MICROEMULSION: PRACTICAL APPLICATIONS AND CONCEPTS

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ABSTRACT

Delivery of hydrophobic drugs is the major limitation for the drug discovery companies. Present limitation with the water insoluble drugs can be overcome by using techniques like microemulsion. Microemulsions are potential drug delivery systems because of their improved drug solubilization, long shelf life, and ease of preparation and administration. The formulation of microemulsion for pharmaceutical use requires a thorough understanding of the basic concepts of surfactants, co-surfactants, phase diagramme and behavior etc. Microemulsions distinctive phases - oil external, water external and middle phase-can be used for drug delivery, depending upon the type of drug and the site of action. In this article, we present some basics concepts needs to be understand for developing microemulsion as drug carrier systems, starting with basic application and moving to a thorough review of the basic microemulsion theories and concepts.

KEYWORDS: *Microemulsion, solubilization, surfactant, phase diagramme*

Introduction

Pharmaceutical scientists intend to deliver the active pharmaceuticals to the target organ at therapeutically relevant levels, with negligible discomfort and side effects to the patient. This delivery is significantly influenced by the physical and chemical properties of the drug. The biopharmaceutical classification system of drugs was defined by Amidon et al Class I and Class II drugs exhibit high GI permeability. In contrast to Class II, Class I covers drugs with high water solubility. Class I drugs are well absorbed, but in some cases their bioavailability can still be low because of the first pass metabolism. Compounds of Class II with solubility below 10 mg/ml present difficulties related to solubilization during formulation. Class III and IV drugs are compounds having characteristically high solubility and low permeability, and low solubility and low permeability, respectively. Class III drugs feature variability in both the rate and extent of absorption (1).

Due to their characteristics, Class IV drugs exhibit many problems in their successful delivery. In the conventional pharmaceutical industry, it is well known that many promising drugs that are discovered never make it to the market because of difficulties in delivery. This means that such drugs need to be preparing with smart drug delivery systems and or delivery technology to make them acceptable for the treatment of patients. Some of these drugs are insoluble while others are eliminated by the acidity of the stomach, or are cleared from the blood too rapidly to be effective. Intravenous delivery may serve as an alternative in such cases, but may require either very frequent administration or large a volume of drug injected each time. Dispersions of oil and water are commonly employed as a pharmaceutical carrier. Microemulsions have attracted much interest in recent years in terms of their drug delivery potential (2). One way to deliver oil-soluble drugs is to incorporate the drug into an inert lipid vehicle, such as microemulsions, oils, surfactant dispersions, and liposome. The concept of microemulsion was first introduced by Hoar and Schulman in 1943; they prepared the first microemulsions by dispersing oil in an aqueous surfactant solution and adding an alcohol as a co-surfactant, leading to a transparent, stable formulation (3). At present, at least four drug products are available in the pharmaceutical markets that are delivered in emulsion form; they are: Sandimmune and Sandimmun Neoral (cyclosporine A), Norvir (ritonavir), and Fortovase (saquinavir). A significant improvement in the oral bioavailability of these drug compounds has been demonstrated. Therefore, much attention is focused on using emulsions as a vehicle to deliver oil-based drugs. Recently, microemulsions have been used to

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deliver oil-based drugs. Microemulsions offer several advantages over the usual (coarse) emulsions. Microemulsions are thermodynamically stable and the droplets of microemulsions are of very small size. In stable microemulsion, droplet diameter is usually within the range of 10-100 nm (100–1000 Angtrum), and therefore these systems are also termed as nanoemulsions (NE) (4).

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

1. O/W Microemulsion
2. W/O Microemulsion
3. Bicontinuous Microemulsion

Advantages of microemulsion as delivery system

- They are thermodynamically stable.
- They act as super solvents, improving the solubility and thermodynamic activity of the drug.
- The small particle size of the microemulsion as well as both the hydrophilic and lipophilic domains of microemulsion enhances the percutaneous uptake of the drugs - They act as potential reservoir of the drugs, through which pseudo-zero order kinetics can be obtained.
- The small size of the droplets give large interfacial area from which drug can be quickly released, improving the oral absorption of poorly water soluble drugs.
- Ease of preparation with no significant energy contribution.
- They can improve the efficacy of a drug allowing the dose reduction and side effect minimization.
- They prevent hydrolysis and oxidation of the drug when the drug is in oil phase.

Disadvantages of Microemulsions

- In many cases high concentration of surfactant and co-surfactants is required to formulate a stable microemulsion.
- A relatively small numbers of pharmaceutically acceptable excipients are available to be used in microemulsion formulation.

Applications of microemulsions: pharmaceutical and non-pharmaceutical

Microemulsions have received a lot of attention in both research and industry due to their unique properties. The characteristic properties of

Table 1. Microemulsion Vs emulsion

Property	*Emulsion*	*Microemulsion*
Composition	Water, oil and emulsifier	Water, oil, emulsifier and co-surfactant
Appearance	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.
Viscosity	Viscous liquid	Less viscous
Particle size	1-20 μ m	10-100 nm
Interfacial tension	5-50 dynes/cm	$10^{-2} - 10^{-3}$mN/m
Interfacial film	Tough	Highly flexible
Manufacturing	Tedious, high sheer needed	Easy and spontaneous
Free energy	More	Zero or negative
Stability	Thermodynamically unstable	Thermodynamically stable

microemulsions are: extremely low interfacial tension, large interfacial area, and capability to solubilize two immiscible liquids. The distinctive advantages of microemulsions are: small particle size and high thermodynamic stability. One of the main applications of microemulsions is in the pharmaceutical industry. Oil-based drugs are easily dissolved in oil but have a very low solubility in water (5-7). Due to this disadvantage, oil-based drugs have a poor bioavailability after oral administration because of the low solubility and absorption rate in gastrointestinal lumen. Microemulsions are suitable carriers for oil-based drugs because oil-based drugs can be dispersed easily in gastrointestinal juice in microemulsion form. Microemulsions can enhance the oil-based drugs absorption due to their small particle size. Also the drugs can be stored longer because of the stability of microemulsions. The only disadvantage of microemulsions as drug carriers is that the toxicity of the drugs tends to increase due to a large amount of the surfactant utilized in microemulsion formulation. Microemulsions have many other applications. For example, hair care product which contains an amino-functional polyorganosiloxane (a nonionic surfactant) is prepared in microemulsion form. In microemulsion form, the fragrance and the flavored oils can be stabilized very well. As microemulsions can easily solubilise organic components, they can be used as detergents to remove grease, oil and protein during the cleaning and washing processes. In the oil industry, microemulsions are used to enhance the oil recovery from the reservoir. A lot of oil remains trapped in the reservoir because of the high interfacial tension between oil and brine. One way to reduce the interfacial tension and extract the residual oil from the porous media is to inject surfactant to form microemulsions. This mode of enhanced oil recovery is called surfactant/microemulsion flooding method. Other applications of microemulsions include: fuels to purge soot, and paint to resist scrub. These applications show a promising and significant contribution of microemulsion to the chemical industry (8, 9).

Microemulsion structure

Microemulsions are not static impenetrable structures but very labile systems where rapid exchanges of individual components between the various environments as well as the spontaneous fluctuations of the interfacial film occur continuously. The two major phases exist for a microemulsion depending upon the composition:

Droplet Phases

At high water concentrations, microemulsions consist of small oil droplets surrounded by an interfacial film consisting of both surfactant and co-surfactant molecules dispersed in aqueous phase (o/w microemulsions), whereas at lower water concentrations the situation is reversed and the system consists of water droplets dispersed in oil w/o microemulsion (10).

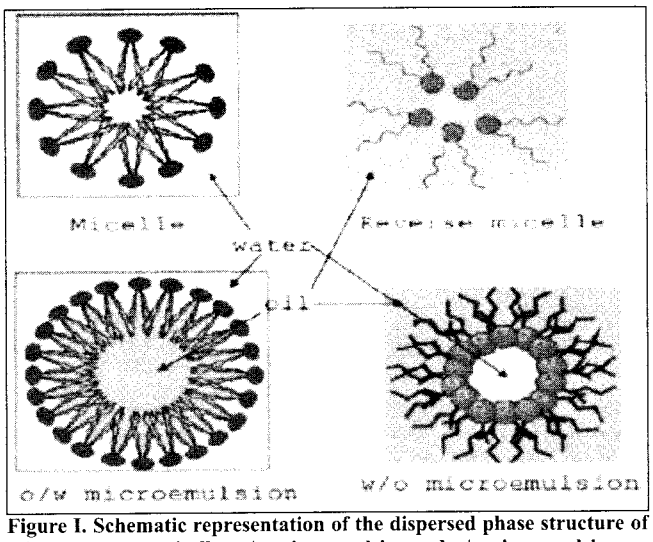

Figure I. Schematic representation of the dispersed phase structure of micelles, reverse micelles, o/w microemulsion and w/o microemulsion

Bicontinuous Phases

A gradual transition from o/w to w/o microemulsion is possible by changing the volume fraction of oil and water. The intermediate region, which has approximately equal volumes of oil and water, is often composed of lamellar or bicontinuous structures where both oil and water exist as a continuous phase in the presence of continuously fluctuating surfactant-stabilized interface with a net curvature of zero (11).

Theories of microemulsions

Many approaches have been used to explore the mechanisms of microemulsion formation and stability. These are:

1. Interfacial or mixed film theories: The spontaneous formation of microemulsion droplets was considered to be due to the formation of a complex film at the oil-water interface by the surfactant and co-surfactant. This caused a

reduction in oil water tension to very low values (from close to zero to negative). This film in equilibrium with both oil and water was considered to be liquid and duplex in nature with a two dimensional spreading pressure π_i, which determined the interfacial tension γ_i,

$$\gamma_i = \gamma_{o/w} - \pi_i$$

Where, $\gamma_{o/w}$ represents the oil/water interfacial tension without the film. When large amount of surfactant and co-surfactant are adsorbed to form the interface, the spreading pressure π_i may become larger than $\gamma_{o/w}$. A negative interfacial tension results and energy is available to increase the interfacial area, effectively reducing the droplet sizes. This negative interfacial tension is a transient phenomenon, and at equilibrium it becomes zero or a small positive value (12).

2. Solubilization theories: Shinoda and Friberg considered microemulsions to be thermodynamically stable monophasic solutions of water-swollen (w/o) or oil-swollen (o/w) spherical micelles. Rance and Friberg illustrated the relationship between reverse micelles and w/o microemulsions with the phase diagrams where addition of 50% p-xylene to inverse micellar region of ternary system of water, pentanol and SDS gave rise to transparent w/o region i.e. microemulsion.

3. 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 system and change in entropy of the system such that

$$\Delta G_f = \gamma \Delta A - T \Delta S,$$

Where, ΔG_f is the free energy of formation, γ is the surface tension of the oil-water interface, ΔA is the change in interfacial area on microemulsification, ΔS is the change in entropy of the system and T is the temperature. With macroemulsions, the interfacial energy is much larger than the entropy and hence the process of emulsification is non-spontaneous i.e. energy is needed to produce the emulsion by the use of high speed mixers. Since free energy of formation is positive, the emulsion tends to break down by flocculation and coalescence, which reduces the interfacial energy. To reduce this, one creates energy barrier by the use of emulsifiers (which seldom reduces $\gamma < 0.1 mNm^{-1}$). With microemulsions, the dispersion of the droplets in the continuous phase increases the entropy of the system and producing a negative free energy change, which is not very significant in case of large droplets microemulsions. It has also been shown that the accumulation of surfactant and co-surfactant at the interface results in reduction of bulk concentration and decrease in chemical potential, generating an additional negative free energy change, the so called 'dilution effect'. Microemulsions form because the negative free energy changes due to adsorption of surfactants at the interface plus the entropy of dispersion of droplets in the continuous phase overcome the positive product of the small interfacial tension and the large interfacial area. In this case, the free energy of the system becomes zero or negative (13).

This explains the thermodynamic stability of the microemulsions. Thus the main driving force for microemulsion formation is the ultra low interfacial tension, which is usually achieved by the use of two or more emulsifiers, one predominantly water soluble and other predominantly oil soluble called co-surfactant, which reduce the interfacial tension (γ) to the order of $<10^{-2}$ mNm^{-1} generally required for the microemulsion formation.

Formulation and preparation of microemulsion

It can be seen that there is a real and continuing need for the development of new and effective drug delivery systems for water insoluble or sparingly water soluble drugs. One such approach might be pharmaceutical microemulsions.

In microemulsions, one can design the interface having nanometer sized droplets. The interfacial rigidity of the microemulsion droplets plays a key role in the flux of the drugs from such droplets to the cells and tissues. Tailoring of microemulsion systems to control the flux of the drugs can be done so as to customize drug delivery according to individual patient needs. However, material chosen should be biocompatible, non toxic, clinically acceptable and use the emulsifiers in an appropriate concentration ranges to form stable Microemulsions.

In microemulsion formulation, three factors are considered:

First, emulsifiers (surfactants) are to be carefully chosen so that an ultra low interfacial tension ($<10^{-2}$

mn/m) can be obtained at the oil water interface which is a primary requirement to produce microemulsion. This low interfacial tension leads to spontaneous emulsification of oil/water or water/oil.

The **second** requirement is that the concentration of surfactant must be high enough to provide the number of surfactant molecules needed to stabilize the nano-sized droplets in the product by providing an ultra low interfacial tension. However, it is precisely the tuning and right choice of the structure of surfactant and co-surfactant that can reduce the concentration of surfactant required for the microemulsion formation. The emulsifier partitions into three compartments; water, oil and the interface between the oil and water by proper adjustment of hydrophilic and hydrophobic groups of surfactant. The surfactant molecule can preferentially partition into the interface and minimize the concentration in the bulk oil/water phases. Therefore, the understanding of the partitioning behavior of surfactant in water, oil and the interface is of considerable importance for the formulation of microemulsion.

The **third** major consideration in formulating microemulsion is the flexibility or the fluidity of the interface to promote the formation of microemulsions. Therefore, short chain alcohols (C_4- C_7) are often added as co-surfactant in oil, water and surfactant mixture to produce microemulsions. The penetration of short chain alcohols into the interfacial film produces a more fluidized interfacial film by allowing the long hydrophobic tail of the C_{16} or C_{18} surfactants to move freely at the interface. The formulation of microemulsion usually involves three to five components oil phase, aqueous phase and a primary surfactant & in many case a secondary surfactant (co-surfactant) and sometimes an electrolyte (14). Their formation is highly specific process involving spontaneous interaction among the constituent molecules Sohail et al. (15)

Selection of components

Although there are no strict rules for choosing the appropriate microemulsion components, still choosing surfactant is a crucial step.

Surfactants

The surfactant(s) chosen must have:

- Lower interfacial tension to a very small value to aid dispersion.
- Provide a flexible film that can readily deform round small droplets.
- Be of appropriate HLB character to provide the correct curvature at the interfacial region for the desired microemulsion type.

The surfactant used to stabilize the system can be of following types:

(i) Non-ionic: e.g. polyoxyethylene surfactants, such as Brij 35 or sorbita monooleate (span 80), polysorbates (80, 20, 60), Cremophore EL, Labrasol Triton X 100, Lauroglycol 90, Labrafil M.

(ii) Zwitterionic: e.g. Phospholipids are a notable example which exhibits excellent biocompatibility.

(iii) Cationic: Quaternary ammonium alkyl salts form one of the best known classes of cationic surfactants viz. hexadecyltrimethyl ammonium bromide (CTAB) and twin tailed surfactant didcecylammoniumbromide (DDAB).

(iv) Anionic: The most widely studied surfactant is probably bis-2-ethylhexylsulphosuccinate (AOT) which is twin tailed and is particularly effective stabilizer of w/o microemulsions.

Co-surfactant

In most of the cases, single chain surfactants alone are unable to reduce the oil water interfacial tension to sufficient level to form a stable microemulsion. Thus, a co-surfactants which is usually a medium chain fatty alcohol, acid or amine is taken along with the surfactant to lower the interfacial tension to a very small or even transient negative value. At this value fine droplets get formed due to the interface expansion and more of surfactant/co-surfactant get adsorbed on the surface until the bulk condition is depleted enough to make the interfacial tension positive again.

This process called the spontaneous emulsification forms the microemulsion. The presence of co-surfactants in microemulsion helps by:

a) Further reducing the interfacial tension by the 'dilution effect' whilst increasing the fluidity of the interface by decreasing the rigidity constant K, thereby increasing the entropy of the system.

b) Increasing the mobility of the hydrocarbon tail and allowing greater penetration of the oil into this region.

c) Influences the solubility properties of the aqueous and oily phases due to its partitioning between these phases.

Examples of co-surfactants include non ionic surfactants, alkanoic acids, alkanediols and alkylamines. Amongst all these the most widely used co-surfactants are the medium chain length alcohols as they are significantly less toxic and irritant as compared to other solvents.

Phase Behavior

Mostly a microemulsion consists of an oil phase, surfactant, co-surfactant and an aqueous phase i.e. four basic components. The phase behavior of such systems can be best described by the use of a pseudo-ternary phase diagrams, where a constant ratio of any two components is used and other two are varied (16).

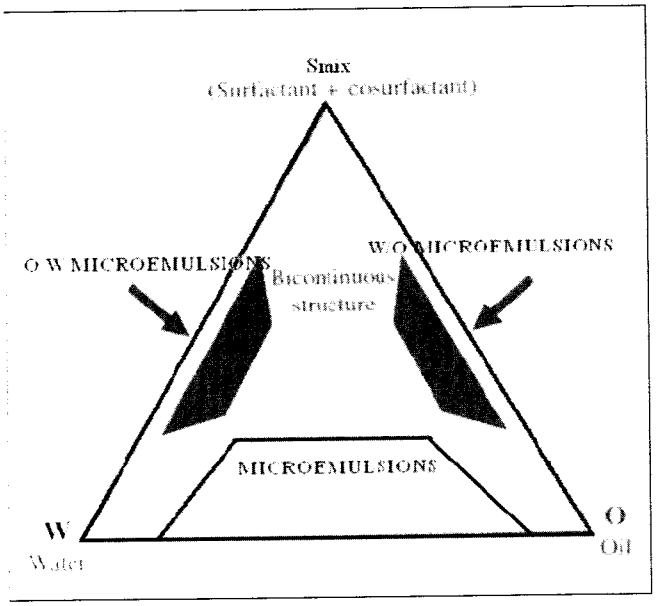

Figure 2: Hypothetical Phase Regions of Microemulsion Systems

Characterization of microemulsions

Microemulsions have been characterized using an extensive array of techniques. The characterization of microemulsions is a difficult task due to their complexity, diversity of structures and components involved in systems, as well as the limitations associated with each technique but such knowledge is essential for their successful commercial utilization. Therefore, corresponding studies using a combination of techniques are usually required to obtain a comprehensive view of the physicochemical properties and structure of Microemulsions.

Generally microemulsions are evaluated for the following characteristics:

Viscosity: Viscosity provides an indication of rod like or worm like micelles and the type of microemulsion.

Conductivity: Conductivity measurement using conductometers provide a means of determining whether the microemulsion is oil-continuous or water-continuous.

Refractive index: Done using simple refractometers.

Dielectric measurements: Provides a powerful means of probing both the structural or dynamic features of the microemulsion system.

Microemulsion structure: Particle size of microemulsion can be determined using scattering methods like dynamic and static light scattering, small-angle neutron scattering (SANS), small angle X-ray scattering (SAXS) and transmission electron microscopy.

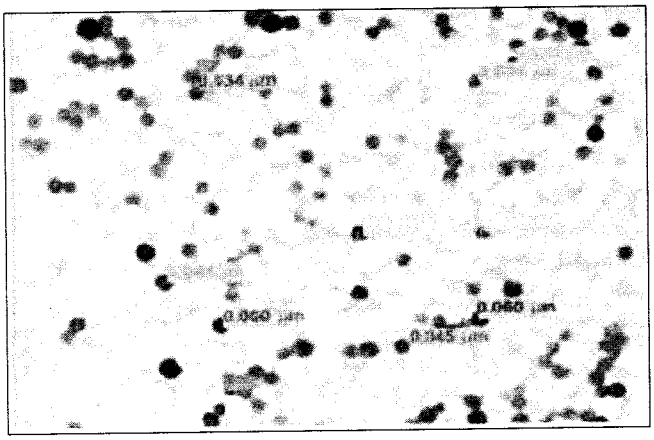

Figure 3. Microphotograph of drug nanoemulsion by TEM

Self-diffusion coefficient: This is related to the transdermal potential and is measured by pulsed gradient NMR, yields information on the mobility and the microenvironment.

Thermodynamic stability: Temperature and freeze-thaw tests are used to measure the stability of microemulsions:

i. Freeze thaw cycle

Microemulsions have to keep in deep freezer (at -20°C) for 24h. After 24h the microemulsions were removed and kept at room temperature. The thermodynamically stable microemulsions returned to their original form within 2-3 minutes. 2-3 such cycles were repeated.

ii. Centrifugation studies

Microemulsions after freeze thaw cycle were subjected to centrifugation studies where they were made to undergo centrifugation for 30 minutes at 5,000 rpm in a centrifuge. The stable formulations will not show any phase separation or turbidity.

iii. Heating cooling cycle

Microemulsion has to keep at 37±0.5°C for 24 hrs. After that the microemulsion will kept at room temperature. The stable nanoemulsion should not show any sign of turbidity, cracking, creaming during the entire cycle (17).

CONCLUSION

Till date microemulsions have been shown to be able to control drug delivery, increase drug solubility, increase bioavailability and reduce patient variability, reduce side effects.

Furthermore, it has proven possible to formulate that is suitable for most routes of administration. There is still however a substantial sum of fundamental effort characterizing the physico-chemical performance of microemulsions that needs to be carry out before they can live up to their potential as multipurpose drug delivery vehicles. 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, and also the physical aspect of their formulation development.

REFERENCES

1. Amidon GL, Lennernas H, Shah VP, et al. A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of In Vitro Drug Product Dissolution and In Vivo Bioavailability. Pharm Res. 1995;12:413-420.
2. Bourrel M, Schechter RS. Microemulsions and Related Systems. Marcel Dekker, New York, 1988:179-234.
3. Bidyut KP, Satya PM. Uses and applications of microemulsions. Current Science. 2001;80:8-25.
4. Eccleston GM. Microemulsion. Encyclopedia of Pharmaceutical Technology. Marcel Dekker, New York, 1992;9:375-421.
5. Kumar P, Mittal KL. Handbook of Microemulsion Science and Technology. Marcel Dekker Inc., New York, 1999;755-771.
6. Mason TG, Wilking JN, Meleson K, et al. Nanoemulsions: formation, structure and physical properties. J Physics. 2006;96(18):R635-R666.
7. Solans C, Kunieda H. Industrial Applications of Microemulsions. Marcel Dekker Inc. New York, Tadros TF.1997;199-223.
8. Vyas, SP, Khar RK. Submicronemulsions: Targeted and Controlled Drug Delivery, CBS publishers, New Delhi, 1st edn, 2002;280-302.
9. Spernath A, Aserin A. Microemulsion as carriers for drugs and nutraceuticals, Adv Colloid Interf Science. 2006;128-130.
10. Gasco MR, Gallarate M, Pattarino F. In vitro permeation of azelaic acid from viscosized microemulsions. Int J Pharm. 1991;69:193-196.
11. Kreilgaard M. Influence of microemulsions on cutaneous drug delivery. Adv Drug Del Rev. 2002;54(1):S77-98.
12. Ktistis G, Niopas I. A study on the in-vitro percutaneous absorption of propranolol from disperse systems. J Pharm Pharmacol. 1998;50(4):413-418.
13. Shevachman M, Garti N, Shani A, et al. Enhanced percutaneous permeability of diclofenac using a new U-type dilutable microemulsion. Drug Dev Ind Pharm. 2008;34(4):403-12.
14. Sintov, A.C., Shapiro, L. New microemulsion vehicle facilitates percutaneous absorption in vitro and cutaneous bioavailability in vivo. J Control Rel. 2004;93:173-183.
15. Akhter S, Jain GK, Ahmad FJ, et al. Investigation of Nanoemulsion System for Transdermal Delivery of Domperidone: Ex-vivo and in vivo Studies. Current Nanoscience. 2008;4:381-390.
16 Razdan R, Devarajan PV. Microemulsions, Indian Drugs. 2003;40(3):139–146.
17. Shah DO. Micelles: Microemulsions and Monolayers: Science and Technology. Marcel Dekker, New York, 1998:1-14.