Review Article *ISSN: 2277-8713*
Mutchu Giriprasad, IJPRBS, 2013; Volume 2(2): 276-290 *IJPRBS*

ISSN: 2277-8713
INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

AN OVERVIEW OF NEW DRUG DELIVERY SYSTEM: MICROEMULSION

MUTCHU GIRIPRASAD, DASARI NAGARAJU, GANAPANENI KRISHNA CHAITANYA, K. SASI KANTH, SREEKANTH NAMA, CHANDU BABU RAO

IJPRBS-QR CODE

PAPER-QR CODE

Department of Pharmaceutics, Priyadarshini Institute of Pharmaceutical Education & Research(PIPER), 5th Mile, Pulladigunta, Kornepadu (V), Vatticherukuru (M), Guntur-522017, Andhra Pradesh, India.

Accepted Date:
22/04/2013
Publish Date:
27/04/2013
Keywords
Micro emulsion,
Advantages,
Novel drug delivery system,
Applications

Corresponding Author
Mr. Mutchu Giriprasad

Abstract

A micro emulsion is a transparent or nearly transparent, quasi-homogeneous, thermodynamically stable mixture of two immiscible liquid stabilized by surfactant (or mixture of surfactant). As pharmaceuticals drug delivery systems, micro emulsion have unique properties, including clarity, high stability and ease of preparation. Due to their physicochemical properties, micro emulsion often advantages over traditional topical and transdermal drug delivery systems. Moreover, micro emulsion dispersion are promising candidates as means for controlled drug delivery, and as drug carriers for oral, topical, and parenteral administration furthermore, micro emulsion have been shown to process promising potential in the fields of cosmetic and various consumer products. A brief overview regarding the preparation, characterization and application of micro emulsion has been given in this review article

INTRODUCTION:

Emulsions are heterogeneous system in which one immiscible liquid is dispersed as droplets in another liquid. Such a thermodynamically unstable system is kinetically stabilized by addition of one further component or mixture of components that exhibit emulsifying properties. One emulsion that is further dispersed into another continuous phase is called *double emulsion*, *multiple emulsion* or *emulsified emulsion*. The droplet-size distribution of emulsion droplets is 0.5-50.0µm. The inner droplet size distribution of w/o emulsion in multiple emulsions is usually smaller than 0.5µm, where as the outer, external multiple emulsions is quite large and can exceed 10µm. Another emulsion system is "micro emulsion" and can define a system of water, oil and amphiphile, which is a single optically isotropic. The droplets in a micro emulsion are in the range of 0.1-1.0µm [1]. The existence of this theoretical structure was later confirmed by use of various technologies and we can today adopt the definition given by Attwood as follows: "A micro emulsion is a system of water, oil and amphiphilic compounds (surfactant and co-surfactant), which is a transparent, single optically isotropic and thermodynamically stable liquid" [2].

Micro emulsion is homogenous, thermodynamically stable dispersion of water and oil stabilized by relatively large amounts of surfactant(s) frequently in combination with co surfactant(s) [3-8].

Micro emulsion shows diverse structural organization due to the use of wide range of surfactant concentration, water-oil ratios, temperature *etc*. (Lawrence *et al*., 2005). In case of emulsion, it contains three components, namely oil, water and surfactant; whereas micro emulsions generally require a forth component *i.e.* co surfactants, which include linear alcohols of medium chain length that is miscible with water. The combination of surfactant and co-surfactant promotes the generation of extensive interfaces through the spontaneous dispersion of oil in water, or vice-versa. The large interfacial area between oil and water consists of a mixed interfacial film containing both surfactant and co surfactant molecules. The interfacial tension at the oil-water interfaces in emulsions approaches zero, which also

contributes to their spontaneous formation. Micro emulsions are regarded as micelles extensively swollen by large amounts of solubilized oil [9, 10].

Three types of micro emulsions are most likely to be formed depending on the composition:

1. Oil in water (O/W) micro emulsions wherein oil droplets are dispersed in the continuos aqueous phase.

2. Water in oil (W/O) micro emulsions wherein water droplets are dispersed in the continuous oil phase.

3. Bi-continuous micro emulsions wherein micro domains of oil and water are inter dispersed within the system.

In all the three types of micro emulsions, the interface is stabilized by an appropriate combination of surfactants and/or co-surfactants [11].

Micro emulsion displays a rich behavior regarding the release of solubilized material. Also, one can reach sustained release if the interactions between drug and surfactant and/or partitioning of drug between oil and water phase strongly affect the drug release [12]. O/W micro emulsion is also formulated as aqueous vehicles for oil-soluble drug to be administered by the percutaneous, oral or parenteral routes. Micro emulsion components are classified into oils, surfactants and co-surfactants. Oils are moderate to large alkyl hydrocarbons (140-900 Da) that might contain ester or carboxylic acid moieties. Surfactant are complex mixture of phospholipids characterized with molecular weight range of 500-700 Da and two structurally distinct part of opposite lipophilicity/hydrophilicity properties are small (60-190 Da) mono or multi-hydroxy alcohols or carboxylic acids that might contain ether linkages. The co-surfactant is also added to stabilize micro emulsion, which is also amphiphillic with an affinity for both oil and aqueous phases and partitions to an applicable extent into the surfactant interface. A wide variety of molecules can function as co-surfactant including non-ionic surfactant, alcohol, alkanoic acids, alkanoids and alkylamines [13].

In order to investigate a drug delivery potential of micro emulsion vehicle, it is necessary to characterize their microstructure as well as a microstructure

of drug loaded micro emulsion. The formulation process and gradual change in micro emulsion microstructure can be monitored quantitatively by measuring the electrical conductivity and rheological properties of the system [1]. A part from the micro emulsion structure and composition, the incorporated drug molecules participate in the microstructure of the system and may influenced it due to molecular interactions, specially if the drug possesses amphiphilic and/or mesogenic properties [14].

Comparison between emulsion and micro emulsion

Emulsions and micro emulsions are both stable dispersions of oil-in-water or water-in-oil. In emulsion systems, the structures are large enough to scatter light and as such they appear as cloudy colloidal solutions in comparison. The gross physical differences between micro emulsion and emulsion systems can be determined by visual examination *i.e.* micro emulsions show no tendency to phase separate and are usually optically transparent, whereas emulsions are opalescent or turbid and the phases inevitably separate.

Advantages of micro emulsion based system

1. Micro emulsions act as super solvents of drug. They can solubilize hydrophilic and lipophilic drugs including drugs that are relatively insoluble in both aqueous and hydrophobic solvents. This is due to existence of micro domains of different polarity within the same single-phase solution.

2. Micro emulsions are thermodynamically stable system and the stability allows self-emulsification of the system whose properties are not dependent on the process followed.

3. Micro emulsion based system has long self life.

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

5. The formation of micro emulsion is reversible they

may become unstable at low or high temperature but when the temperature returns to the stability range, the micro emulsion reforms [15].

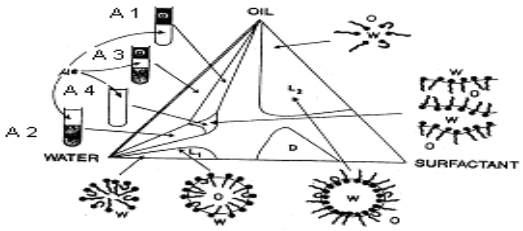
PREPARATION OF MICROEMULSION

It is well established that large amounts of two immiscible liquids (*e.g.* water and oil) can be brought into a single phase (macroscopically homogeneous but microscopically heterogeneous) by the addition of an appropriate surfactant or a surfactant mixture. Micro emulsions can have characteristic properties such as ultralow interfacial tension, large interfacial area and capacity to solubilize both aqueous and oil-soluble compounds. Micro emulsions can be prepared by controlled addition of lower alkanols (butanol, pentanol and hexanol) to milky emulsions to produce transparent solutions comprising dispersions of either water-in-oil (W/O) or oil-in-water (O/W) in nanometer or colloidal dispersions (~100nm). The lower alkanols are called co surfactants; they lower the the interfacial tension between oil and water sufficiently low. The miscibility of oil, water and amphiphile (surfactant plus co surfactant) depends on the overall composition which is system specific. Ternary and quaternary phase diagrams can describe the phase manifestations and are essential in the study of micro emulsions [16].

The knowledge on the phase manifestations of the pseudo-ternary (water/amphiphile/oil) or explicitly quaternary (water/surfactant/cosurfactant/oil) mixtures has been systematized. At low surfactant concentration, there is a sequence of equilibria between phases, commonly referred to as Winsor phases (Winsor, 1954), which are **Winsor I (A-1)**: With two phases, the lower (oil/water) micro emulsion phase in equilibrium with the upper excess oil; **Winsor II (A-2)**: with two phases, the upper micro emulsion phase (water/oil) in equilibrium with excess water; **Winsor III (A-3)**: With three phases, middle micro emulsion phase (O/W plus W/O, called bicontinuous) in equilibrium with upper excess oil and lower excess water; **Winsor IV (A 4)**: In single phase, with oil, water and surfactant homogeneously mixed. Inter-conversion among the above mentioned phases can be achieved by adjusting proportions of the constituents. Simultaneous presence of two micro emulsion phases, one in contact with water and the other in contact with oil, is also possible. This may be considered as an extension of Winsor's classification forming

the fifth category. A composite representation of the above-mentioned features of micro emulsion forming systems is depicted in Figure 1 [17].

Figure:1- Schematic ternary phase diagram of water–oil–surfactant mixtures representing Winsor classification and probable internal structures. L1, a single phase region of normal micelles or oil-in-water (O/W) micro emulsion; L2, reverse micelles or water-in-oil (W/O) micro emulsions; D, anisotropic lamellar liquid crystalline phase.



CHARACTERIZATION OF MICROEMULSION

In contrast to their ease of production, micro emulsions are very difficult to characterize principally because of their wide variety of structures. For this reason, the use of several techniques is often required in order to characterize micro emulsion systems. An understanding of the properties of the vehicle is an important requirement for optimizing drug delivery. Additionally, factors affecting drug release, stability, and structure need to be understood in order to establish the potential, and also limitations of micro emulsion formulations. A variety of techniques, such as NMR spectroscopy, electrical conductivity, self-diffusion, small-angle neutron scattering, quasi-elastic light scattering, and fluorescence spectroscopy, have been employed to characterize these systems[17].

Microscopy

Although polarizing microscopy confirms the optical isotropy of the micro emulsion system, conventional optical microscopy cannot be used for studying micro emulsion systems because of the small droplet size diameter which is typically less than 150 nm. However, transmission electron microscopy (TEM) combined with freeze fracture techniques have been successfully applied for the study and characterization of micro emulsions [18]. The sensitivity of micro emulsion structure to temperature and the potential introduction of experimental artifacts during manipulation are of some concern with this approach. Other problems are: (1) high micro

emulsion vapour pressure, which is not compatible with low pressures used in microscopy, (2) electrons may induce chemical reactions, thus, altering micro emulsion structure, and (3) lack of contrast between the micro emulsion structure and its environment. The introduction of controlled environmental chambers as well as improvements in thermal fixation now permit very fast sample cooling rates to be achieved without crystal formation. The techniques of Cryo-TEM and freeze fracture-TEM, which have evolved from these advances, permit direct visualization of the micro emulsion structure with fewer problems of artifactual results [19].

NMR

Self-diffusion is the random movement of a molecule in the absence of any concentration gradient, and this movement reflects the environment where the molecule is localized. If a molecule is confined in a close aggregate, such as micelles, its self-diffusion will be two or three orders of magnitude lower than the expected self-diffusion coefficient from a pure solvent. Therefore, in w/o micro emulsions, the self-diffusion of water molecules is slow, whereas, the diffusion of the oil molecules is high. Conversely, for O/W micro emulsions the reverse is found. In bicontinuous structures, both oil and water molecules exhibit high self-diffusion coefficients. Micro emulsion structure has been characterized as using self-diffusion measurements of the components, obtained by proton Fourier transform pulse-gradient spin-echo NMR (PGSENMR) [20-24].

Fluorescence spectroscopy

Fluorescence spectroscopy measures the ease of movement of the fluorescent probe molecules in the micro emulsions. This is controlled by diffusion, which varies inversely with the viscosity of the medium and with the micro emulsion type. In water-continuous micro emulsions, the propagation of the excitation is inhibited because of the slow diffusion of the water-insoluble fluorescent (*e.g.* pyrene) molecules. On the other hand, oil continuous micro emulsions should produce a similar excimer formation to that of the pure oil [25].

Interfacial tension

The formation and the properties of micro emulsion can be studied by measuring the interfacial tension. Ultralow values of interfacial tension are correlated with phase behavior, particularly, the existence of surfactant phase or middle-phase micro emulsions in equilibrium with aqueous and oil phases. Spinning-drop apparatus can be used to measure the ultralow 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. To determine the nature of the continuous phase and to detect phase inversion phenomena, the electrical conductivity measurements are highly useful. A sharp increase in conductivity in certain W/O micro emulsion system was observed at low volume fractions and such behavior was interpreted as an indication of a "percolative behavior" or exchange of ions between droplets before the formulation of bi-continuous structures. Dielectric measurements are a powerful means of probing both structure and dynamic feature of micro emulsion systems [15].

\Scattering techniques for micro emulsion characterization

Small-angle X-ray scattering techniques have been used to obtain information on droplet size and shape. Using synchrotron radiation sources, in which sample-to-detector distances are bigger, significant improvements have been achieved. With synchrotron radiation more defined spectra are obtained and a wide range of systems can be studied, including those in which the surfactant molecules are poor X-ray scatters. Small-angle neutron scattering, however, allows selective enhancement of the scattering power of different micro emulsion pseudo phases by using protonated or deuterated molecules.

Static light scattering technique has also been widely used to determine micro emulsion droplet size and shape. In this technique, the intensity of scattered light is generally measured at various angles and for different concentration of micro emulsion droplets.

Dynamic light scattering, which is also referred as photon correlation spectroscopy (PCS), is used to analyze the fluctuations in the intensity of scattering by droplets due

to Brownian motion. The self-correlation is measured that gives information on dynamics of the system. This technique allows the determination of z-average diffusion coefficients D. In the absence of inter-particle interactions, the hydrodynamic radius of the particles can be determined from the diffusion coefficient using the Stokes-Einstein equation as follows: $D = kT/6\pi\eta RH$, Where, k is Boltzmann constant, T is the absolute temperature and η is the viscosity of the medium, RH is the relative humidity [26].

APPLICATIONS OF MICROEMULSION

Micro emulsion in pharmaceuticals

Parenteral administration: Parenteral administration (especially via the intravenous route) of drugs with limited solubility is a major problem in the pharmaceutical industry because of the extremely low amount of drug actually delivered to a targeted site. Micro emulsion formulations have distinct advantages over macro emulsion systems when delivered parenterally because of the fine particle, micro emulsion is cleared more slowly than the coarse particle emulsion and, therefore, have a longer residence time in the body. Both O/W and W/O micro emulsion can be used for parenteral delivery.

Oral administration: Oral administration of micro emulsion formulations offer several benefits over conventional oral formulation including increased absorption, improved clinical potency, and decreased drug toxicity [27]. Therefore, micro emulsion has been reported to be an ideal delivery of drugs such as steroids, hormones, diuretic and antibiotics. Pharmaceutical drugs of peptides and proteins are highly potent and specific in their physiological functions. However, most are difficult to administer orally. With on oral bioavailability in conventional (i.e. non-micro emulsion based) formulation of less than 10%, they are usually not therapeutically active by oral administration. Because of their low oral bioavailability, most protein drugs are only available as parenteral formulations. However, peptide drugs have an extremely short biological half life when administered by parenteral route, so require multiple dosing [28].

Topical administration: Topical administration of drugs can have advantages over other methods for several

reasons, one of which is the avoidance of hepatic first pass metabolism of the drug and related toxicity effects. Another is the direct delivery and targetability of the drug to the affected area of the skin or eyes [29].

Ocular and pulmonary delivery: Ocular and pulmonary delivery for the treatment of eye diseases, drugs are essentially delivered topically. O/W micro emulsions have been investigated for ocular administration, to dissolve poorly soluble drugs, to increase absorption and to attain prolong release profile. For instance micro emulsions containing pilocarpine were formulated using lecithin, propylene glycol and PEG 200 as co-surfactant and iso-propyl myristate (IPM) as the oil phase. The formulations were of low viscosity with a refractive index lending to ophthalmologic applications.

Micro emulsions in biotechnology

Many enzymatic and bio catalytic reactions are conducted in pure organic or aqua-organic media. Biphasic media are also used for these types of reactions. The use of a pure polar 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.

Solubilization of drug in micro emulsion

Micro emulsion possesses interesting physicochemical properties, *i.e.* transparency, low viscosity, thermodynamic stability, high solubilization power. Because of these specific properties of micro emulsion can be useful as a drug delivery system. Different categories of drugs can be solubilized in micro emulsion systems for their better therapeutic efficacy [26].

Micro emulsions as coatings and textile finishing

The coating application area is a very promising and rapidly-growing field of micro emulsion technology, because the micro emulsified resins overcome many of the shortcomings of the more traditional water-based systems without creating the health and pollution problems and flammability hazards of the solvent-based

coatings. Due to their stability and small droplet size, micro emulsions are ideal, where stability and homogeneity of the finished product is desired. Paint formulations using micro emulsions have shown higher scrub resistance, better colour intensity and more stain resistance than those prepared by emulsions. In principle, three different possibilities of using micro emulsions exist for coating applications: (1) for producing micro dispersions by using micro emulsified monomers, (2) for transferring non-water-soluble polymers into water, and (3) for obtaining specific effects by polymerization in w/o system. An example of such a system is acrylate lattices stabilized by isothiouronium groups, which have been successfully polymerized to yield particle sizes of 0.08mm. The micro emulsions of the vinyl resins can be produced by converting them to ionomers in the presence of carefully selected solvent and co-solvent systems. Average particle sizes of about 0.02–0.14mm are formed depending on the system [31,32].

A micro emulsion as fuels

A micro emulsion-based fuel in the presence of water is one of the advantages of stable micro emulsion and they are successfully used to reduce soot formation. When the water is vaporized during the combustion, this will lower the heat released and the combustion temperature. As a direct consequence, the emission rate of gases like nitrogen oxides (NO*x*) and carbon monoxide (CO) will decrease. The presence of water is also supposed to cause improved fuel atomization, minimization of particulate emission and sooting, and improved fuel economy in terms of price and miles/volume of the fuel. Another interesting feature of micro emulsion-based fuel is their capacity to increase the octane number of gasoline and the corresponding octane number for diesel oils. Octane number improvers include formamide, glycols, urea, etc. In diesel fuels, many problems are overcome due to the high combustion temperatures (160–325°C). It is normal that diesel micro emulsions contain watersoluble cetane number improvers [33].

Micro emulsions as lubricants, cutting oils and corrosion inhibitors

Micro emulsions or reverse micellar solutions are in use as lubricants, cutting oils and corrosion inhibitors for several decades. The presence of surfactant in micro emulsion causes corrosion inhibition and the increased water content compared to pure oil leads to higher heat capacity. On one hand the corrosive agents, because of solubilization in micro emulsion cannot react with the metal surface and on the other, the metal surface is protected by the adsorbed hydrophobic surfactant film. However, solubilization is selective, and in some cases, other mechanisms might play a role in corrosion prevention. In micro emulsions, water with much higher thermal conductivity, imparts higher heat capacity to the system. Such formulations can be used in cutting oil; the oil lubricates the cutting surface, and the water helps to remove the frictional heat generated during the cutting process.

Micro emulsions in cosmetics

In many cosmetic applications such as skin care products, emulsions are widely used with water as the continuous phase. It is believed that micro emulsion formulation will result in a faster uptake into the skin. Cost, safety (as many surfactants are irritating to the skin when used in high concentrations), appropriate selection of ingredients (*i.e.* surfactants, co surfactants, oils) are key factors in the formulation of micro emulsions [34].

CONCLUSION

In the recent years micro emulsions have attracted a great deal of attention not because of there importance in industrial application but also their intrinsic interest. Micro emulsions are an attractive technology platform for the pharmaceutical formulators as it has excellent solubilization properties, transparency and the relatively simple formulation process. There is still a considerable amount of fundamental work characterizing the physico-chemical behaviors of micro emulsions that need to be performed before they can live to their potential as multipurpose drug delivery vehicle. Although the number of micro emulsions for cosmetic application of highly biocompatible for transdermal delivery system.

REFERENCES

1. Lawrence MJ, Rees GD. Micro emulsion-based media as novel drug delivery systems. *Adv Drug Deliv Rev,* 45(1), 2000, 89-121.

2. Attwood D. Micro emulsions. In Kreuter J (ed.) *Colloidal drug delivery systems.* Marcel Dekker, New York, 1994.

3. Osborne DW, Ward AJ, O'Neill KJ. Micro emulsions as topical delivery vehicles: *in vitro* transdermal studies of a model hydrophilic drug. *J Pharm Pharmacol,* 43, 1991, 450-54.

4. Schmalfuss U, Neubert R, Wohlrab W. Modification of drug penetration into human skin using micro emulsions. *J Control Rel,* 46, 1997, 279-85.

5. Aboofazeli R, Patel N, Thomas M, Lawrence JM. Investigations into the formation and characterization of phospholipids micro emulsions. IV. Pseudo-ternary phase diagrams of systems containing water-lecithin-alcohol and oil: The influence of oil. *Int J Pharm,* 125, 1995, 107-16.

6. Trotta M, Pattarino F, Gasco MR. Influence of counter ion on the skin permeation of methotrexate from water-oil micro emulsion. *Pharm Acta Helv,* 71, 1996, 135-40.

7. Tenjarla S. Micro emulsions: An overview and pharmaceutical application. *Crit Rev Ther Drug Carrier Syst,* 16, 1996, 461-21. Vol 2|Issue 1| 2012 |5-12.

8. Friberg E.S. Micelles, micro emulsions, lipid crystals, and the structure of stratum corneum lipids. *J Soc Cosmet Chem,* 41, 1990, 155-57.

9. Dekker M. In Kreuter J (ed.) Colloidal drug delivery systems, *J Control Release,* 35(2-3), 1995, 181-82.

10. Ruckenstein E. *J Colloids Interphase Science,* 66, 1978, 369.

11. Schulman JH, Stoekenius D, Prince LM. Mechanism of formation and structure of micro emulsions by electron microscopy. *J Phy Chem,* 63, 1959, 1677.

12. Kumar P, Mital KL. Handbook of micro emulsion: science and technology, Marcel Dekker, New York, 1999.

13. Tripos Inc., Alchemy 2000 Reference Manual. USA, 1998.

14. Mueller-Goymann CC, Kriwet K, Eder I, Papantoniou I. Micro emulsions and related systems for the dermal application of drugs. *Bull Tech Gattefosse,* 88, 1995, 43-54.

15. Vyas SP, Khar RK. Submicron emulsions, eds. *Targeted and Controlled Drug Delivery—Novel Carrier Systems*. New Delhi, India: CBS Publishers; 2002, 282 – 02.

16. Shaji J, Reddy MS. Micro emulsion as drug delivery system. *Pharma times,* 36(7), 2004, 17-24.

17. Kunieda H, Asaoka H, Shinoda K. *J. Phys. Chem,* 92, 1988, 185.

18. Bellare JR, Haridas MM, Li XJ. Characterization of microemulsions using fast freeze fracture and cry-electron microscopy. In Kumar P, Mittal KL. (ed.) *Handbook of micro emulsion science and technology.* Marcel Dekker, New York, 1999, 411–35.

19. Danino D, Bernheim-Groswasser A, Talmon Y. Digital cryogenic transmission electron microscopy: an advanced tool for direct imaging of complex fluids. Colloids and surfaces: *A physicochemical and engineering aspects,* 113–22, 2001, 183–85.

20. Carlfors J, Blute I, Schmidt V. Lidocaine in micro emulsions: A dermal delivery system. *J Dispers Sci Technol,* 12, 1991, 467–82.

21. Rushforth DS, Sanchez-Rubio M, Santos-Vidals LM, Wormuth KR, Kaler EW, Cuevas R, Puig JE. Structural study of one-phase micro emulsions. *J Phys Chem,* 90, 1986, 6668–73.

22. Lagourette B, Peyrelasse J, Boned C, Clausse M. Percolative conduction in micro emulsion type systems. *Nature,* 281, 1979, 60–61.

23. Thevenin MA, Grossiord JL, Poelman MC. Sucrose esters/cosurfactant micro emulsion systems for transdermal delivery: Assessment of bicontinuous structures. *Int J Pharm,* 137, 1996, 177–86.

24. Bhattacharya S, Stokes JP, Kim MW, Huang JS. Percolation in an oil-continuous micro emulsion. *Phys Rev Lett,* 55, 1985, 1884.

25. Subramanian N, Ghosal SK, Moulik SP. Enhanced in vitro percutaneous absorption and in vivo anti-inflammatory effect of a selective cyclooxygenase inhibitor using

microemulsion. *Drug Dev Ind Pharm,* 31, 2005, 405–16.

26. Winsor PA. Solvent properties of amphiphilic compounds. Butterworth, London, 1954.

27. Ho H, Hsiao CC, Sheu MT. Preparation of micro emulsions using polyglyceryl fatty acid esters as surfactant for the delivery of protein drugs. *J Pharm Sci,* 85(2), 1996, 138.

28. Kovarik JM, Muller EA, Van Bree JB, Tetzioff W, Kutz K. Reduced inter and intra individual variability in cyclosporin pharmacokinetics from micro emulsion formulation. *J Pharm Sci,* 83 (3), 1994, 444.

29. Ho H, Huang MC, Chen LC, Hsia A, Chen KT, Chiang HS, Spur BW, Wong PYK, Sheu MY. The percutaneous delivery of prostaglandin E1 and its alkyl esters by micro emulsions. *Chin Pharm J,* 50, 1998, 257–266.

30. Malmsten M. Micro emulsions in pharmaceuticals. In, Kumar P, Mittal KL (ed.) *Handbook of microemulsion, Science and Technology.* Marcel Dekker, Inc., New York, 1999, 755 – 71.

31. Atik SS, Thomas JK. Photochemistry in polymerized micro emulsion systems. *J Am Chem Soc*, 104 (22), 1982, 5868–5874.

32. Barni E, Savarino P, Viscardi G, Carpignano R, Di Modica D. Micro emulsions and their potential applications in dyeing processes. *J Disper Sci Technol,* 12, 1991, 257 - 271.

33. Gillberg G. *Emulsions and emulsion technology.* In, Lissant KJ, Marcel D, (ed.). New York, 1984, 1–43.

34. Shinoda K, Shibata Y, Lindman B. Interfacial tensions for lecithin micro emulsions including the effect of surfactant and polymer addition. *Langmuir,* 9 (5), 2003, 1254–57.

35. Tokuoka Y, Uchiyama H, Abe M, Christian SD. *Langmuir,* 11, 1995, 725.

36. El-Nokaly M, Hiler G, McGrady J. Micro emulsions and emulsions in foods (eds. El-Nokaly M and Cornell D., *Am Chem Soc,* Washington DC, 1991, 26–43.