Journal of Pharmaceutical, Chemical and Biological Sciences
February 2014; 1(1):39-51
Available online at http://www.jpcbs.info

Review Article

Microemulsions: Current Trends in Novel Drug Delivery Systems

Pranjal Kumar Singh[1*], Mohd. Kashif Iqubal[2], Vikesh Kumar Shukla[3], Mohd. Shuaib[4]

[1, 2, 4] Department of Pharmacy, Kalka Institute for Research and Advanced Studies, Meerut, Uttar Pradesh, India
[3] Department of Pharmacy, IIMT College of Medical Sciences, Meerut, Uttar Pradesh, India

ABSTRACT

Microemulsions are one of the best candidates as novel drug delivery system because of their long shelf life, improved drug solubilization with ease of preparation and administration. Microemulsions are thermodynamically stable and optically isotropic liquid solutions of oil, water and amphiphile. They have emerged as novel vehicles for drug delivery which allow controlled or sustained release for ocular, percutaneous, topical, transdermal, and parenteral administration of medicaments. Microemulsions can be easily distinguished from normal emulsions by their low viscosity, transparency and more accurately their thermodynamic stability. Microemulsions have great range of applications and uses such as in pharmaceuticals, agrochemicals, cutting oils, biotechnology, food, cosmetics, analytical applications, environmental detoxification etc. The main objective of this review paper is to discuss microemulsions as drug carrier system with other possible applications.

Key words: Microemulsions, thermodynamically stable, amphiphile, solubilization

Received: 12 February 2014 Revised and Accepted: 19 February 2014

* Corresponding author: **Email:** Pranjal.pharmacy@gmail.com

INTRODUCTION

The formulation and development of novel drug delivery system with the nature of enhancing the effectiveness of existing of drug is an ongoing process in pharmaceutical research. Since there are many types of drug delivery systems that have been developed. The microemulsion concept was introduced in 1940s by Hoar and Schulman who generated a clear single-phase solution by triturating a milky emulsion with hexanol [1]. They prepared the first microemulsion by dispersing oil in an aqueous surfactants solution and adding an alcohol as a co-surfactant, leading to transparent stable formulation. Microemulsion is defined as microemulsion are clear, transparent, thermodynamically stable dispersions of oil and water, stabilized by an interfacial film of surfactant frequently in combination with a co-surfactant [2].Alternative names for these systems are often used, such as swollen micelle, transparentemulsion, solubilized oil and micellar solution**.** Microemulsions are bicontinuous systems that are essentially composed of bulk phases of water and oil separated by a surfactant/cosurfactant rich interfacial region [3]. These systems have advantages over conventional emulsions in that they are thermodynamically stable liquid systems and are spontaneously formed [4]. Microemulsions are currently the subject of many investigations because of their wide range of potential and actual utilizations. The high capacity of microemulsions for drugs makes them attractive formulations for pharmaceuticals. These systems also offer several benefits for oral administration, including increased absorption, improved clinical potency and decreased toxicity [5].

Advantages of Microemulsion system [6-11]

1. Microemulsions are easily prepared and require no energy contribution during preparation this is due to better thermodynamic stability.
2. The formation of microemulsion is reversible. They may become unstable at low or high temperature but when the temperature returns to the stability range, the microemulsionreforms.
3. Microemulsions are thermodynamically stable system and allows self-emulsification of the system.
4. Microemulsions have low viscosity compared to emulsions.
5. Microemulsions act as supersolvents for drug, can solubilise both hydrophilic and lipophilic drugs including drugs that are insoluble in both aqueous and hydrophobic solvents.
6. Having the ability to carry both lipophilic and hydrophilic drugs.
7. The dispersed phase, lipophilic or hydrophilic (O/W, or W/O microemulsions) can act as a potential reservoir of lipophilic or hydrophilic drugs, respectively.
8. The use of microemulsion as delivery systems can improve the efficacy of a drug, allowing the total dose to be reduced and thus minimizing side effects.

Disadvantages of Microemulsion Systems [6-8]

1. Having limited solubilizing capacity for high-melting substances.
2. Require large amount of Surfactants for stabilizing droplets.
3. Microemulsion stability is influenced by environmental parameters such as temperature and pH.

BASIC DIFFERENCES BETWEEN MACROEMULSION AND MICROEMULSION [12-14]

Sl.No	MACROEMULSION	MICROEMULSION
1.	They are lyophobic in nature.	They are the border between lyophilic and lyophobic.
2.	Droplet diameter 1 to 20 mm.	Droplet diameter 10 to 100 mm.
3.	Macroemulsion droplets exist as individual entities.	Microemulsion droplets disappear within fraction of seconds.
4.	Emulsion droplets are roughly spherical droplets of one phase dispersed into the other phase.	Microemulsions are the structures of various droplets like bi-continous to swollen micelles.
5.	Macroemulsions requires quick agitation for their formation.	Microemulsions are obtained by gentle mixing of ingredients.
6.	Most of the emulsions are opaque (white) in appearance.	Microemulsions are transparent or translucent in nature.

TYPES OF MICROEMULSIONS [15-18]

Microemulsions are thermodynamically stable, but are only found under carefully defined conditions. According to Winsor, there are four types of microemulsion phases exists in equilibria, these phases are also referred as Winsor phases. They are,

1. Oil- in- water microemulsion or winsor I
2. Water – in oil microemulsion or winsor II
3. Bicontinuousmicroemulsion or winsor III
4. Single phase homogeneous mixture or winsor IV

Oil- in- water microemulsion or winsor I

In Oil-in-water type of microemulsions droplets of oil is surrounded by a surfactant (and may be cosurfactant) film that forms the internal phase distributed in water, which is the continuous phase. This type of microemulsion generally has a larger interaction volume than the w/o microemulsions.

Water - in - oil microemulsion or winsor II

In Water-in-oil type of microemulsions droplets of water surrounded by a continuous oil phase. These are recognized as “reversemicelles”, where the polar headgroups of the surfactant are facing into the droplets of water, with the fatty acid tails facing into the oil phase. A w/o microemulsion used orally or parenterally may be destabilized by the aqueous biological system.

Bicontinuousmicroemulsion or winsor III

In bicontinuousmicroemulsion system the amount of water and oil present are similar, In this case, both water and oil exist as a continuous phase. An irregular channel of oil and water are combined, and looks like a “sponge-phase”. Transitions from o/w to w/o microemulsions may pass through this bicontinuous state. Bicontinuous microemulsion, may show non-Newtonian flow and plasticity. These properties make them especially useful for topical delivery of drugs or for intravenous administration.

Single phase homogeneous mixture or winsor IV

In single phase homogeneous mixture or winsor IV the oil, water and surfactants are homogenously mixed.

INGREDIENTS OF MICROEMULSION [18-20]

Various ingredients are used in the formulation and development of microemulsions. Mainly oil and surfactants are used in microemulsion they should be biocompatible, non-toxic and clinically acceptable. Main components of microemulsion are

1. Oil phase
2. Aqueous phase
3. Surfactant
4. cosolvent

Oil phase [21]

Oil is one of the most important components of microemulsion because it can solubilise the required dose of the lipophilic drug and it increases the fraction of lipophilic drug transported via the intestinal lymphatic system. Oil is defined as any liquid having low polarity and low miscibility with water. The examples of such phase are cyclohexane, mineral oil, toulene, & vegetable oil etc.

Aqueous phase

Generally the aqueous phase contains hydrophilic active ingredients and preservatives. Sometimes Buffer solutions are used as aqueous phase.

Surfactant [22]

The term surfactant (surface-active-agent) denotes a substance which exhibits some superficial or interfacial activity & used to lower the surface or interface tension. It has affinity for polar & nonpolar solvents. Surfactants are the molecules that contain a polar head group and a polar tail. Surfactant molecules self-associate due to various inter- and intra-molecular forces as well as entropy considerations. For example, when surfactant is mixed with oil and water, they accumulate at the oil/water interface, because it is thermodynamically favorable. The surfactant molecules can arrange themselves in a variety of shapes. They can form spherical micelles, a hexagonal phase, lamellar (sheet) phases, rodshaped micelles, reverse micelles, or hexagonal reverse micelles. At low concentrations of dispersed (internal) phase, spherical, isolated droplets are present in the microemulsions. The various types of surfactants that help in the progressive development of microemulsion system are

1. Cationic
2. Anionic
3. Non-ionic
4. Zwitterionic surfactants.

Cationic surfactant

Cationic Surfactants when come in contact with water they come into amphiphiliccation and anion form, most often of halogen type. A very large quantity of this class corresponds to nitrogen compounds such as quaternary ammoniums and fatty amine salts, with one or several long chain of the alkyl type, often coming from natural fatty acids. The most well-known examples from the cationic surfactant class are hexadecyl trimethyl-ammonium bromide and didodcecyl ammonium bromide. These surfactants are in general more expensive than anionics.

Anionic surfactant

When anionic Surfactants are dissociated in water in an amphiphilic anion, and a cation, which is in general an alkaline metal (Na, K) or a quaternary

ammonium. These are the most commonly used surfactants. The anionic charge in these surfactants comes from the ionized carboxyl group. Anionic surfactants account for about 50 % of the world production. Alkalialkanoates, also known as soaps, are the most common anionic surfactants. This is the most well-known type of surfactant when it comes to their shape and function. The three most important anionic groups in all of these surfactants are carboxylate, sulfonate and sulfate groups.

Non-ionic surfactant

Non-ionic surfactant is stabilized by dipole and hydrogen bond interactions with the hydration layer of water on its hydrophilic surface. They do not ionize in aqueous solution, because their hydrophilic group is of non-dissociable type, such as phenol, alcohol, ester, or amide. A large proportion of these nonionic surfactants are made hydrophilic by the presence of a polyethylene glycol chain.

Zwitterionic surfactant

Zwitterionic surfactants contain both positively and negatively charged groups and form microemulsions by addition of co-surfactants. Phospholipids, such as lecithin, obtained naturally from soybean or egg are common zwitterionic surfactants. Unlike other ionic surfactants, which are somewhat toxic, lecithin which contains diacyl phosphatidylcholine as the major constituent show excellent biocompatibility. Other important class of zwitterionic surfactants is the betaines, such as alkylbetaines, and heterocyclic betaines .

Cosolvent [23]

It has been observed that single-chain surfactants are unable to reduce the o/w interfacial tension sufficiently to form a microemulsion. The addition of co-surfactants allows the interfacial film to be flexible to take up different curvatures required to form microemulsion over a wide range of excipients. If a single surfactant film is desired, the lipophilic chains of the surfactant should be sufficiently short, or contain fluidizing groups (e.g. unsaturated bonds). Basic co-surfactants are short chain alcohols (ethanol to butanol), glycols such as propylene glycol, medium chain alcohols, amines or acids. The use of co-surfactant is to destroy liquid crystalline or gel structures that come in place of a microemulsion phase.

METHOD OF FORMULATION [24, 25]

Microemulsions are prepared when interfacial tension at the oil/water is kept at very low level. Interfacial layer is kept very much flexible and fluid concentration of surfactants should be high enough to give surfactant molecules to be stabilized the microemulsion at an extremely low interfacial tension.

Two main method are reported for the formulation of microemulsion, these are

1. Phase Inversion Method
2. Phase Titration Method

Phase Inversion Method [26]

In the phase inversion method phase inversion of microemulsions occurs by addition of excess amount of the dispersed phase. During phase inversion quick physical changes occur including changes in particle size that can affect drug release both *in vivo* and *in vitro*. For non-ionic surfactants, this can be completed by changing the temperature, forcing a transition from oil in water microemulsion at low temperatures to water in oil microemulsion at higher temperatures (transitional phase inversion). During cooling, the system crosses a point of zero spontaneous curvature and minimal surface tension, promoting

the formation of finely dispersed oil droplets. This method is also known as phase inversion temperature (PIT) method. Other than temperature, other parameters such as pH value or salt concentration may be considered more effectively instead of the temperature alone. Additionally, a transition in the spontaneous radius of curvature can be obtained by changing the water volume fraction. By successively adding water into oil, initially water droplets are formed in a continuous oil phase. By increasing the water volume fraction changes the spontaneous curvature of the surfactant from initially stabilizing a w/o microemulsion to an o/w microemulsion at the inversion point.

Phase Titration Method [27]

Microemulsions are formulated by the spontaneous emulsification method (phase titration method) and can be shown with the help of phase diagrams. A mixture of fatty acid and oil is added to a caustic solution to prepare a microemulsion, then after it is titrated with a cosurfactant, an alcohol, until the system turned clear. Microemulsions are formed along with various association structures (including emulsion, micelles, lamellar, hexagonal, cubic, and various gels and oily dispersion) depending on the chemical composition and concentration of each component. It is found that as the chain length of the surfactant increased, microemulsions with significant transmittances by visible spectrum can be formed with oils of longer chain lengths. It is also found that different alcohols affect the formation of microemulsions in different ways. The best results, in terms of the greatest percent transmittance coupled with the widest range of oil (dispersed in water) concentration, are obtained from short or branched alcohols.

THEORIES OF MICROEMULSION FORMULATION [28-30]

The formulation of microemulsion is based on various theories that effect and control their stability and phase behavior. These theories are

1. Thermodynamic theory
2. Solubilisation theory
3. Interfacial theory

Thermodynamic theory [29]

Formuation and stability of microemulsion can be expressed on the basis of a simplified thermodynamic machanism. The free energy of microemulsion formation can be dependent on the extent to which surfactant lowers the surface tension of the oil–water interface and the change in entropy of the system, thus

DG f = γDA - T DS

Where,

DG f = Free Energy of formation,

γ =Surface Tension of the oil–water interface,

DA = Change in interfacial area on microemulsification,

DS = Change in entropy of the system which is effectively the dispersion entropy, and

T = Temperature.

It is found that when a microemulsion is formed, DA is changed to a large extent due to the large number of very small droplets formed. It is must to know that while the value of γ is positive at all times, it is very small, and is offset by the entropic component. The dominant favorable entropic contribution is the very large dispersion entropy arising from the mixing of one phase in the other in the form of large numbers of small droplets. However, favorable entropic contributions also come from other dynamic processes such as monomer-micelle surfactant exchange and

surfactant diffusion in the interfacial layer. When large reductions in surface tension are found by significant favorable entropic change, a negative free energy of formation is achieved. In that case, microemulsification is spontaneous and the resulting dispersion is thermodynamically stable.

Solubilisation theory

The formation of microemulsion is oil soluble phase and water phase by micelles or reverse micelles in micellar gradually become larger and swelling to a certain size range results.

Interfacial theory [30]

The interface mixed-film theory i.e a negative interfacial tension theory, according to this theory the micro-emulsion has been capable to form instantaneous and spontaneously generate a negative interfacial tension in the surfactant and co-surfactant in working together. The film, which may consist of surfactant and cosurfactant molecules, is considered as a liquid ‘‘two dimensional’’ third phase in equilibrium with both oil and water. Such a monolayer could be a duplex film, i.e. giving different properties on the water side and oil side. According to the duplex film theory, the interfacial tension γT is given by the following expression

$\gamma T = \gamma(O/W)$ --- π

Where,

γ (O/W)a = Interfacial Tension(reduced by the presence of the alcohol).

γ (O/W)a is significantly lower than γ(O/W) in the absence of the alcohol.

FACTOR AFFECTING FORMULATION OF MICROEMULSION SYSTEM [31-33]

Property of surfactant

Surfactant contains two group lipophilic and hydrophilic groups. Hydrophilic single chain surfactants such as cetylethyl ammonium bromide dissociate completely in dilute solution and have a tendency to form o/w microemulsion. When the surfactant is in presence of salt or when high concentration of surfactant is used, degree of dissociation of polar groups becomes lesser and resulting system may be w/o type.

Property of Oil Phase

Oil phase also influence curvature by its ability to penetrate & Swell the tail group region of the surfactant monolayer, swelling of tail results into an increased negative curvature to w/o microemulsion.

Packing Ratio [34]

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

Temperature [35]

Temperature is extremely important in determining the effective head group size of nonionic surfactants. At low temperature, they are hydrophilic and form normal o/w system. At higher temperature, they are lipophilic and form w/o systems. At an intermediate temperature, microemulsion coexists with excess water and oil phases and forms bicontinuous structure.

EVALUATION PARAMETERS OF MICROEMULSION SYSTEM

Physical appearance

For Physical appearance microemulsion can be inspect visually for homogeneity, fluidity and optical clarity.

Scattering Techniques [36]

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

Limpidity Test (Percent Transmittance) [37]

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

Drug stability [38]

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

Globule size and zeta potential measurements [39]

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

Assessment of the Rheological Properties (viscosity measurement) [40]

The rheological properties play an important role in stability. It can be determined by Brookfield digital viscometer. Change in the rheological characteristics help in determining the microemulsion region and its separation from other region. Bicontinuous microemulsion are dynamic structures with continuous fluctuations occurring between the bicontinuous structure, swollen reverse micelle, and swollen micelles.

Electrical conductivity [41]

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

Drug solubility [42]

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

In-vitro drug release [43, 44]

The diffusion study can be carried out on a modified Franz diffusion cell, within volume of 20mL. The receptor compartment was filled with of buffer .The donor compartment was fixed with

cellophane membrane, containing the microemulsion formulation and the plain drug solution, separately. At predetermined time intervals samples were withdrawn from the receptor compartment and analyzed for drug content, using a UV spectrophotometer at specific wavelength.

APPLICATION OF MICROEMULSION SYSTEM

Microemulsion in Pharmaceutical

From last two decades there has been a revolution in the utilization of microemulsion systems in a variety of pharmaceuticals.

- **Parenteral Delivery [45]**

Parenteral administration (especially via the intravenous route) of drugs with limited solubility is a major problem in industry because of the extremely low amount of drug actually delivered to a targeted site. Microemulsion formulations have distinct advantages over macroemulsion systems when delivered parenterally because of the fine particle microemulsion is cleared more slowly than the coarse particle emulsion and, therefore, have a longer residence time in the body.

- **Oral Delivery [46]**

Microemulsion formulations offer the several benefits over conventional oral formulation including increased absorption, improved clinical potency, and decreased drug toxicity. Therefore, microemulsions have been reported to be ideal delivery of drugs such as steroids, hormones, diuretic and antibiotics.

- **Topical delivery [47]**

Topical administration of drugs can have advantages over other methods for several reasons, one of which is the avoidance of hepatic first-pass metabolism, salivary and degradation of the drug in stomach and related toxicity effects. Another is the direct delivery and targetability of the drug to affected areas of the skin or eyes. Now a day, there have been a number of studies in the area of drug penetration into the skin. They are able to incorporate both hydrophilic (5-flurouracil, apomorphine hydrochloride etc) and lipophilic drugs (estradiol, finasteride, ketoprofenetc) and enhance their permeation. Since formation of microemulsion formation requires high surfactant concentration, the skin irritation aspect must be considered especially when they are intended to be applied for a longer period.

- **Ocular and Pulmonary Delivery[48]**

For the treatment of eye diseases, drugs are essentially delivered topically. O/W microemulsions have been investigated for ocular administration, to dissolve poorly soluble drugs, to increase absorption and to attain prolong release profile.

Other pharmaceutical applications [49,50,51,52]

- Nasal delivery
- Drug targeting
- Cellular targeting
- Brain targeting
- Periodontal delivery
- Tumor targeting

Other application

- **Microemulsions in analytical applications[53]**

Microemulsions are widely used in the field of analytical techniques such as chromatography etc. In microemulsion electrokinetic chromatography (MEEKC), characterization of solute hydro - phobicity was carried out, which provides a quick

and reproducible method to obtain hydrophobic parameters for solvents. Microemulsions are able to enhance analytical spectroscopic techniques by functioning as solubilized media, spectral shift reagents, intensity amplification agents, etc. The utilization of microemulsion media in analytical spectroscopy and the analytical sensitivities of the three systems o/w, w/o and bi continuous microemulsion have been assessed. A series of studies have been reported on the determination of aluminium, zinc, copper, manganese ions using both microemulsion and mixed microemulsion systems.

- **Microemulsions in biotechnology[54]**

Many biocatalytic and enzymatic reactions are conducted in aquo-organic or pure organic as well as in biphasic media .Their use is seriously limited because they can inactivate or denature the biocatalysts. Recently, interest on micro-emulsions is being focused for various applications in biotechnology, viz, enzymatic reactions, immobilization of proteins and bioseparation.

- **Microemulsions in enhanced oil recovery[55]**

The understanding of the mechanisms of enhanced oil recovery (EOR) using surfactant and microemulsion can help in obtaining unrecoverable underground oil. If the interfacial tension between the crude oil and reservoir brine can be reduced to around 10-3 mN/m, a substantial fraction of the residual oil in the porous media in which it is trapped can be mobilized. Low interfacial viscosity of the system is also advantageous.

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

CONCLUSION

Microemulsions have a very crucial importance in the drug delivery system as well as in the industrial process. They can be used to optimize drug targeting without a concomitant increase in systemic absorption. The role of microemulsion in providing novel solutions to overcome the problems of poor aqueous solubility of highly lipophilic drug compounds and provide high, more consistent and reproducible bioavailability. Microemulsions can also be used to achieve drug targeting however challenges remain, primarily because of the layers of barriers that these systems need to overcome to reach to the target. Microemulsion has been shown to be able to protect labile drug, control drug release, and reduce patient variability. Furthermore it has proven possible to formulate preparations suitable for most routes of administration. In today's world Microemulsion is accepted as full of potential for novel drug delivery systems. Current research work is focused on the preparation of safe, efficient and more compatible microemulsion constituents which will further enhance the utility of these novel vehicles.

REFERENCES

1. T.P. Hoar and J.H. Schulman. Transparent water-in-oil dispersions, the oleopathic hydro micelle. Nature 1943; 152: 102–103.
2. J. H. Schulman et al. Mechanism of formation and structure of micro emulsions by electron microscopy. The Journal of Physical Chemistry 1959; 63: 1677–1680.
3. Danielsson and B. Lindman. The definition of a microemulsion, Colloids and Surfaces 1981; 3: 391–392.
4. Shinoda K and Lindman B. Organised surfactant systems: Microemulsions. Langmuir 1987; 3: 135–149.
5. M. Jayne Lawrencea and Gareth D. Reesb. Microemulsion-based media as novel drug delivery systems. Advanced Drug Delivery Reviews 2000; 45: 89–121.
6. Kumar. K. Senthil et al. Microemulsions as Carrier for Novel Drug Delivery: A Review. International Journal of Pharmaceutical Sciences Review and Research 2011; 10: 37-45.
7. Patel R. Mrunali. Microemulsions: As Novel Drug Delivery Vehicle. 2007; 5.
8. Madhav. S and Gupta. D. A review on microemulsion based system. *International Journal of Pharmaceutical Sciences and Research* 2011; 2 (8): 1888.
9. Ghosh, P.K. and Murthy R.S.R. Microemulsions: A Potential Drug Delivery System. Current Drug Delivery 2006; 3: 167-180.
10. Chandra A. and Sharma P.K. Microemulsions: An Overview. Pharmainfonet 2008; 6 (2).
11. Patel M.R. et al. Microemulsions: As Novel Drug Delivery Vehicle. Pharmainfonet 2007; 5 (6).
12. Kayes F. B. Disperse systems In Pharmaceutics: The Science of Dosage Form Design. International Student Edition Ed: Aulton. M.E. Churchill Livingstone 1999; 110.
13. Emsap. W.J. et al. Disperse Systems in Modern Pharmaceutics. Fourth Edition. Ed: Banker. G.S. Rhodes, C.T. Marcel Dekker Inc. New York. 2002; p260.
14. Sarkhejiya Naimish A et al. Emerging Trend of Microemulsion in Formulation and Research. International Bulletin of Drug Research. 2000; 1 (1): 54-83.
15. Kunieda H. et al. The Journal of Physical Chemistry 1988; 92: 185.
16. Mukherjee K. et al. *Journal of Colloid* and *Interface* Science 1997; 187: 327.
17. Aboofazeli R and Lawrence M.J. Investigations into the formation and characterization of phospholipid microemulsions. I. Pseudo-ternary phase diagrams of systems containing water- lecithin-alcohol-isopropyl myristate. International Journal of Pharmaceutics 1993; 93: 161-175.
18. JhaSajal Kumar et al. Microemulsions- Potential Carrier for Improved Drug Delivery. Internationale Pharmaceutica Sciencia 2011; 1(2): 25-31.
19. Vyas S P. Theory and practice in novel drug delivery system. CBS Publishers New delhi. 2009; p115.
20. Prince L. M. A theory of aqueous emulsions I. Negative interfacial tension at the oil/water interface. *Journal of Colloid* and *Interface* Science 1976; 23: 165-173.
21. Martin A. Coarse Dispersions In Physical Pharmacy. Fourth Edition B.I. Waverly Pvt. Ltd. New Delhi. 1994; p495.
22. Rao Y.S. et al. Microemulsions: A Novel Drug Carrier System. International Journal of Drug Delivery Technology 2009; 1(2): 39-41.
23. Grampurohit N. et al. Microemulsions for Topical Use-A Review. *Indian Journal* of *Pharmaceutical* Education and Research 2011; 45(1):100-107.

24. Shaji J. and Reddy M.S. Microemulsions as drug delivery systems. Pharma Times 2004; 36 (7): 17 – 24.
25. Kayes F.B. Disperse systems In Pharmaceutics: The Science of Dosage Form Design. International Student Edition Ed: Aulton. M.E.; Churchill Livingstone 1999; p110.
26. Sushama Talegaonkar et al. Microemulsions: A Novel approach to enhanced drug delivery. Recent patents on drug delivery and formulation.2008; 2: 238-257.
27. Shafiqun Nabi S. et al. Formulation development and optimization using nanoemulsion technique: A technical note. AAPS Pharm Sci Tech 2007; 8: 1-6.
28. Paul, B.K. and Moulik S.P. Uses and Applications of Microemulsions. Current Science 2001; 80 (8): 990 – 1001.
29. Amit A. Kale and Vandana B. Patravale. Development and Evaluation of Lorazepam Microemulsions for Parenteral Delivery. AAPS PharmSciTech 2008; 9: 966-971.
30. Vandana Patel et al. Development of Microemulsion for Solubility Enhancement of Clopidogrel. Iranian Journal of Pharmaceutical Research 2010; 9(4): 327-334.
31. Park K M and Kim C K. Preparation and evaluation of flurbiprofen loaded Microemulsions for parental delivery. International Journal of Pharmaceutics 1999; 181: 173-179.
32. Peira E. and Transdermal permeation of apomorphine through hairless mouse skin from microemulsions. International Journal of Pharmaceutics 2001; 226: 47-51.
33. Rhee Y S. et al. Transdermal delivery of ketoprofen using Microemulsions. International Journal of Pharmaceutics 2001; 226: 161-170.
34. Ashok Patel and Pradeepvavia R. Preparation and In-vivo Evaluation of Self-Microemulsifying Drug Delivery System Containing fenofibrate. The AAPS Journal 2007; 226: 344-352.
35. Peltola S. et al. Microemulsions for topical delivery of estradiol. International Journal of Pharmaceutics 2003; 254: 99-107.
36. Constantinides PP. et al. Formulation and intestinal absorption enhancement evaluation of water-in-oil microemulsions incorporating medium-chain glycerides. Pharmaceutical Research 1994; 11: 1385–90.
37. Constantinides PP. et al. Water-in-oil microemulsions containing medium-chain fatty acids/salts: formulation and intestinal absorption enhancement evaluation. Pharmaceutical Research 1996; 13(2): 205–105.
38. Jadhav. K.R. et al. Design and Evaluation of Microemulsion Based Drug Delivery System. International Journal of Advances in Pharmaceutical Sciences. 2010; 1: 156-166.
39. Brime B. et al. Amphotericin B in oil-water lecithin-based microemulsions: formulation and toxicity evaluation. Journal Pharmaceutical Sciences 2002; 91(4): 1178–85.
40. Thakker K D. and Chern W H. Development and Validation of In Vitro Release Tests for Semisolid Dosage Forms - Case Study. Dissolution Technologies 2003; 15: 10-15.
41. Shaikh I M. et al. Topical delivery of aceclofenac from lecithin organogels: preformulation study. Current Drug Delivery 2006; 3(4): 1727.
42. Tomsic M. et al. Water–Tween 40®/Imwitor 308®–isopropyl myristate microemulsions as delivery systems for ketoprofen: Smallangle X-ray scattering study. International Journal of Pharmaceutics 2006; 327: 170– 177.
43. Martin A. Coarse Dispersions In: Physical Pharmacy. Fourth Edition. B.I. Waverly Pvt. Ltd. New Delhi. 1994; p495.

44. Giustini M. et al. Microstructure and dynamics of the water-in-oil CTAB/*n*-pentanol/*n*-hexane/water microemulsion: spectroscopic and conductivity study. Journal Physical Chemistry1996; 100: 3190 3198.
45. Hsiu-O Ho. et al. Preparation of microemulsions using polyglycerol fatty acid esters as surfactant for the delivery of protein drugs. Journal of Pharmaceutical Sciences 1996; 85: 138-143.
46. Corswant C. et al. Triglyceride –based microemulsion for intravenous administration of sparingly soluble substances. Journal of Pharmaceutical Sciences 1998; 87: 200-208.
47. Dreher F. et. al. Interaction of a lecithin microemulsion gel with human *stratum corneum*and its effect on transdermal transport. Journal of Controlled Release 1997; 45:131 140.
48. Lv FF. et al. Studies on the stability of the chloramphenicol in the microemulsion free of alcohols. European Journal of Pharmaceutics and Biopharmaeutics 2006; 62: 288-294.
49. Syamasri Gupta and S.P. Moulik. Biocompatible microemulsions and their prospective uses in drug delivery. Journal of Pharmaceutical Sciences. 2008; 97: 22-45.
50. Shiokawa T. et al. Effect of Polyethylene Glycol Linker Chain Length of Folate-Linked Microemulsions Loading Aclacinomycin A on Targeting Ability and Antitumor Effect In itro and In vivo. Clinical Cancer Research 2005; p11.
51. Talegaonkar S and Mishra P. Intranasal delivery: An approach to bypass the blood brain barrier. Indian Journal of Pharmacology 2004; 36: 140-147.
52. Hasse. A. and Keipert S. Development and characterisation of microemulsions for ocular application. European Journal of Pharmaceutics and Biopharmaeutics 1997; 43; 179–183.
53. Malmsten. M. Microemulsions in pharmaceuticals In Handbook of Microemulsion. Science and Technology. Marcel Dekker. Inc. New York. 1999; p 755.
54. Fathy I. et al. Evaluation of the anti-inflammatory and analgesic effects of piroxicam loaded microemulsion in topical formulations. International Journal of Pharmacy and Pharmaceutical Science 2011; 3(2): 6670.
55. Shishu Rajan Sunita and Kamalpreet. Development of Novel Microemulsion-Based Topical Formulations of Acyclovir for the Treatment of Cutaneous Herpetic Infections. AAPS Pharm Sci Tech 2009; 10: 559-565.