Research Journal of Pharmaceutical, Biological and Chemical Sciences

Microemulsions: Developmental aspects

Khanna Surabhi*[1], Katare OP[2], Nasa Atul[3], Garg Arun[4]

[1]Maharaja Surajmal Institute of Pharmacy, Guru Gobind Singh Indraprastha University, Delhi
[2]University Institute of Pharmaceutical Sciences Panjab University, Chandigarh
[3]Sr. Drugs Inspector, Govt of NCT of Delhi
[4]Advanced Institute of Pharmacy, Palwal

ABSTRACT

In recent years, the focus of pharmaceutical research is gradually shifting to the development of drug delivery systems rather than finding newer chemical entities for an all-round improvement in drug therapy. Multiferous materials and principles have been employed to generate a wide variety of carrier classes such as polymer-based particulate systems (microspheres, microcapsules, nanoparticles, and transdermal patches) and rigid, semi-rigid and vescicular lipoidal colloid drug delivery vehicles (liposomes, niosomes, microemulsions, micelles). In the above approaches, the latter has achieved a favorable position because of their non-particulate nature, components of bio-origin and provisions for modifications in the constructs so that they can be tailored to suit the target site. Microemulsions offer several advantages as drug delivery systems as these are thermodynamically stable and stability allows for self emulsification of the system with microemulsion acting as supersolvent of the drug. The dispersed phase lipophilic or hydrophilic can behave as potential reservoir for lipophilic or hydrophilic drug respectively. These systems are easy to prepare and no significant energy contribution is required for their preparation. Microemulsions have low viscosity as compared to conventional emulsions and viscosity can even be tailored using specific gelling agents like carbopol and gelatin. Also the formation of microemulsion is reversible. These become unstable at low temperatures but once the temperature is brought to stability range, microemulsions are reformed. Microemulsions find applications in drug delivery; these can solubilise various lipophilic and hydrophilic drugs. Microemulsions also find miscellaneous applications as lubricants, cutting oils and corrosion inhibitors. These also find application in detergency and cosmetics as well as microemulsion derived systems comprising of liquid membranes, SEDDS and SMEDDS. The present review focuses on the advantages offered by these systems and the developmental aspects including the theory of microemulsification.
Keywords: Microemulsions, phase diagram, film curvature and HLB, formulation, stability

Corresponding author
Email:surabhivohra@gmail.com

INTRODUCTION

In recent years, the focus of pharmaceutical research is gradually shifting to the development of drug delivery systems rather than finding newer chemical entities for an all round improvement in drug therapy. It has been realized that the efficacy and safety of the molecules is related to factors that influence the way they are transported and targeted to the receptor site. This has led to the evolution of a very promising field of NDDS which encompass the collaboration and concerted efforts from the experts of varied fields to help design and develop drug carrier systems of different physicochemical and biological backgrounds.

Tremendous efforts have been put forth by the drug delivery scientists to explore and exploit the potential of diversified branches such as physical, chemical, biophysical, pharmacological, immunological, supramolecular chemistry, nanotechnology together with information technology to engineer carriers with a high degree of site specificity and safety.

Multiferous materials and principles have been employed to generate a wide variety of carrier classes such as polymer based particulate system (microspheres, microcapsules, nanoparticles and transdermal patches) and rigid, semi rigid and vesicular lipoidal colloid drug delivery vehicles (liposomes, niosomes, microemulsions, micelles). In the above approaches, the latter has achieved a favourable position because of their non–particulate nature, components of bio–origin and provisions for modification in the constructs so that they can be tailored to suit the target site. Many such popular systems include erythrocytes, niosomes, pharmacosomes, ufasomes, cryptosomes, dendrimers and various surfactant associated colloids including microemulsion and vesicular systems like liposomes.

After gaining momentum in the research of these supramolecular systems, there has been a quest to find simpler but efficacious answers within the existing domain. The supramolecularly structured microemlusified systems are such systems which have emerged out of already prevailing biphasic emulsified vehicles. An increasing number of opportunities have been realized to achieve drug delivery goals while making technology more feasible and practicable.

Microemulsions as Drug Delivery Systems

Microemulsions can be defined as thermodynamically stable, isotropically clear dispersions of two immiscible liquids, consisting of microdomains of one or both liquids stabilized by an interfacial film of surface active molecules. Microemulsions are superior to macroemulsions because they are thermodynamically stable, optically clear and form spontaneously without the need of high shear equipment.

Microemulsions were brought to attention by Schulman and co-workers in 1943 [1]; however, the term 'Microemulsion' was first suggested in 1959 by Schulman et al. The formulation of microemulsion usually involves a combination of three to five components; namely oil, water, surfactant, cosurfactant and electrolyte. The order of mixing of various components is expected not to influence the formation of microemulsion, but an activation energy barrier must be overcome during their formation.

The basic difference between emulsions and microemulsions is that emulsions may exhibit excellent kinetic stability while fundamentally being thermodynamically unstable and in due time the phases will separate out. In appearance, emulsions are cloudy, while microemulsions are clear and translucent. Emulsions require a large input of energy during their method of preparation but for microemulsions, energy requirement is considerably low.

A stricter definition of Samuelson and Lindman describes microemulsions as optically clear, isotropic and thermodynamically stable liquid solutions of oil, water and amphiphile. It includes micellar and reverse micellar solutions, microdroplets of oil and water and biocontinuous structures and excludes the various surfactant aggregates and transparent emulsions containing very small droplets that are of long-lived kinetic stability.

Merits of Microemulsion-based systems

Microemulsions exhibit several advantages as drug delivery systems [2]:

- Microemulsions are thermodynamically stable systems and stability allows for self-emulsification of the system whose properties are not dependent on the process followed.
- Microemulsions act as 'supersolvents' of drug. They can solubilize hydrophilic and lipophilic drugs relatively insoluble in both aqueous and hydrophobic solvents due to existence of microdomains of different polarity within the same single phase solution.
- The dispersed phase, lipophilic or hydrophilic (oil-in-water, o/w or w/o microemulsion) can behave as a potential reservoir of lipophilic or hydrophilic drug respectively. The drug gets partitioned between dispersed and continuous phases and when the system comes into contact with a semi-permeable membrane, the drug can be transported through the barrier. Drug release with pseudo-zero order kinetics is then obtained depending on volume of dispersed phase, partition coefficient and the transport rate of the drug.

- The mean diameter of microemulsion droplets is below 0.22 μm and hence such systems can be sterilized by filtration.
- Same microemulsion can carry both lipophlic and hydrophilic drugs.
- Because of thermodynamic stability, microemulsions are easy to prepare and hence no significant energy contribution is required for the preparation. Microemulsions have low viscosity as compared to other emulsions. Viscosity can even be tailored using specific gelling agents like Carbopol.
- The use of microemulsions as delivery systems can improve the efficacy of drug as the total dose is reduced thereby minimizing the side-effects.
- The formation of microemulsions is reversible. These may become unstable at low temperature & as temperature is brought to stability range, microemulsions are reformed.

There are certain limitations which should be considered before the use of microemulsions in the field of pharmaceuticals and as drug delivery systems. The components, mainly the surfactants and cosurfactants should be pharmaceutically acceptable and biocompatible. Toxicity may occur at high surfactant concentration and other factors such as maintainance of thermodynamic stability in the temperature range between 0º and 40ºC, salinity, constant pressure during storage, low solubilisation capacity for high molecular weight drugs etc. limit the use of microemulsions in pharmaceutical and medicinal fields.

DEVELOPMENTAL ASPECTS

Phase Behaviour Studies

Phase behaviour studies play a crucial role in development of lipid based colloidal or isotropic (emulsified) systems. A close study of various components and conditions is warranted to see their impact on the kind of assembly they ultimately adopt [3].

Nonionic o/w microemulsions have recently been studied to determine the effect of oil type on phase behaviour [4]. Mainly three important key components have been identified which influence the state of the resultant product out of the various kinds of interactions taking place. These include oil, water and surfactant(s). A number of association structures including ordinary emulsions, micellar and mesomorphic phases of various constructions such as lamellar, hexagonal, cubic and various gels and oily dispersions are formed depending on:

1. Chemical nature of various components [surfactants, cosurfactant , cosolvent and the composition of aqueous phase]
2. Concentration of various components
3. Experimental conditions [temperature, pressure, pH, ionic strength, toxicity etc.].

The complex series of interaction that occur when different ratios of components are mixed, are determined by the following types of phase diagrams [5]: quaternary, ternary, pseudoternary and pseudobinary phase diagrams which can describe the phase manifestations and are essential in the study of microemulsions.

Quaternary Phase Diagrams

These are made up of a regular tetrahedron composed of four equilateral triangles that can be used to plot the compositions of four component systems, with the pure components represented by each corner of the tetrahedron and the edges representing the binary mixtures. But quaternary diagrams are :

● Time consuming to prepare
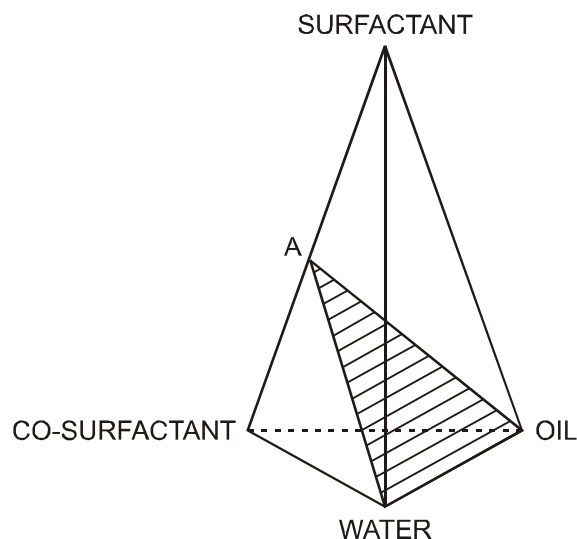● Often difficult to interpret

Figure 1: Multidimensional representation of the phase behaviour of a four component system; hatched area represents fixed surfactant/ cosurfactant ratio.

Pseudo-Ternary Phase Diagrams : In practice, it is more usual to investigate planar sections of the tetrahedron diagrams [pseudo ternary phase diagram] by either keeping the composition of one component fixed and varying the other

three, or by using a constant ratio for two components, generally the surfactant, cosurfactant or cosolvent.

Prepared systems can be classified according to the existence of sequence of equilibria between phases, commonly referred to as **Winsor phases**. These are:

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

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

Winsor III :   with three phases, middle microemulsion phase [o/w + w/o called biocontinuous] in equilibrium with upper excess oil and lower excess water.

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

Winsor V :   is the simultaneous presence of two microemulsions phases, one in contact with water and other in contact with oil.
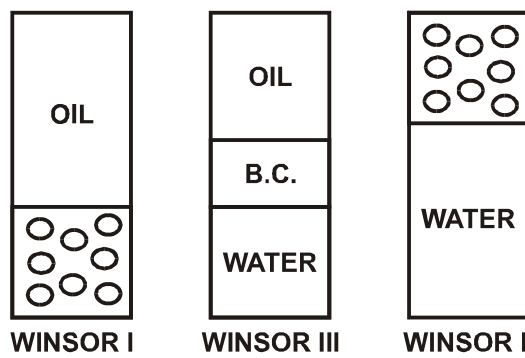

Figure 2:   **Winsor I, II and III systems.**
Type I oil-in-water microemulsion in equilibrium with excess oil;
Type II, water-in-oil microemulsion in equilibrium with excess water;
Type III, bicontinuous structures in equilibrium with excess oil and water.

Interconversions among the above mentioned phases can be achieved by varying the proportions of constituents. Pseudo ternary phase diagrams of systems containing water-lecithin-IPM and either an alkanoic acid, amine, alkanediol, polyethylene glycol alkylether or alcohol as cosurfactant have been reported by Aboofazeli et al in 1994 [6] and it was concluded that the area of existence of various phase regions was dependent upon the nature of

cosurfactant used. Pseudo-ternary phase diagrams of systems containing water-lecithin-alcohol-IPM were also prepared [6].
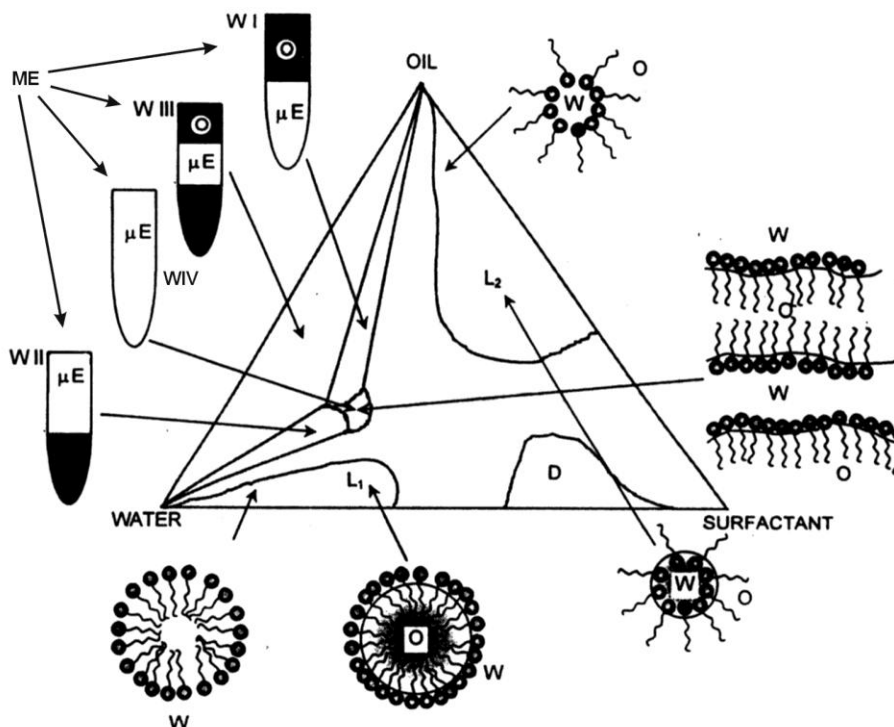

Figure 3: Schematic diagrams showing ternary phase diagram of Winsor phases [WI, WII, WIII and WIV] exists at surfactant concentration; o, oil; w, water; L_1, A single phase region of normal micelles or o/w microemulsions; L_2, Reverse micelles or w/o microemulsions; D, Anisotropic lamellar liquid crystalline phase.

Ternary Phase Diagram : Due to the complexity of multi-component systems, the behaviour of specific three component microemulsions formed from oil, water and a double-chained surfactant [the anionic sodium bis-2-ethylhexylsulfosuccinate, or the cationic surfactant didodecyltrimethylammonium bromide or DDAB] have been widely studied as prototype models for determining general behaviour of microemulsions [7].

These surfactants are only sparingly soluble in either oil or water and form microemulsions in the absence of cosurfactants in such a way that the phase behaviour can be completely represented by a ternary diagram.

Pseudo-Binary Phase Diagrams : An alternate method of presenting data is in the form of pseudo-binary phase diagrams [8-10]. Non-ionic surfactants do not generally need a cosurfactant for microemulsion formation. With such systems, temperature is generally the most crucial factor because the non-ionic surfactant becomes more lipophilic with increase in temperature.

Since the properties of solubilized oil-water systems are not radically different at low concentration, pseudo-binary phase diagrams, where the weight fractions of water and oil at a fixed surfactant weight percent, is presented as a function of temperature, are often constructed. This involves considerably less effort than determining ternary diagrams at a variety of temperatures. A simplified schematic pseudobinary phase diagram representing such systems is shown in fig4.
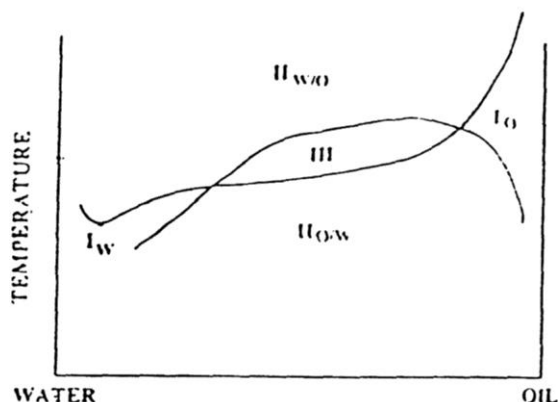

Figure 4. **Typical pseudo-binary phase diagram of weight fraction of oil and water as a function of temperature, with a fixed amount of nonionic surfactant.**

The single phase isotropic region at high and low water concentration. I_w and I_o, correspond to o/w and w/o microemulsions respectively.

The intermediate three phase region, III represents a transition between o/w and w/o phases. The inversion temperature, PIT of the system is found in this region.

The two-phase region in the lower part of the phase diagram II o/w, is composed of water with dissolved surfactant & oil. II w/o upon mixing an o/w at higher temperature represents a two phase region composed of water and oil with dissolved surfactant from which w/o macroemulsions is formed on mixing.

The main limitation of these phase diagrams is that these do not indicate the stability of the system formed.

Stability of Microemulsions

It was recognized by Schulman and Montagne in 1961 [11] that low interfacial tension contributes to the thermodynamic stability of microemulsion. It was realised that the stabilization of microemulsions required a low solubility of surfactant in both oil and water phases, resulting in a preferential absorption of

the surfactant at the water-oil interface and a consequent lowering of the interfacial tension.

The interfacial tension may be decreased to a very small and even a transient negative value where the interface would expand to form fine dispersed droplets and subsequently absorb more surfactant and cosurfactant molecules until the bulk surfactant and cosurfactant concentration is depleted enough to make the interfacial tension positive again. This process, known as "Spontaneous Emulsification" leads to microemulsion formation.

In addition to interfacial tension, many other factors such as interfacial curvature, fluidity and entropy should be considered for the formation and stability of microemulsions. The formation of small microemulsion droplets requires a greater degree of bending of the surfactant interfacial film than that of macroemulsions. To bend an interface, work has to be done against both the interfacial tension and the bending stress.

To express the bending stress of an interface as a function of curvature, consider that at an equilibrium condition, the interface with a very low interfacial tension assumes an optimal configuration and curvature, known as spontaneous curvature $1/R_0$, at which bending energy is minimal; Ro being the equilibrium natural radius of the interface.

The bending energy of the interface may be expressed by a constant K, known as "curvature elasticity". The constant 'K' thus indicates the ease of interfacial deformation. A large 'K' value corresponds to a 'rigid' interface at which large energy is required to bend the interface; a small K value represents a 'fluid' interface at which little energy is necessary for bending. Hence 'K' is also called the 'rigidity constant'. This can be illustrated schematically by the following fig. 5.
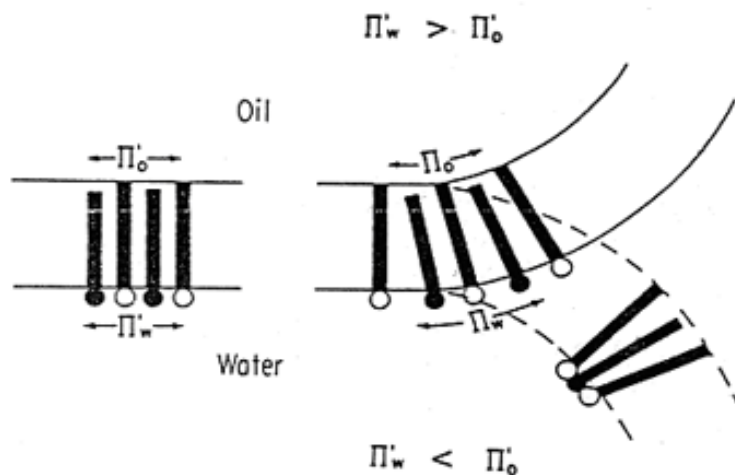

Figure 5 : Schematic illustration of the mechanism of curvature of a microemulsion film.

Safran and Turkevich in 1983 [12], have expressed the energetic term of the interfacial free energy of microemulsion droplets by both-interfacial tension and bending energy of an uncharged interface as :

$$F_1 = n[4\pi\gamma R^2 + 16\pi k(1-R/R_o)^2]$$

where n = no. density of droplets

γ - interfacial tension

R – droplet radius

For a charged interface, an electric double layer term has to be included in above equation.

K value has been found to be of the order of 10^{-14} ergs for microemulsion [13]. The effect of bending energy term is significant only when the interfacial tension is close to zero.

When K is close to K_bT, K_b being the Boltzmann constant, the interface is subject to bending instability and becomes highly fluid due to thermal fluctuations. This bending instability and fluidity of interface may cause lowering of interfacial tension resulting in the spontaneous emulsification phenomenon.

The role of interfacial 'fluidity' has also been manifested in the formulation of microemulsions [13-14]. When K is larger than K_bT; oil, water and surfactant together may form a birefringent lamellar phase, and when K is small, isotropic microemulsions are obtained [14]. The addition to cosurfactants increases the fluidity of the interface resulting in a structural transition from a birefringent lamellar phase to an isotropic microemulsion.

This corroborates the concept that interfacial fluidity plays an important role in the formation and stability of microemulsion. The fluidity of an interface can be increased by choosing a surfactant and cosurfactant with widely different sizes of hydrocarbon moiety, or by adjusting the temperature, so that the hydrophilic and lipophilic properties of the surfactant balance [15].

The increase of entropy due to thermal fluctuations of the interface can be approximated by the mixing entropy of oil and water. The decrease in free energy of the system due to dispersion entropy must exceed the increase of free energy caused by the newly created interfacial area due to emulsification, thus resulting in spontaneous emulsification and stabilization of a microemulsion. Using a titration method, Rosano and Lyons in 1985 verified that the formulation of microemulsion is entropically driven [16].

Various thermodynamic factors contributing to the formulation of microemulsion have also been suggested. Ruckenstein and Chi in 1977 expressed the change of the Gibbs free energy of microemulsion formulation in terms of three individual contributions as [17]:

$$\Delta G_M(R) = \Delta G_1 + \Delta G_2 + \Delta G_3$$

ΔG_1 - interfacial free energy including a positive term due to the creation of charged interface and a negative term due to formation of electrical double layer.

ΔG_2 - free energy of interdroplet interaction composed of a negative term from vander Waals attraction and a positive term from repulsive double layer interactions, and

ΔG_3 - entropy term accounting for the dispersion of microemulsion droplets in the continuous medium.

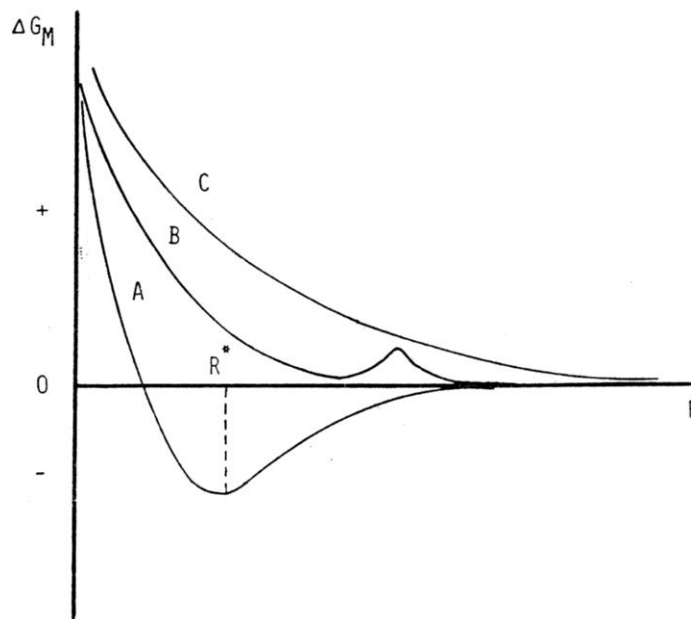The result ΔG_M is plotted as a function of droplet radius R as shown in fig 6.

Figure 6.   **Schematic illustration of the change of the Gibbs free energy of microemulsion formation ΔG_M**

Curve A shows that a microemulsion with the most stable droplet size R* can be formed at negative minimum ΔG_M.

Curves B and C correspond to unstable emulsion systems because the minimal free energy of the systems occur at infinite radius [phase separation].

Curve B may represent a 'kinetically' stable system since a potential barrier must be overcome prior to final phase separation.

When interfacial tension is less than 2×10^{-2} dyne/cm, a stable microemulsion can form. It is seen that the dispersion entropy predominantly contributes to the thermodynamic stability of microemulsions.

The criterion for forming athermodynamically stable dispersion system with low interfacial tension has been proposed as :

$$\frac{-d(\ln \gamma)}{d(\ln R)} \geq 2$$

The form of this inequality may vary and the average equilibrium radius of droplets increase with decreasing interfacial tension for microemulsion, the reverse being true for macroemulsions. The thermodynamic approach has also been reviewed by Kahlweit et al., 1990.

Solubilization in microemulsions : Swollen Micelles Formation

Solubilization is one of the most prominent features of microemulsion systems as it provides a means to incorporate an insoluble compound into a solvent together with altering the structure and properties of microemulsions.

It is seen that w/o microemulsions generally have greater solubilisation capacity and form more readily than o/w microemulsions. Three solubilization sites are available in surfactant aggregates as depicted in Fig7. [18,19]
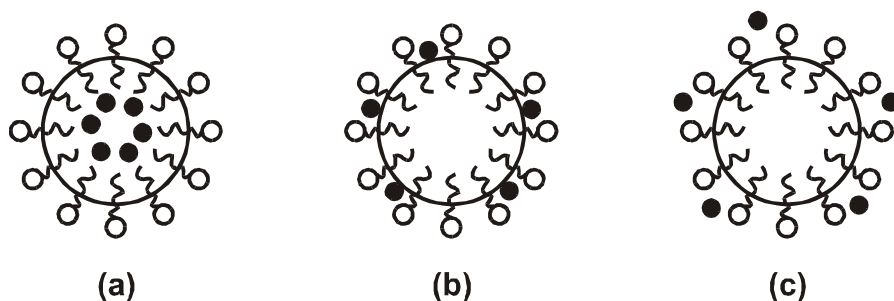

(a)   (b)   (c)

Figure 7: Schematic view of three possible solubilization sites in surfactant aggregates : (a) micelle interior (b) palisade layer; (c) micellar surface.

Taking a normal micelle as an example, hydrocarbons and other nonpolar compounds are considered to be incorporated in the micelle-interior [swollen micelles, Fig 7a]. Some solubilized molecules (solubilizate) may distribute themselves among the surfactant molecules near the surface [Fig 7b]; poor solubilizate molecule may adsorb at the interface [Fig 7c].

Solubilization in microemulsions is normally considered in the context of swollen micelles as it depends on the degree of swelling of a droplet by solubilization.

Numerous factors may effect solubilization of microemulsions [20,21]. The solubilization volume (V) of a spherical microemulsion droplet is related to the radius of swollen core of the droplet by :

$$V = AR/3$$

where A = total interfacial area (depending on the emulsifier concentration).

R = radius of swollen core.

At constant total interfacial area (or emulsifier concentration), solubilization is directly related to the droplet size and hence the curvature of the interface. It is obvious, that when R is infinite (zero curvature), solubilization is maximum.

In addition to droplet size, the stability of microemulsion droplets also influences solubilization. Strong interactions among microemulsion droplets can cause an instability of the system leading to a phase separation or structural change of the system. For e.g., a long-range electrostatic repulsion among normal micelles or o/w microemulsions can lead to structural transition from isotropic to anisotropic structures such as hexagonal or lamellar phases. Strong attractive forces among droplets can cause coagulation or coalescence of the droplets and a consequent phase separation of the microemulsions [22].

FORMULATION ASPECTS

Microemulsion Formulation

Microemulsions are usually developed empirically since no adequate theory exists to predict from which materials they are formed. Their formulation usually involves a combination of three to five components ; an oil phase, aqueous phase, primary surfactant, secondary surfactant or cosurfactant and sometimes an electrolyte. These isotropic systems are usually more difficult to formulate than ordinary emulsions because their formation is a highly specific process involving spontaneous interactions amongst the constituent molecules. Thus it is essential

for a systematic study of microemulsion composition to establish phase diagrams for the system under investigation. From these, the extent of microemulsion region can be identified and its relation with other phases established.

The key to prepare microemulsion lies in controlling the curvature and fluidity of the interfacial film that leads to a large increase of total interfacial area of the system. Thus, the spontaneous formation of microemulsion can only occur when the interfacial tension is so low that the increase in free energy of the system due to newly created surfaces can be compensated by the increased entropy due to fluctuating interfacial films and dispersion of the droplets. So, a relatively large amount of surfactant is required to lower the interfacial tension in formulating conventional microemulsions. A cosurfactant such as short-chain alcohols from C_3 to C_6 is often added to form microemulsions.

Choice of components : Role of surfactant and cosurfactant

In order to reduce the interfacial tension, it is necessary to maximize the interfacial area of the surfactant. To do so, a surfactant with a balanced hydrophilic and lipophilic property is desirable. The surfactant(s)chosen must :-

- lower interfacial tension to a very small value to aid dispersion processes during the preparation of microemulsion.
- provide a flexible film that can readily deform round small droplets
- be of the appropriate hydrophile-lipophile character to provide the correct curvature at the interfacial region for the desired microemulsion type o/w, w/o or bicontinuous.

These conditions have been achieved in several ways, for e.g.,

- by using a combination of an anionic or cationic surfactant of high HLB with a cosurfactant of lower HLB;
- a double-chained surfactant of the appropriate molecular composition; or
- a single chained nonionic surfactant of the PEG-alkyl ether type at appropriate temperature.

It has been proposed that in order to design a three component [water, oil and surfactant] microemulsion, the surfactant hydrocarbon volume V, effective chain length l_c and the head group area a_o should satisfy the relation $V/a_0 l_c = 1$. A surfactant with a balanced oil and water solubility can meet this criterion. On the other hand, a highly water soluble or oil soluble surfactant will have $V/a_0 l_c$ value far from 1 and thus will only produce o/w or w/o microemulsions with small droplet size limited solubilization capacity.

Surfactant – Cosurfactant mixtures

The most important role of cosurfactant in the formation of microemulsion is to increase the interfacial fluidity by penetrating into the surfactant film and consequently creating void space among the surfactant molecules. A cosurfactant with a hydrocarbon moiety of a different size to that of the surfactant is often used. The use of cosurfactant in microemulsions is not mandatory. It is possible to prepare microemulsion by using a double or branched-chain surfactant at a temperature above the thermotropic phase transition temperature of the hydrocarbon moiety. For many nonionic surfactants, microemulsions can also form at low surfactant concentration without cosurfactant when the temperature of the system is at the PIT as suggested by Shinoda et al., 1977 [23]. QSPR relationship models for pseudoternary microemulsions formulated with nonionic surfactants and cosurfactants has been attempted and it was found that data mining computer aided molecular modeling, descriptor calculation and multiple linear regression techniques can be used to produce statistically significant and predictive models for o/w and w/o microemulsions [24].

In addition to its effect on interfacial fluidity, cosurfactant also influences the geometric packing of surfactant and consequently alters the curvature of the interfacial films. Thus the selection of surfactant and cosurfactants is crucial not only to the formation of microemulsion but also to solubilization in microemulsions. Other variables such as the chemical nature of oil, salinity and temperature can also influence the curvature of the interfacial film. Some of these factors are summarized in table1 :

Table 1 :   Factors Affecting Spontaneous Curvature of monolayers

Variable	Curvature effect	Cause
Increase of oil chain length	More positive	Less penetration of surfactant tail region
Addition of shorter chain cosurfactants	More positive	Alcohol swells head region more than tail region
Addition of shorter chain cosurfactants	More negative	Alcohol swells surfactant chain region more than head region
Addition of salt (ionic surfactant)	More negative	Screened repulsion between polar head groups

Variable	Curvature effect	Cause
Addition of salt (nonionic surfactant)	More negative	Head group size reduced by dehydration
Branched or double-chained surfactant	More negative	Increased tail group area
Increased temperature (nonionic surfactant)	More negative	Head group size reduced by dehydration
Increased temperature (ionic surfactant)	More positive	Increased surfactant counter-ion dissociation

Thus the cosurfactant is added to further lower the interfacial tension between the oil and water phases, fluidize the hydrocarbon region of the interfacial film and influence film curvature.

Cosurfactants of short to medium-chain length alcohols ensure that the interfacial film is flexible enough to deform readily around droplets, as their intercalation between the primary surfactant molecules decreases both the polar head group interaction and the hydrocarbon chain interactions. Lamellar liquid crystalline phases rather than microemulsion phases are often formed with longer-chain length cosurfactants.

Medium-chain length alcohols such as pentanol and hexanol are used as effective cosurfactants but are not suitable for pharmaceuticals due to their high irritation potential. Less irritant non-ionic surfactants [polyoxylene alcohol ethers] have been suggested as cosurfactants.

A list of surfactants and cosurfactants that have been used for the preparation of microemulsions is summarised as follows:

Table 2 : List of surfactants

1. Soybean lecithin Epikuron 200 (Phosphatidyl Choline purity >94%)	(Aboofazeli and Lawrence, 1994a) [25]
2. Egg lecithin Ovothin 200 (Phosphatidyl Choline purity 92%)	(Aboofazeli and Lawrence, 1994a) [25]
3. Lyso lecithin	(Trotta *et al.,* 1996) [26]

4.	Sodium dodecyl sulphate (SDS)	(Miyata *et al.,* 1996) [27]
5.	Sodium bis(2–ethylhexyl) sulphosuccinate (Aerosol OT)	Trotta *et al.,* 1996 [26]
6.	Dioctyl sodium sulphosuccinate	(Osborne *et al.,* 1991b) [28]
7.	Sodium dexoycholate	(Das *et al.,* 1989) [29]
8.	Labrasol (Polyethyl ene glycol–8–caprylic acid)	(Krielgaard *et al.,* 2000) [30]
9.	Polyoxyethylene surfactants Polyoxyethylene–10–dodecyl ether ($C_{12}E_{10}$) Polyoxyethylene–10–oleyl ether ($C_{18:1}E_{10}$ or Brij 97) N,N–Dimethyldodecylamine–N–oxide (DDAO) N,N–Dimethyloleylamine–N–oxide (DOAO)	(Warisnoicharoen *et al.,* 2000) [4]
10.	Polyoxyethylene/Polysorbate/Tween 20,40,60,80	(Attwood *et al.,* 1992b) [31]
11.	Sorbitan Monolaurate (Span)	(Taha *et al.,* 2002) [24]
12.	Alkyl Polyglycol ethers	(Kahlweit *et al.,* 1983) [32]
13.	Triton X–100 (p–tertalkyl phenyl polyoxyethylene ether)	(Mitra *et al.,* 1996)[33]
14.	Igepal (720) polyoxyethylated nonylphenol)	(Mitra *et al.,* 1996) [33]
15.	Hexadecyl trimethyl ammonium bromide (CTAB)	(Mackay, 1990) [34]

Table 3 : List of cosurfactants

Ethanol	(Thevenin *et al.,* 1996)	*n*–pentanoic acid	(Aboofazeli and Lawrence 1994b) [25]
Propanol	(Thevenin *et al.,* 1996)	*n*–hexanoic acid	(Aboofazeli and Lawrence 1994b) [25]
Isopropanol	(Thevenin *et al.,*	*n*–butylamine	(Aboofazeli and

	1996)		Lawrence 1994b) [25]
Butanol	(Thevenin *et al.,* 1996)	*n*–pentylamine	(Aboofazeli and Lawrence 1994b) [25]
sec–Butanol	(Aboofazeli and Lawrence 1994)	*n*–hexylamine	(Aboofazeli and Lawrence 1994b) [25]
Isobutanol	(Aboofazeli and Lawrence 1994)	*sec*–butylamine	(Aboofazeli and Lawrence 1994b) [25]
tert–butanol	(Aboofazeli and Lawrence 1994)	*tert*–butylamine	(Aboofazeli and Lawrence 1994b)[25]
Pentanol	(Thevenin *et al.,* 1996)	2–aminopentane	(Aboofazeli and Lawrence 1994b)[25]
Hexanol	(Thevenin *et al.,* 1996)	3–aminopentane	(Aboofazeli and Lawrence 1994b)[25]
Heptanol	(Thevenin *et al.,* 1996)	1,2–butanediol	(Aboofazeli and Lawrence 1994b)[25]
Octanol	(Thevenin *et al.,* 1996)	1,2–pentanediol	(Aboofazeli and Lawrence 1994b)[25]
Sorbitol	(Attwood *et al.,* 1992b)	1,2–hexanediol	(Aboofazeli and Lawrence 1994b)[25]
1–Decanol	(Taha *et al.,* 2002)	Propylene glycol	(Moreno *et al.,* 2000b) [35]

Some newly evolved cosurfactants are as follows :

Cremophor RH40 (polyoxyl 40 hydrogenated castrol oil) [36]

Plurol oleique (polyglyceryl–6–dioleate) [37]

Plurol isostearique (isostearic acid of polyglycerol)[30]

Distearoyl phosphatidyl ethanolamine–N–poly(ethyleneglucol)2000 (DSPE–PEG) [38]

Poloxamer [39]

Polyoxythylene–10–oelyl ether (Brij 96V) [40]

Polysorbate 80 (Tween80) [35]

Span 20 [41]

Sodium monohexyl phosphate [26]

Sodium monooctyl phosphate [26]

N,N–Dimethyl dodecylamine–N–oxide (DDNO) [42]

N,N–Dimethyl octylamine–N–oxide (DONO) [42]

Cinnamic alcohol [33]

Cinnamic aldehyde [33]

Film-curvature and hydrophile-lipophile balance (HLB): The Surfactant packing ratio

The relative sizes of the hydrophilic and hydrophobic groups of the surfactant molecules i.e., the HLB must be correctly balanced for given oil and aqueous solution to produce a microemulsion. The HLB also determines the type of microemulsion, o/w, w/o or bicontinuous, through its influence on molecular packing and film curvature.

The packing ratio P, defined as $P=V/a_0 l_c$ provides a direct measure of HLB. O/W structures are favoured if the effective polar part is more bulky than the hydrophobic part [P < 1], and the interface curves spontaneously towards water [positive curvature]. The w/o structures are formed when the interface curves in the opposite direction [P > 1, negative curvature]. At zero curvature, when the HLB is balanced ($P \cong 1$), either biocontinuous or lamellar structures may form according to the rigidity of the film. The relationship between surfactant HLB, molecular packing and film curvature is illustrated in Fig8.
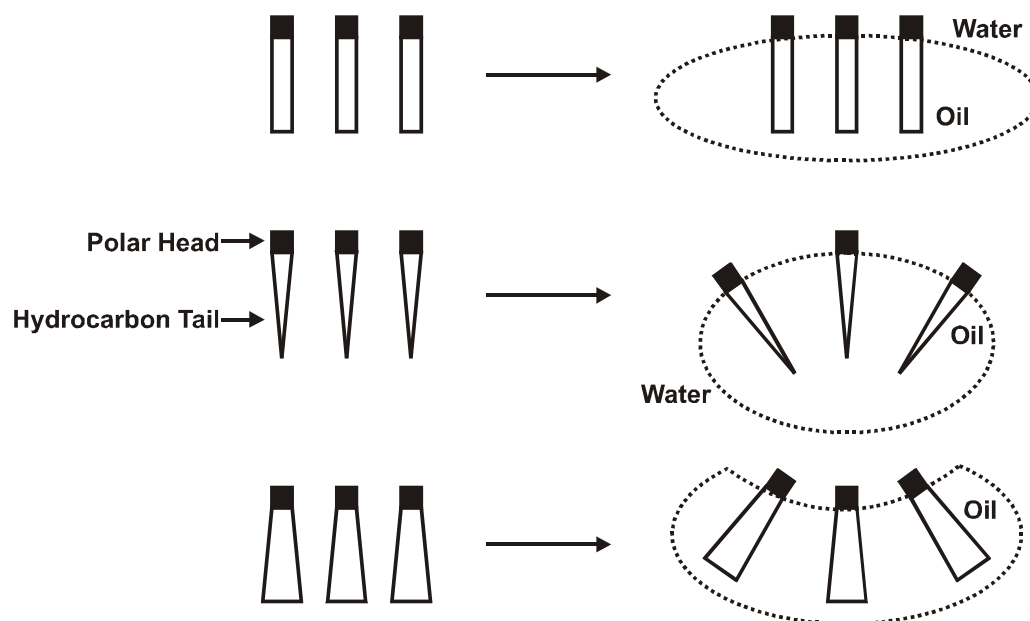
Figure 8 : **A steric model correlating the shape of the amphiphile to the spontaneous curvature of the interface.**

The effective areas of the head and tail groups of the surfactant molecules, which are a measure of the differential tendency of water to swell the head group and of oil to swell the tail area in the specific formulation, are to be considered when estimating the surfactant HLB in a particular system.

Although ionic surfactants are not strongly influenced by temperature, a temperature rise does cause an increase in positive curvature due to counter ion dissolution. Temperature is extremely important in determining the effective head group size of nonionic surfactants, as their hydration characteristics vary continuously with temperature.

The oil component influences curvature by its ability to penetrate and hence swell the tail group region of the surfactant monolayer. Short-chain oils such as alkanes, penetrate the tail group region to a greater extent than long-chain alkanes and hence swell this region to a greater extent, resulting in an increased negative curvature and reduced effective HLB. The change in microemulsion structure with the HLB of the surfactant and the volume fractions of water and oil has been reviewed by Khan et al., 1986 [43]. The effect of chain lengths of n-alcohols on the formation of single phase microemulsions in n-heptane / n-alcohol / sodium dodecyl sulphate / water systems has also been determined by Miyata et al., 1995 [44].

Preparation of Microemulsions

Since microemulsions are thermodynamically stable, they can be prepared simply by blending oil, water, surfactant and cosurfactant with mild agitation. The usual method of preparing microemulsions is to dissolve the surfactant in oil and add the solution to water with gentle shaking. The solution rapidly becomes first translucent and then optically clear after a few seconds. With nonionics, the surfactant may be dissolved in water first.

The order of mixing the components is generally considered not to be critical since microemulsions form spontaneously. Rosano and co-workers [16] demonstrated that, although microemulsification is a spontaneous process, the driving forces are small and the time taken for these systems to reach an equilibrium interfacial tension can be long. Large transitory fluctuations in interfacial tension can occur during the microemulsion mixing process, as the components arrange themselves in such a way that the resulting interfacial and bulk microstructures lead to an overall minimisation in the free energy. The time to establish equilibrium is influenced by the order of mixing. This is established more slowly, if the cosurfactant is injected into the oil phase, as its greater solubility in this phase hinders its diffusion into the aqueous phase.

CONCLUSION

The design and development of drug delivery systems is nowadays more focused on the way therapeutic chemical entities are targeted to the receptor site. The promising field of NDDS extends this approach to help design carrier systems that can be tailored to suit the target site. Various surfactant association colloids including vescicular systems, microemulsions, pseudo latexes, micelles and reverse micelles which can mimic natural substrates offer immense potential in evolving this concept of biomimetism. Over the past few years, microemulsions have attracted more interest as drug delivery systems. Part of this interest appears as a consequence of their transparency, ease of preparation and long term stability. These properties as well as their ability to incorporate drugs of different lipophilicity are some of the reasons why microemulsions are considered for pharmaceutical purposes. The present review focuses on the developmental aspects and the theory behind microemulsification.

REFERENCES

[1]   Hoar, T.P. , Schulman, J.H., Transparent water in oil dispersions : oleopathic hydro – micelle, Nature (London), 1943, 152, 102

[2]   Kuneida, H., Solans, C., In: Industrial applications of microemulsions, Marcel Dekker, New York, 1997, 21

[3]   Chen, S.H., Lin, T.l., In: Surfactants in solutions, 1986, Plenum Press, Vol 6, New York, 1315-1330

[4]   Warisnoicharoen, W., Lansley, A. B., Lawrence, M.J., Nonionic oil in water microemulsions : the effect of oil type on phase behaviour, *Int. J. Pharm.,2000,* 198, 7-27

[5]   Paul, B.K., Moulik, S.P., Uses and applications of microemulsions, *Curr. Sci.,* 2001, 80 (8), 990-1001

[6]   Aboofazeli, R., Lawrence, C.B., Wicks, S.R., Lawrence, M.J., Investigations into the formation and characterization of phospholipid microemulsions III Pseudo ternary phase diagrams of systems containing water- lecithin- isopropyl – myristicate and either an alkanoic acid, amine, alkane diol, polyethylene glycol alkyl ether or alcohol as cosurfactant, *Int. J. Pharm., 1994,* 111, 63-72

[7]   Prig, J.E., Rangel- Zanundio, L.I., Roles of cosurfactant and cosolvent in surfactant water flood, *Langmuir, 1988,* 4, 806- 812

[8]   Shinoda, K., Lindman, B., Colloidal behaviour of surfactant systems : micelles, microemulsions and liquid crystals, *Langmuir,1987,* 3, 135-149

[9]   Friberg,S.E., Benable, R.L., Microemulsions. In: Encyclopedia of Emulsion Technology, (P. Bechner Ed.) Marcel Dekker, Inc., New York, 1983, Vol.1, 287–336.

[10]   Moulik, S.P., Digout, L.G., Palepu, R., Studies on the interfacial composition and thermodynamic properties of w/o microemulsions, *Langmuir, 2000,* 16(7), 3101-310

[11]   Schulman, J.H., Stoeckenius, W., Prince, L.M., Mechanism of formation and structure of microemulsions by electron microscopy, *J. Phys. Chem.,1959,* 63, 1677

[12]   Safran and Turkevich, Phase diagrams for Mciroemulsions, Phys. Rev. Lett., 1983, 50, 24, 1930-1933

[13]   Di Meglio, Theory of Microemulsions: comparisons with experimental behaviour, langmuir, 1988, 4, 802-806

[14]   deGennes, P.G., Taupin, C., Microemulsions and the flexibility of oil/water interfaces , *J. Phys. Chem.,*1982, 86, 2294–2304.

[15]   Shinoda, K., Kunieda, H., Conditions to produce so called microemulsions : factors to increase mutual solubility of oil and water by solubilizer, *J. Coll. Int. Sci.,*1973, 42, 381- 387

[16] Rosano, H.L., Cavello, J.L., Lyons, G.B., Mechanism of formation of six microemulsion systems. In: (Rosano, M.L. and Clausse, M. Eds.) Microemulsion system, Marcel Dekker, Inc., N.Y., 1987, 259–275.

[17] Ruckenstien, E., Chi, J.C., Stability of microemulsions, *J. Chem. Soc. Faraday Trans, 1971,* 71, 1690-1707

[18] Shinoda,K., Nakagawa,T., Tamamushi,B., Isemura, T, Colloidal surfactants, 1963, Academic Press, New York

[19] Elworthy Alvarez, effects of temperature on conductivity of AOT/Isooctane/water microemulsions, J.chem Engg. Data 1999, *44* (4), pp 846–849

[20] Mukherjee, S., Miller, C.A. , Fort, T., Theory of drop size and phase continuity in microemulsions, I Bending effects with uncharged surfactants, *J. Coll. Int. Sc.,*1983, 91 (1), 223

[21] Jeng., Solubilisation and phase equilibria of water in oil microemulsions;effect of spontaneous curvature and elasticity of interfacial films Jr. Coll Inter.Sci. 1987, 120, 2, 320-329

[22] Miller, Thermodynamics of microemulsions: Combined effects of dispersion entropy of drops and bending energy of surfactant films AIChE Journal, 1980, 26,2, 212-220

[23] Shinoda, K., Kuneida, H., In: Microemulsions, (L.M. Prince ed.), Academic Press, New York, 1977, 57

[24] Taha M. O., Ghazawi M., Amara H., Khalil E., Development of quantitative structure property relationship models for pseudoternary microemulsions formulated with nonionic surfactants and cosurfactants : application of data mining and molecular modeling , *Eur. J. Pharm. Scs.,*2002, 15, 461-478

[25] Aboofazeli, R., Lawrence, M.J., Investigations into the formation and characterization of phospholipid microemulsions I Pseudo ternary phase diagrams of systems containing water – lecithin – alcohol- isopropyl myristicate, *Int. J. Pharm.,1993,* 93, 161- 175

[26] Trotta, M., Cavalli, R, Uzagio, E., Gasco, M.R., Phase behaviour of microemulsion systems containing lecithin and lysolecithin as surfactants, *Int. J. Pharm.,1996,* 143, 67-73

[27] Miyata, I., Miyamoto, H., Yonese, M., Effect of Chain Lengths of n–Alcohol on the formation of single–phase microemulsions in n–Heptane / n–Alcohol / sodium Dodecyl sulfate / water systems. *Chem. Pharm. Bull., 1996,* 44(5), 1049–1055.

[28] Osborne, D.W., Wand, A.J., O'Neill, K.J., Microemulsions as topical drug delibvery vehicles, Part I. Characterization of a model system, *Drug Dev. Ind. Pharm., 1991,* 14, 1202–1219

[29] Das M L, Model biological microemulsions: Part I--Phase behaviour and physicochemical properties of cholesteryl benzoate and sodium deoxycholate contained microemulsions, Ind. Jr. Biochem. Biophys.,1989, 26,1,24-29

[30]   Kreilgaard, M., Pederson, E.J., Jaroszewski, J. W., NMR characterization and transdermal drug delivery potential of microemulsion systems, *J. Cont. Rel., 2000,* 69, 421-433

[31]   Attwood, D., Mallon, C., Taylor, C.J.,   Phase studies of oil in water phospholipid microemulsions, 1992, *Int. J. Pharm.,* 84, R5-R8

[32]   Kahlweit, M., Strey, R., Haase, D., Kuneida, H., Schmeling, T., Faulhaber, B., Borkovee, M., Eicke, H.F., Busse, G., Eggers, F., Funck ,T.H., Richman, H., Dittrich, A., Jahn, W., How to study microemulsions, *J. Coll. Int. Sc., 1983,* 118, 436-453

[33]   Mitra, N., Mukherjee, L., Bhattacharya, P.K., Moulik, S.P., Biological microemulsions V: Mutual mixing of oils, amphiphites and water in ternary and quaternary combinations, *Indian J. Biochem. Biophys.,1996,* 33, 206–212.

[34]   Mackay, Electrochemistry of solutes in microemulsions: Electrostatically bound aqueous ions, surfactant-like ions and oil soluble molecules, Coll. And Sur. , 1991, 56, 1-12

[35]   Moreno M. A., Frutos P., Ballesteros M. P., Lastres J. L., Castro D., Release of Nortriptyline hydrochloride from oil – water microemulsions , *Chem. Pharm. Bull.*, 2000, 48(11), 1623-1627

[36]   Rhee, Y., Choi, J., Park, E., Chi, S., Transdermal delivery of ketoprofen using microemulsion, *Int. J. Pharm., 2001,* 281, 167–170.

[37]   Spiclin, P., Garperlin, M., Kmetee, V., Stability of ascorbyl Palncitate in topical microemulsion, *Int. J. Pharm.,2001,* 222, 271–279.

[38]   Park,K., Kim,C., Preparation and evaluation of flurbiprofen loaded microemulsions for parentral delivery, *Int. J. Pharm.,1999,* 181, 173-17

[39]   Santos P., Watkinson, Lane, Application of Microemulsions in Dermal and Transdermal Drug Delivery, Skin Pharmacol. Physiolog. 2008, 21, 246-259

[40]   Brime B., Moreno M., Frutos G., Ballesteros P., Frutos P., Amphotericin B in oil- water lecithin based microemulsions : Formulation and toxicity evaluation , *J. Pharm. Scs*. , 2002, 91(4), 1178-1185

[41]   Scchmalfub U., Neubert R., Wohlrab W., Modification of drug penetration into human skin using microemulsions, *J. Cont. Rel.,*1997, 46, 279-285

[42]   Mehta, S.K., Dewan, R.K., Bala, K., Percolation phenomenon and the study of conductivity, viscosity and ultrasonic velocity in microemulsions, *Phys. Rev, 1994,* E50, 4759-4762

[43]   Khan, A., Lindstrom, B., Shinoda, K. , Lindman, B., Change of microemulsion structure with the HLB of surfactant and the volume fractions of water and oil, *J. Phys. Chem.,1986,* 90 (22), 5799

[44]   Miyata, I., Miyamoto, H., Yonese, M., Effect of Chain Lengths of n–Alcohol on the formation of single–phase microemulsions in n–Heptane / n–Alcohol / sodium Dodecyl sulfate / water systems. *Chem. Pharm. Bull., 1996,* 44(5), 1049–1055.