution'.

In practice, the key difference between emulsions and microemulsions are that the former, whilst they may exhibit excellent kinetic stability, are fundamentally thermodynamically unstable and will eventually phase separate [4]. Another important difference concerns their appearance; emulsions are cloudy while microemulsions are clear or translucent. In addition, there are distinct differences in their method of preparation, since emulsions require a large input of energy while microemulsions do not. The latter point has obvious implications when considering the relative cost of commercial production of the two types of system [5].

Microemulsions forms spontaneously with an average droplet diameter of 10 to 140 nm [6]. Microemulsions contain definite boundary between oil and water phases at which surfactant is located. Conventional surfactant molecules comprised polar head group region and an apolar tail region. Microemulsions may be asymmetric in shape, frequently adopting the shape of prolate ellipsoid [7]. Microemulsions can be applied as liquid membrane carriers to transport lipophilic substance through an aqueous medium or to carry hydrophilic substances across lipoidal medium [8]. As the size of the particle is much smaller than the wavelength of visible light, microemulsions are transparent and structure cannot be observed through an optical microscope [9]. Microemulsions are liquid behave as a Newtonian liquid .They are not very viscous [10, 11].

Microemulsions have generated considerable interest over the years as potential drug delivery systems [12,13]. Formulations based on microemulsions have several characteristics viz., enhanced drug solubilization, good thermodynamic stability and ease of manufacturing [14, 15]. Microemulsions are versatile systems and can be used to deliver drugs via several routes. These systems have been extensively studied for topical administration. As topical vehicles, microemulsions can increase the local or systemic delivery of a drug by different mechanisms [15-17]. The existence of micro domains of different polarity within the same single phase solution enables both water soluble and oil soluble materials to be solubilized. The diffusional barrier of the skin may be modified depending on the composition of microemulsion. Also an increased thermodynamic activity of the drug may favour its partitioning in the skin [18].

Advantages of microemulsion over coarse emulsion include its ease of preparation due to spontaneous formation, thermodynamic stability, transparent and elegant appearance, increased drug loading, and enhanced penetration through the biological membranes, increased bioavailability and less inter and intra-individual variability in drug pharmacokinetics. Recently, microemulsions were reviewed for several applications, such as topical use, oral use, parenteral use and cosmetics [19]. So it is promising for dermal delivery of drugs as an efficient route of drug administration [20, 21]. However some gelling agents have been used to increase the viscosity of microemulsion and form microemulsion-based gel(MBG)[22]. which are more suitable for topical application when compared with microemulsion as a vehicle for drug delivery [23, 24].

A microemulsion is a good candidate for oral delivery of poorly water-soluble drugs because of its ability to improve drug solubilization. Absorption rate of a drug increases as its thermodynamic activity in the vehicle increases [25]. The thermodynamic activity can be expressed approximately in terms of relative solubility (the ratio of the current concentration of the drug to the concentration in saturated vehicle) [26].

MEs offer advantages over traditional creams and lotions as topical drug delivery. They were used to solubilise drugs and to improve topical drug availability [27]. They are able to increase the rate and depth of moisturizing agents into skin. It has been suggested that MEs may dissolve the ordered structure of the stratum corneum lipids, leading to the loss of barrier properties of the skin [28].

Advantages of Microemulsion Based Systems: [11, 29, 30]

Microemulsions exhibit several advantages as a drug delivery system

1. Microemulsions are thermodynamically stable system and allows self-emulsification of the system.

2. Microemulsions act as supersolvents for drug, can solubilise both hydrophilic and lipophilic drugs including drugs that are relatively insoluble in both aqueous and hydrophobic solvents.

3. The dispersed phase, lipophilic or hydrophilic (oil-in-water, O/W, or water-in-oil, W/O microemulsions) can act as a potential reservoir of lipophilic or hydrophilic drugs, respectively. Drug release with pseudo-zero-order kinetics can be obtained, depending on the volume of the dispersed phase, the partition of the drug and the transport rate of the drug.

4. The mean diameter of droplets in microemulsion is below 0.22 mm. This yield a large interfacial area, from which the drug is released rapidly into external phase when absorption (in vitro or invivo) takes place, maintaining the concentration in the external phase close to initial levels.

5. Having the ability to carry both lipophilic and hydrophilic drugs.

6. Microemulsion are easy to prepare and require no significant energy contribution during preparation this is due to better thermodynamic stability.

7. Microemulsions have low viscosity compared to primary and multiple emulsions.

8. The use of microemulsion as delivery systems can improve the efficacy of a drug, allowing the total dose to be reduced and thus minimizing side effects.

9. The formation of microemulsion is reversible. They may become unstable at low or high temperature but when the temperature returns to the stability range, the microemulsion reforms.

Disadvantages of Microemulsion Based Systems: [11, 29, 30]

1. Require large amount of S/Cs for stabilizing droplets.

2. Limited solubilizing capacity for high-melting substances used in the system.

3. The surfactant should be nontoxic for use in pharmaceutical applications.

4. Microemulsion stability is influenced by environmental parameters such as temperature and pH. These parameters change as microemulsion delivered to patients.

Limitations: [11,29-30]

Factors which limit the use of microemulsion in pharmaceutical applications.

1. The concentration of surfactants and co-surfactants used must be kept low for toxicological reasons.

2. Microemulsion also suffers from limitations of phase separation.

3. For intravenous use, the demand of toxicity on the formulation is rigorous and very few studies have been reported so far.

4. Use of those surfactants which are included in "generally regarded as safe" (GRAS) category can reduce toxicity.

STRUCTURE OF MICROEMULSION

Microemulsions or Micellar emulsion are dynamic system in which the interface is continuously and spontaneously fluctuating [31]. Structurally, they are divided in to oil in water (o/w), water in oil (w/o) and bi-continuous microemulsions. In w/o microemulsions, water droplets are dispersed in the continuous oil phase while o/w microemulsions are formed when oil droplets are dispersed in the continuous aqueous phase. In system where the amounts of water and oil are similar, the bi-continuous microemulsions may result [32]. The mixture oil water and surfactants are able to form a wide variety of structure and phase depending upon the proportions of component.

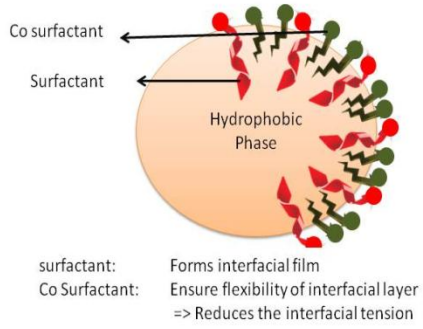


Fig. 1: Microemulsion Structure

Types of microemulsion systems: [29, 33-35]
According to Winsor, there are four types of microemulsion phases exists in equilibria, these phases are referred as Winsor phases. They are,

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

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

Winsor III: With three phases, middle microemulsion phase (o/w plus w/o, called bi-continuous) in equilibrium with upper excess oil and lower excess water.

Winsor IV: In single phase, with oil, water and surfactant homogenously mixed.

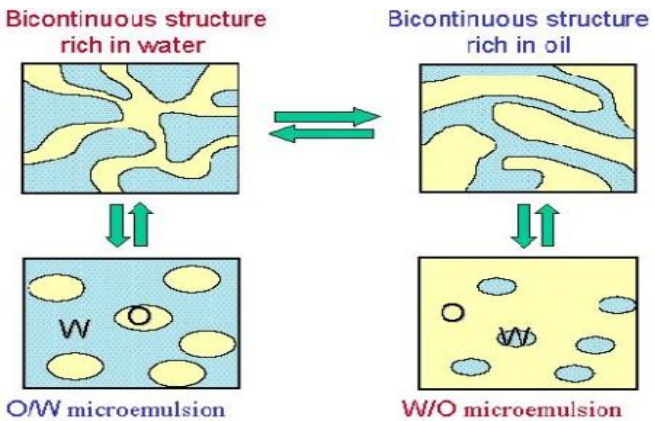


Fig. 2: O/W, W/O and Bi-continuous Microemulsions

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,

$$Gf = \gamma a - TS$$

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.

When 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 was required, it is recognized that while value of A is positive at all times, it is very small and it is offset by the entropic component. The dominant favourable 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 favourable 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 favourable entropic change. In such cases, microemulsion is spontaneous and the resulting dispersion is thermodynamically stable [35-37].

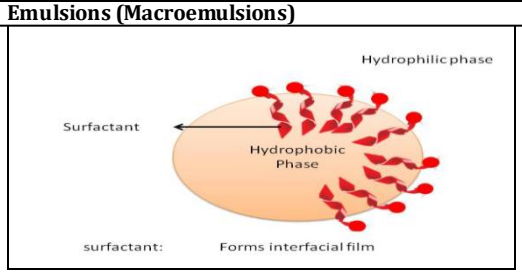
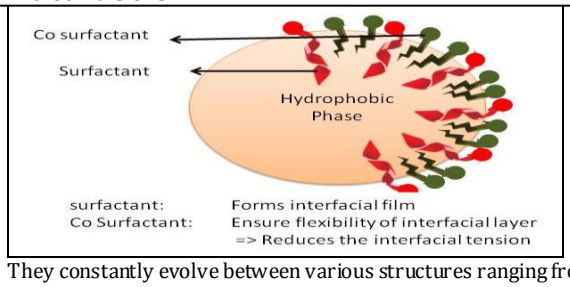
Factors to be considered during preparation of microemulsion

Three important conditions

1. Selection of surfactants is a critical process as an ultra low interfacial tension (< 10^{-3} mN/m) is to be attained at the oil / water interface which is a prime requirement to produce microemulsions.2. Concentration of surfactant must be high enough to provide the number of surfactant molecules needed to stabilize the micro droplets to be produced by an ultra low interfacial tension.

3. The interface must be flexible or fluid enough to promote the formation of microemulsions,

Table 1: Comparison With Emulsions (Macroemulsions) [29, 38-40,43]

S. No.	Emulsions (Macroemulsions)	Microemulsions
		
1.	Emulsions consist of roughly spherical droplets of one phase dispersed into the other.	They constantly evolve between various structures ranging from droplet like swollen micelles to bi-continuous structure.
2.	Droplet diameter: 1 – 20 mm.	10 – 100 nm.
3.	Most emulsions are opaque (white) because bulk of their droplets is greater than wavelength of light and most oils have higher refractive indices than water.	Microemulsions are transparent or translucent as their droplet diameter are less than ¼ of the wavelength of light, they scatter little light.
4.	Ordinary emulsion droplets, however small exist as individual entities until coalesance or Ostwald ripening occurs.	Microemulsion droplet may disappear within a fraction of a second whilst another droplet forms spontaneously elsewhere in the system.
5.	They may remain stable for long periods of time, will ultimately undergo phase separation on standing to attain a minimum in free energy. They are kinetically stable thermodynamically unstable.	More thermodynamically stable than macroemulsions and can have essentially infinite lifetime assuming no change in composition, temperature and pressure, and do not tend to separate.
6.	They are lyophobic.	They are on the borderline between lyophobic and lyophilic colloids
7.	Require intense agitation for their formation.	Generally obtained by gentle mixing of ingredients.

Components of Microemulsion System

The availability of oils and surfactant is abundance but their use 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, and clinically acceptable. The emphasis is on selecting the component which comes under "generally regarded as safe" (GRAS) [35].

1. Oil phase
2. Aqueous phase
3. Primary surfactant
4. Secondary surfactant (co-surfactant)
5. Co-Solvent

1. Oil phase

The oil being one of the most important excipients in the formulation not only because it can solubilise the required dose of the lipophilic drug, it can increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract depending on the molecular nature of the triglyceride.

The oil component influences curvature by its ability to penetrate and hence swell the tail group region of the surfactant monolayer. Short chain oils penetrate the tail group 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).

Following are the different oils are 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.

Saturated and unsaturated fatty acids have penetration enhancing property of their own and they have been studied since a long time.

Fatty acid esters have also been employed as the oil phase. Lipophilic drugs are preferably Solubilise in o/w microemulsions.

Oil is selected according to the solubility of drug. This will minimize the volume of the formulation to deliver the therapeutic dose of the drug in an encapsulated form [35, 43].

2. Aqueous phase

The aqueous phase may contain hydrophilic active ingredients and preservatives. Buffer solutions are used as aqueous phase by some researchers [11].

3. Surfactants

The primary use of surfactant is to lower the interfacial tension to a very small value which will 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.

Surfactants used to stabilize microemulsion system may be

I. non-ionic,
II. zwitterionic,
III. cationic, or
IV. anionic surfactants.

In the formation of microemulsion the surfactant may be ionic or non-ionic, which determines the stabilizing interactions of the hydrophilic end of the surfactant with the aqueous phase. Thus, while a non-ionic surfactant is stabilized by dipole and hydrogen bond interactions with the hydration layer of water on its hydrophilic surface, an ionic surfactant is additionally stabilized by the electrical double layer. Thus, the effect of salt concentration on the stability of an emulsion or a microemulsion is more profound in the case of ionic surfactant than non-ionic surfactants. However for pharmaceutical applications, ionic surfactants are not preferred due to toxicological concerns [41]. Non-ionic surfactants are generally considered to be acceptable for oral ingestion.

Non-ionic surfactants in commercially available solubilized oral formulations include polyoxyl 35 castor oil (Cremophor EL), polyoxyl 40 hydrogenated castor oil (Cremophor RH 40), polysorbate 20 (Tween 20), polysorbate 80 (Tween 80), d-α-tocopherol polyethylene glycol 1000 succinate (TPGS), Solutol HS-15, sorbitan monooleate (Span 80), polyoxyl 40 stearate, and various polyglycolyzed glycerides including Labrafil M-1944CS, Labrafil M-2125CS, Labrasol, Gellucire 44/14, etc[42].

It is generally accepted that low HLB (3-6) surfactants are favoured for the formulation of w/o microemulsion, whereas surfactants with high HLB (8-18) are preferred for the formation of o/w microemulsion. Surfactants having HLB greater than 20 often require the presence of co-surfactants to reduce their effective HLB to a value within the range required for microemulsion formation [43].

4. Co-surfactants

It has been found that single-chain surfactants alone are unable to reduce the o/w interfacial tension sufficiently to enable a microemulsion to form. The presence of co-surfactants allows the interfacial film sufficient flexibility to take up different curvatures required to form microemulsion over a wide range of composition. If a single surfactant film is desired, the lipophilic chains of the surfactant should be sufficiently short, or contain fluidizing groups (e.g. unsaturated bonds). Short to medium chain length alcohols (C3-C8) are commonly added as co surfactants which further reduce the interfacial tension and increase the fluidity of the interface. Typical co-surfactants are short chain alcohols (ethanol to butanol), glycols such as propylene glycol, medium chain alcohols, amines or acids. The use of co-surfactant is to destroy liquid crystalline or gel structures that form in place of a microemulsion phase and co-surfactant free microemulsion in most system cannot be made except at high temperature.

The role of a co-surfactant is as following

1) Increase the fluidity of the interface.

2) Destroy liquid crystalline or gel structure which would prevent the formation of microemulsion.

3) Adjust HLB value and spontaneous curvature of the interface by changing surfactant partitioning characteristic.[43,44]

5. Co-solvents

The production of stable microemulsion requires relatively high concentrations (generally more than 30% w/w) of surfactants. Organic solvents such as, ethanol, propylene glycol (PG), and polyethylene glycol (PEG) are suitable for oral delivery, and they enable the dissolution of large quantities of either the hydrophilic surfactant or the drug in the lipid base. These solvents can even act as co-surfactants in microemulsion systems. [43, 44]

Solubility studies for microemulsion preparation [11, 46]

The solubility of drug in various oils (Glyceryl Mono-& dicaprate, isopropyl myristate, sunflower oil, soya bean oil, Labrafac® CC), surfactant (Cremophor® EL, Labrasol®), and co-surfactants (Transcutol® P, isopropyl alcohol, PEG-600, and glycerol) was determined. Excess drug (100 mg) was added to each cap vial containing five millilitres selected vehicle was added and vortexed for half an hour and placed in shaker for 48 hours at 25°C than content were centrifuged at 5000 rpm for 10 minutes. The undissolved drug, as well as the solubilised drug in the supernatant, was quantified by UV spectroscopy and the mass balance was obtained.

Construction of pseudoternary phase diagram [47]

Pseudoternary phase diagrams comprises of oil, Smix and water were developed using the aqueous titration method, specific ratio of Smix, oil were taken in vial and vortexed for five minutes followed by addition of water with micropipette, the addition of water was continued until addition of one more drop produce turbidity. They were also visually observed for phase clarity and flowability. The volume of aqueous phase was noted and Phase diagrams were then constructed using Tri plot v1-4 software.

These values were then used to determine the boundaries of the Microemulsions domain corresponding to the chosen value of oils, as well as the surfactant or cosurfactant mixing ratio. To determine the effect of drug addition on the microemulsions boundary, phase diagrams were also constructed in the presence of drug using drug-enriched oil as the hydrophobic component.

METHOD OF PREPARATION [48, 49]

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 equilibrium 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 Fig. (**3**) 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.

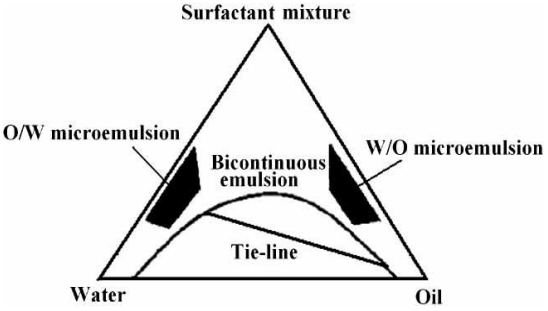


Fig. 3: Pseudoternary phase diagram of oil, water and surfactant showing microemulsion region.

2. Phase Inversion Method

Phase inversion of microemulsions occurs as a result of 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. Short-chain surfactants form flexible monolayers at the o/w interface resulting in a bicontinuous microemulsion at the inversion point.

Hypothetical Phase Diagram [50]

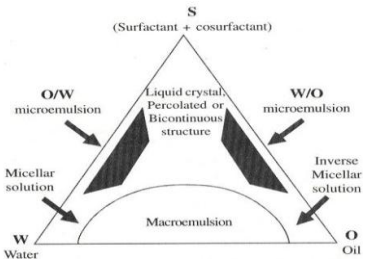


Fig. 4: Hypothetical Phase region of Microemulsion system

From above figure, we can see that,

- When there is high concentration of oil, surfactant forms reverse micelles capable of solubilizing more water molecules in their hydrophilic interior.
- Continued addition of water in this system may result in the formation of W/O microemulsion in which water exists as droplets surrounded and stabilized by interfacial layer of the surfactant / co-surfactant mixture.
- At a limiting water content, the isotropic clear region changes to a turbid, birefringent one.
- Upon further dilution with water, a liquid crystalline region may be formed in which the water is sandwiched between surfactant double layers.
- Finally, as amount of water increases, this lamellar structure will break down and water will form a continuous phase containing droplets of oil stabilized by a surfactant / co-surfactant (O/W microemulsions)

Factors Affecting Formation and Phase Behavior of Microemulsions

1. Factor affecting formation of Microemulsion system [51,52]

The formation of oil or water swollen microemulsion depends on the packing ratio, property of surfactant, oil phase, temperature, the chain length, type and nature of co-surfactant.

Packing ratio

The HLB (Hydrophilic Lipophilic Balance) of surfactant determines the type of microemulsion through its influence on molecular packing and film curvature. The analysis of film curvature for surfactant associations leading to microemulsion formation has been explained by Israelachvili et al (1976) and Mitchell and Ninham (1977) in terms of packing ratio, also called as critical packing parameter.

$$\text{Critical Packing Parameter (CPP)} = v/a * l$$

Where,

v is the partial molar volume of the hydrophobic portion of the surfactant,

a is the optimal head group area and l is the length of the surfactant tail.

- If CPP (0-1) interface curves towards water (positive curvature) and o/w systems are favoured
- CPP is greater than 1, interface curves spontaneously towards oil (negative curvature) so w/o microemulsions are favoured
- At zero curvature, when the HLB is balanced (p is equivalent to 1), then either bi continuous or lamellar structures may form according to the rigidity of the film (zero curvature).

Property of Surfactant, Oil Phase and Temperature

The type of microemulsion formed depends on the nature of surfactant. Surfactant contains hydrophilic head group and lipophilic tail group. The areas of these groups, 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 counter-ion 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 Co-Surfactant

In the formation of alcohols are widely used as a co-surfactant in microemulsions. Addition of shorter chain co-surfactant 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 co-surfactant favours w/o type w/o type by alcohol swelling more in chain region than head region.

2. Factor Affecting Phase Behaviour [51,53]

- **Salinity**

At low salinity, the droplet size of o/w microemulsion increases. This corresponds to increase in the solubilization of oil. As salinity

further increases, the system becomes bi- continuous over an intermediate salinity range. Increase in salinity leads to formation of continuous microemulsion with reduction in globule size. Further increase in salinity ultimately results in complete phase transition.

- **Alcohol concentration**

Increasing the concentration of low molecular weight alcohol as a co surfactant leads to the phase transition from w/o to bi continuous and ultimately to o/w type microemulsion. Exactly opposite phase transition is noticed in case of high molecular weight alcohol.

- **Surfactant Hydrophobic Chain Length**

The increase in length of hydrophobic chain length of the surfactant shows the change of o/w microemulsion to w/o via bi continuous phase.

- **pH**

Change in pH influences the microemulsions containing pH sensitive surfactants. This effect is more pronounced in case of acidic or alkaline surfactants. Carboxylic acids and amines change the phase behaviour from w/o to o/w by increasing the pH.

- **Nature of Oil**

Increase in the aromaticity of oil leads to phase transition from o/w to w/o and is opposite to that of increase in the oil alkane carbon number.

- **Ionic Strength**

As the ionic strength increases the system passes from o/w microemulsion in equilibrium with excess oil to the middle phase and finally to w/o microemulsion in equilibrium with excess water.

Characterization of Microemulsion [48, 54]

Microemulsions can be characterized by different techniques. 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. Therefore, complementary studies using a combination of techniques are usually required to obtain a comprehensive view of the physicochemical properties and structure of microemulsions.

The basic component in a physicochemical characterization of microemulsions systems are

- Phase stability and phase behaviour.
- Microstructure, dimension.
- Shape and surface futures such as specific area, charge and distribution.
- Local molecular rearrangement.
- Interaction and dynamics.

Among these properties particle size, interactions, and dynamics are fundamental importance because they control many of general properties of microemulsions. The release of drug from Microemulsions depends on various process parameters like oil aqueous phase ratio, droplet size, the distribution of drug in the phases of Microemulsions system and rate of diffusion or absorption in both phases.

- **Visual observation**

Microemulsions are visually observed for clarity and flowability.

- **Centrifugation:** [55]

ME systems are subjected to centrifugation at 5000 rpm for 30 minutes and then examined for any phase separation.

Interfacial Tension: [56]

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 from the measurement of the shape of a drop of the low-density phase, rotating it in cylindrical capillary filled with high-density phase.

EVALUATION OF THE SYSTEMS

- **Visual Inspection**

For visual inspection microemulsion can be inspect visually for homogeneity, optical clarity, and fluidity.

- **Examination under Cross-polarizing Microscope** [57, 58]

The microemulsion systems are subjected to examination under crosspolarizing microscope for the absence of birefringence to exclude liquid crystalline systems.

- **Limpidity Test (Percent Transmittance)** [59]

The limpidity of the microemulsion can be measured spectrophotometrically using spectrophotometer.

- **Assessment of the Rheological Properties** [60]

The rheological properties plays an important role in stability. It can be determined by Brookfield digital viscometer.

Accelerated Stability Tests [61, 62]

- **Centrifugation stress testing**

Stability studies is time consuming process, so accelerated stability test is preferred. Microemulsion are centrifuged at 5000 and 10,000 rpm for 30 min were applied in order to assess the physical instabilities like phase separation, phase inversion, aggregation, creaming and cracking of the formulations. Previously thermally tested formulation are taken in centrifuge sample tubes and placed in the centrifuge basket at a well-balanced equilibrium position at ambient temperature conditions.

- **Freeze-Thaw Cycles (FTC)**

To access any change in stability of microemulsion they are subjected to stored at 25°C for 24 h and followed by 24 h at −5°C, the cycle is repeated three times and change is noted.

- **Long Term Stability**

Stability can be examined according to ICH guidelines. The Microemulsion are stored under ambient conditions for 6 months, and the system was examined periodically after 1, 3, and 6 months by visual inspection and measurement of percent transmittance, pH, specific gravity, and rheological evaluation.

- **Determination of the globule size** [63]

The globule size of the microemulsion formulation can be determined by JDS Quasi Elastic Light Scattering, Uniphase, US Instruments. Through the light scattering method, the size determination is much easier than by the photomicroscope method.

Determination of thermalstability [64]

Twenty milliliters of drug-loaded microemulsions are stored in a 25 ml transparent borosil volumetric container at three different temperatures, i.e. 4°, 25° and 40°C, 1°C in BOD for a period of 1 month. Samples are removed periodically for visual inspection to observe any physical changes like loss of clarity, coalescence and turbidity, etc. Also, the samples can be observed for the determination of loss of aqueous phase that is an essential part of the microemulsion stability.

Specific gravity testing at 28°C [64]

To determine the specific gravity, a capillary gravity bottle method is used. Washed and dried, the precaution was necessary during the drying of the gravity bottle as a little amount of moisture could increase the errors in the data of the specific gravity of the samples.

pH of the microemulsions [64-66]

The microemulsion samples is taken into the sample tubes and a µpH meter is used to determine the pH of the different samples as the pH of the formulation is not the only factor and that the stability of the microemulsions also imparts a role to alter the bioavailability of the drug through microemulsion at the site of permeation.

Study of microstructure of Microemulsions [67]

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.

- The cryo-TEM analyses in which samples are directly visualized after fast freeze and freeze fructose in the cold microscope.
- The Freeze Fracture TEM technique in which a replica of the specimen is images under RT conditions.

Identification test for type of microemulsions [68]

- **Dilution test**

If the continuous phase is added in microemulsions, it will not crack or separate into phases. If water is added in o/w type of microemulsions it will remain stable.

- **Staining test**

Water soluble dye such as methylene blue or amaranth is added in water and microemulsion is prepared with oil and surfactant. A drop of Microemulsions is observed under microscope. Background is found to be blue / red and globule will appear colourless respectively.

- **Dilutability test**

The Microemulsions formed is diluted in 1:10, and 1:100, ratios with double distilled water to check if the system shows any signs of separation.

- **Zeta potential measurement** [69]

It must be negative or neutral, which indicate that droplets of micro emulsion having no charge and hence the system is stable. Zeta potential is determined by using Zetasizer. Zeta potential is essentially useful for assessing flocculation since electrical charges on particles influence the rate of flocculation.

- **In Vitro Skin Permeation Study** [70-74]

Skin permeation study is conducted to find the permeation of drug through skin. The study must be carried out under the guideline compiled by Committee for the Purpose of Control and Supervision of Experiments on Animal (CPCSEA, Ministry of Culture, Government of India). Those microemulsion formulation which is found to be best in evaluation studies is used. The abdominal skins obtained from male Wistar rats weighing 230±20 g (age, 6–8 weeks) is used for in vitro permeation experiments formulations. After hair is shaved carefully with an electric clipper, the skin is excised from the abdominal region of each sacrificed rat and the subcutaneous fat and other extraneous tissues is removed without damaging the epidermal surface. The excised rat skins is washed and examined for integrity, and then stored at 4°C for 24 h in phosphate-buffered saline pH 6.8 (PBS), and then used for the permeation experiments. The permeation experiments is performed using Franz diffusion cells fitted with excised rat skins having epidermal surface outward. The effective diffusion area is about 3.14 cm2 (20 mm diameter orifice), and the receptor compartment is filled with 12 ml of PBS. The diffusion cell was maintained at 37±1°C using a recirculating waterbath and the solution in receptor chamber is stirred continuously at 600 rpm throughout the experiment. The specified amount of formulation is gently placed in a donor chamber. At 1, 2, 4, 6, and 8 h aliquot of 2 mL sample is withdrawn from the receptor compartment for spectrophotometric determination and replaced immediately with an equal volume of fresh PBS. Average values of three readings of in vitro permeation data is calculated and the average cumulative amount of drug permeated per unit surface area of the skin is plotted versus time.

The permeation rate of FLZ at steady-state (Jss, micrograms per centimeter per hour) through rat skin is calculated from the slope of linear portion of the cumulative amount permeated through the rat skins per unit area versus time plot.

In order to obtain the permeability coefficient Kp (centimeters per hour), the following equation was used

$$Kp ¼ Jss = Cdonor$$

Where, Kp is the permeability coefficient, Jss is the flux calculated at steady-state, and Cdonor represents the applied drug concentration in the donor compartment.

- **Phase Behaviour Studies** [75]

Phase behaviour 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.

Other useful means and ways of representing the phase behaviour are to keep the concentration of one component or the ratio of two components constant. As the number of components increases, the number of experiments needed to define the complete phase behaviour becomes extraordinary large and the representation of phase behaviour becomes extremely complex. One approach to characterize these multicomponent systems is by means of pseudoternary diagrams that combine more than one component in the vertices of the ternary diagram.

Scattering Techniques for Microemulsions [76-80]

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 informations 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. [23,27]

Static light scattering techniques have also been widely used to determine microemulsion droplet size and shape. In these experiments the intensity of scattered light is generally measured at various angles and for different concentrations of microemulsion droplets. Dynamic light scattering, which is also referred as photon correlation spectroscopy (PCS), is used to analyse the fluctuations in the intensity of scattering by the droplets due to Brownian motion. The self-correlation is measured that gives information on dynamics of the system. [28,32]

- **Nuclear Magnetic Resonance Studies** [81-84]

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.

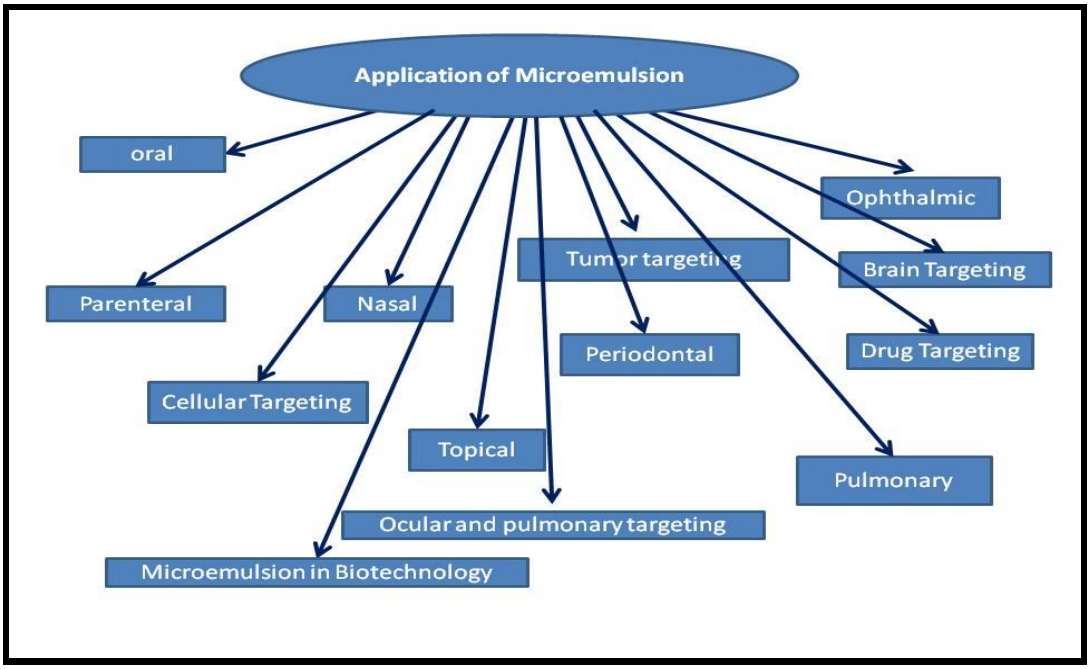


Fig. 5: Represents application of microemulsion.

- **Polydispersity** [85]

This property is characterized by Abbe refractometer.

- **Measurement of electrical conductivity** [86]

The electrical conductivity of microemulsions was measured with a conductivity meter equipped with inbuilt magnetic stirrer. This is done by using conductivity cell consisting of two platinum plates separated by desired distance and having liquid between the platinum plates acting as a conductor.

Application of microemulsion in delivery of drug

Pharmaceutical Applications

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** [87]

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 bioavailability of poorly water soluble drugs by enhancing their solubility in gastrointestinal fluid.

- **Parenteral delivery** [88]

The formulation of parenteral dosage form of lipophilicand 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 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** [89]

Topical administration of drugs can have advantages over other methods for several reasons, one of which is the avoidance of hepatic first-pass metabolism, salivary and degradation of the drug in stomach 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.

- **Ophthalmic delivery** [90, 91]

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.

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.

- **Nasal delivery** [92]

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.

- **Drug targeting** [93]

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.

- **Periodontal Delivery** [94]

Periodontal disease is a collective term for a number of progressive oral pathological afflictions like inflammation and degeneration of the gums, periodontal ligaments, cementum and its supporting bone. It is a major cause of tooth loss. The invention of Brodin *et al*. included a novel pharmaceutical composition comprising local anaesthetic in oil form, surfactant, water and optionally a taste masking agent. The composition was in the form of an emulsion or microemulsion and had thermoreversible gelling properties i.e. it was less viscous at room temperature than after introduction onto a mucous membrane of a patient. The surfactant in the formulation imparted the thermoreversible gelling properties. Preferred surfactants were Poloxamer 188®, Poloxamer 407® and Arlatone 289®. The composition could be used as a local anaesthetic for pain relief within the oral cavity in conjunction with periodontal scaling and root planning and overcame the problem with the existing topical products (jelly, ointment or spray) such as lack of efficacy due to inadequate depth of penetration, too short duration and difficulties in administration due to spread, taste etc.

- **Cellular Targeting** [95, 96]

Nucleic acids delivered to cells are promising therapeutics. The invention of Monahan *et al.* Included insertion of nucleic acid into a reverse micelle for cell delivery. They referred w/o microemulsions to as reverse micelles. The reverse micelle had the property to compact the nucleic acid for easier delivery. To further enhance the delivery, other molecules such as a surfactant having a disulfide bond or a polyion might be added to the nucleic acid-micelle complex. Another advantage of the invention was the use of reverse micelles for gene delivery to the cells. The micelle containing the compacted polynucleotide could be utilized as a reaction vesicle in which additional compounds such as polycation could be added to the DNA. Additionally, the polynucleotide/reverse micelle system was used as a vesicle for template polymerization of the DNA or caging of the DNA in which the polycation was crosslinked. Another advantage was that the micelle might be cleaved under physiological conditions involved along the transfection (process of delivering a polynucleotide to a cell) pathway. Better recovery and purification of the biomolecules could be achieved by utilizing cleavable reverse micelles which was difficult earlier. The invention of Wheeler *et al.* was related to cell delivery of hydrophobic compounds in microemulsion carriers. Microemulsion was comprised of a mixture of oil, a hydrophobic compound, and a polyethylene glycollinked lipid. The purpose of polyethylene glycol-linked lipid was to enhance the stability of the microemulsion compositions. The hydrophobic compound resided in an oil environment which was surrounded by a monolayer of a polar lipid. The polar head of the lipid faced outwards to provide compatibility with the external aqueous environment and the nonpolar tail faced the internal oil environment. A targeting moiety such as biotin, avidin, streptavidin or antibodies might be covalently or noncovalently attached to the lipid monolayer. The composition could also be used for diagnostic and therapeutic purposes.

- **Tumour Targeting** [97, 98]

Maranh ao suggested the utility of microemulsions as vehicles for the delivery of chemotherapeutic or diagnostic agents to neoplastic cells while avoiding normal cells.

They claimed a method for treating neoplasms, wherein neoplasms cells have an increased number of LDL (low density, lipoprotein) receptors compared to normal cells. The microemulsion comprised of a nucleus of cholesterol esters and not more than 20% triglycerides surrounded by a core of phospholipids and free cholesterol and contained a chemotherapeutic drug. Microemulsions were similar in chemical composition to the lipid portion of low density lipoprotein (LDL), but did not contain the protein portion. These artificial microemulsion particles incorporated plasma apolipoprotein E (apo E) on to their surface when they were injected in the bloodstream or incubated with plasma. The apolipoprotein E served as a linking element between the particles of the microemulsion and the LDL receptors. The microemulsions could then be incorporated into cells via receptors for LDL and delivered the incorporated molecules. Thus, higher concentration of anticancer drugs could be achieved in the neoplastic cells that have an increased expression of the receptors. In this way toxic effects of these drugs on the normal tissues and organs could be avoided. In human subjects, they observed no change in the plasma kinetics of the radioactively labeled microemulsion containing carmustine or cytosine-arabinoside thereby confirming that the incorporation of these drugs did not diminish the capacity of the microemulsion to incorporate apo E in the plasma and bind to the receptors. Shiokawa and coworkers reported a novel microemulsion formulation for tumour targeted drug carrier of lipophilic antitumour antibiotic aclacinomycin A (ACM). Their findings suggested that a folate-linked microemulsion is feasible for tumour targeted ACM delivery. The study showed that folate modification with a sufficiently long PEG chain on emulsions is an effective way of targeting emulsion to tumour cells.

- **Brain Targeting** [99-103]

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.

- **Ocular and Pulmonary Delivery** [104]

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.

The formation of a water-in-HFA propellent microemulsion stabilized by fluorocarbon non-ionic surfactant and intended for pulmonary delivery has been described.

- **Microemulsions in Biotechnology** [105]

Many enzymatic and biocatalytic 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 equilibria in favour 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.

Other Applications [106]

- Microemulsion in enhanced oil recovery.
- Microemulsions as fuels.
- Microemulsions as lubricants, cutting oils and corrosion inhibitors
- Microemulsions as coatings and textile finishing.
- Microemulsions in detergency.
- Microemulsions in cosmetics.
- Microemulsions in agrochemicals.
- Microemulsions in food.
- Microemulsions in environmental remediation and detoxification.
- Microporous media synthesis (microemulsion gel technique).
- Microemulsions in analytical applications.
- Microemulsions as liquid membranes.
- Novel crystalline colloidal arrays as chemical sensor materials.

Current and Future Developments

During the last two decades lot of research work has been carried out on microemulsion system **(Table 2, 3)** 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.

Table 2: Research work carried out on microemulsions [46, 85,107-134]

S. No.	Drug	Category	Route
1.	Fluconazole	Antifungal	Topical
2.	Piroxicam	NSAID	Topical
3.	Acyclovir	Antiviral	Topical
4.	Aceclofenac	NSAID	Percutaneous
5.	Ketorolac tromethamine	NSAID	Topical
6.	Celecoxib	NSAID	Topical
7.	Fluconazole	Antifungal	Topical
8.	Sertaconazole	Antifungal	Topical
9.	Diclofenac Sodium	NSAID	Transdermal
10.	Clotrimazole	Antifungal	Vaginal
11.	Fexofenadine	Antihistamines	Oral
12.	Lorazepam	Antiepileptic	Parenteral
13.	Clopidogrel	Antiplatelet	Oral
14.	Flurbiprofen	Analgesics	Parenteral
15.	Apomorphine Hcl	Antiparkinson	Transdermal
16.	Ketoprofen	Analgesics	Transdermal
17.	Fenofibrate	Antihyperlipidemic	Self micro emulsifying
18.	Estradiol	Anticholesteremic	Transdermal
19.	Timolol	Antihypertensive	Opthalmic
20.	Ibuprofen	Analgesic	Parenteral
21.	Piroxicam	Cyclooxygenase Inhibitors	Oral
22.	Progesterone	Hormones	Dermal
23.	Ibuprofen	Analgesic	Topical
24.	Terbinafine	Antifungal	Transdermal
25.	Amphotericin	Antifungal	Parenteral
26.	Dexamethasone	Glucocorticoids	Topical ocular
27.	Itraconazole	Antifungal	Parenteral
28.	Prilocaine Hcl	Local Anesthetics	Transdermal
29.	Chloramphenicol	Antibacterial	Ocular

Table 3: Microemulsions based marketed product [135,136]

S. No.	Brand name	Composition	Manufactured by
1.	Sandimmune Neoral®	Cyclosporin A	Novartis
2.	Norvir ®	Ritonavir	Roche laboratories
3.	Fortovase ®	Saquinavir	Roche laboratories
4.	White Glow	Mulberry Extract	Lotus Herbals

CONCLUSION

Microemulsions are commercially feasible, simple and convenient novel vehicles for delivery of medicaments which can enhance drug absorption with reduced systemic side effects. They can be used to optimise drug targeting without a concomitant increase in systemic absorption. Appropriate excipient 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. Microemulsion have been shown to be able to protect labile drug, control drug release, increase drug solubility, increase bioavailability and reduce patient variability Furthermore it has proven possible to formulate preparations suitable for most routes of administration. Recently, several research papers have been published for the improvement of drug delivery, but still there is a need to emphasis on its characterization part including in vitro evaluation. Many research papers shows higher percentage of surfactant (much higher than CMC level) used for the formation of microemulsion, irrespective of different routes of administration, but there is a lack of toxicological evaluation of the prepared microemulsion, which can be a broad research area in future.

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