EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 9
Issue: 4
127-138
Year: 2022

A REVIEW OF MICROEMULSIONS AS EXCELLENT CANDIDATES FOR OCULAR DRUG DELIVERY SYSTEM

Sourabh Dixit*, Dr. Rajesh Kumar Nema[1], Madhu Sahu[2], Aysha Quraishi[3], Subrata Paul[4], Preetam Mandal[5], Sarika Sahu[6]

Rungta Institute of Pharmaceutical Sciences and Research, Kurud Road, Bhilai, Chhattisgarh.

***Corresponding Author: Sourabh Dixit**
Rungta Institute of Pharmaceutical Sciences and Research, Kurud Road, Bhilai, Chhattisgarh.

Article Received on 23/01/2022 **Article Revised on 13/02/2022** **Article Accepted on 05/03/2022**

ABSTRACT
Ocular drug delivery has remained as one of the most challenging task for pharmaceutical scientists. The unique structure of the eye restricts the entry of drug molecules at the required site of action. Targeted drug delivery has generated a great deal of interest in the field because of its potential to overcome many barriers associated with current therapy many newer carriers are evolving with the advent of technology and the demand of targeted delivery like microemulsions. Microemulsions are an attractive technology platform for the pharmaceutical formulator as they are thermodynamically stable, possess excellent solubilization properties, and their formulation is a relatively straightforward 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. Current momentum in the invention of new drug delivery systems hold a promise towards much improved therapies for the treatment of vision threatening disorders. Previous research works showed higher percentage of surfactant used for the formation of microemulsions, irrespective of different routes of administration, but there is a lack of toxicological evaluation of the prepared microemulsions, which can be a broad research area in future.[1]

KEYWORDS: ocular drug delivery, microemulsion, thermodynamically stable, toxicological evaluations.

INTRODUCTION
Topical application is used as standard treatment of ocular diseases, consisting of solution, suspension and ointment. Ophthalmic drug delivery system is the one of the most attractive & interesting but arduous struggle facing by the pharmaceutical scientists., the major problems related to ophthalmic drug application to the eye is the natural precorneal cleaning of the eye and high tear fluid drainage quickly element the drug solution. The amount of applied drug penetrates into the cornea and reaches therapeutic concentrations in intraocular tissues is only 1-5%. The challenging objective targeted at dealing with these problems is to develop ophthalmic drug delivery systems with increased corneal drug absorption, improved ocular retention and reduced systemic side effects. The human eye is unique & complex structure, its anatomy, physiology and biochemistry renders highly protective organ and almost impervious to foreign agent and also restricts the entry of drug at target site of action. The human eye has two segments, i.e. anterior (cornea, conjunctiva etc.) and posterior (vitreous humor, retina lens etc.). Conventional ophthalmic dosage forms, water-soluble drugs are available as aqueous solutions & water-insoluble drugs are available as suspensions, ointments or gels, they can only deliver the drug to the anterior segment of the eye but not to the posterior segment. One of the major rate limiting barriers is the human corneal epithelium which hinders permeation of hydrophilic drugs and macromolecules. Second rate-limiting barrier is stroma (part of tissue or organ that has a connective & structure) which prevents diffusion of highly lipophilic drugs due to abundant hydrated collagen contents.[1] Another significant barrier includes lacrimal fluid secretion and lachrymal fluid-eye barriers. Due to these barriers, it is very ambitious to develop ocular drug delivery systems which can elude these protective barriers and deliver the drug to the posterior segment of the eye without causing permanent tissue damage.[2] Recent researches focused on the development of new and more effective drug delivery systems such as nanotechnology-based formulations like nanoemulsion/microemulsion, nanosuspension, solid lipid nanoparticle etc.[2-3]

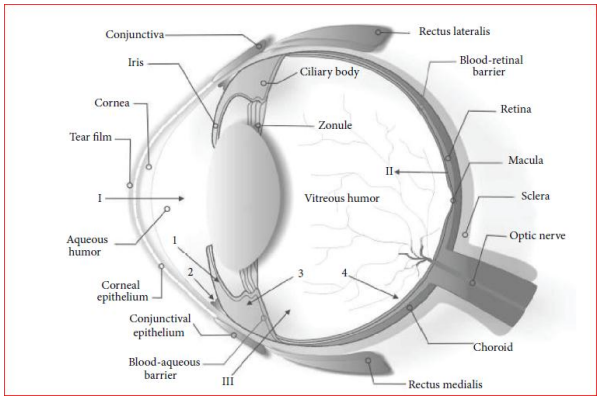

Figure no. 1 Schematic illustration of ocular structures and barriers.

STRUCTURE OF EYE

ANATOMY OF EYE

The **human eye** is an organ which reacts to light and pressure. As a sense organ, the mammalian eye allows vision. Human eyes help provide a three dimensional, moving image, normally colored in daylight. The human eye can differentiate between about 10 million colorsand is possibly capable of detecting a single photon. The eye is analogous to a camera in its basic operation. The eye is highly specialized organs contain photo receptor which processing light energy from the environment to produce action potentials in specialized nerve cells, which subsequently relayed to the optic nerve and then to the brain where the information is processed and consciously appreciated as vision.[4-5-6]

It is a spherical structure with a wall consisting of four layers shown in figure no.1-

1. Sclera
2. Choroids layer
3. Retina
4. Conjunctiva

1. SCLERA

The sclera is commonly known as “the white of the eye.” It is the tough, opaque tissue that serves as the eye’s protective outer coat.

2. CHOROID

The choroid lies between the retina and sclera. It is composed of layers of blood vessels that nourish the back of the eye. The choroid connects with the ciliary body toward the front of the eye and is attached to edges of the optic nerve at the back of the eye.

3. THE CORNEA

The cornea is an optically transparent tissue that conveys images to the back of the eye and covers about one-sixth of the total surface area of the eye ball. composed of the five layers.

I. The Epithelium, The Bowman's Membrane, The stroma, The Descemet's Membrane, The Corneal Endothelium

Composition of tear

The secretion is a clear watery fluid containing numerous salts, glucose, other organic compounds, approximately 0.7% protein and the enzyme, lysozyme, water 98.2%, Nacl-0.66%, protein-0.67%, solids: 1.8%, sugar-0.65%, NPN-0.05%, urea-0.03% & Other mineral elements sodium, potassium and ammonia-0.79%.[7]

ROUTES OF OCULAR DRUG DELIVERY SYSTEM

There are several possible routes of drug delivery into the ocular tissues. The selection of the route of administration depends primarily on the target tissue.[8]

TOPICAL ROUTE

Typically topical ocular drug administration is accomplished by eye drops, but they have only a short contact time on the eye surface. The contact, and thereby duration of drug action, can be prolonged by formulation design (e.g. gels, jellifying formulations, ointments, and inserts).[9]

SUBCONJUNCTIVAL ADMINISTRATION

Traditionally subconjunctival injections have been used to deliver drugs at increased levels to the uvea. The progress in materials sciences and pharmaceutical formulation have provided new exciting possibilities to develop controlled release formulations to deliver drugs to the posterior segment and to guide the healing process after surgery.[10]

INTRAVITREAL ADMINISTRATION

Direct drug administration into the vitreous offers distinct advantage of more straightforward access to the vitreous and retina. It should be noted; however that delivery from the vitreous to the choroid is more complicated due to the hindrance by the RPE (Retinal Pigment Epithelium) barrier.[11]

BARRIERS FOR OCULAR DRUG DELIVERY SYSTEM

In tears have a direct bearing on efficiency of drug absorption into the inner eye. The productive absorption of most ophthalmic drugs results from diffusional process across corneal membrane. The efficiency of absorption process is a function of rate and extent at which the transport processes of eye. The flux of any drug molecule across the biological membrane depends on the physicochemical properties of the permeating molecule and its interaction with the membrane.[12]

The epithelium and endothelium contain on the order of a 100 fold greater amount of lipid material than the stroma. Consequently, depending on the physicochemical properties of a diffusing drug, the resistance offered by the individual layers varies greatly.[13]

Drug Loss from the Ocular Surface

After the infusion of drug into the eye, the lacrimal fluid flow, remove the instilled or infused drug compound from the surface of eye. Even the lacrimal turnover rate is only about 1 micro litter per minute. Another method of non productive drug removal is its systemic absorption in the body instead of ocular absorption.

Nasolacrymal Drainage System / Systemic Drug Absorption

Most of the administered drug is lost through nasolacrimal drainage immediately after dosing. The drainage allows drug to be systemically absorbed across the nasal mucosa and the gastrointestinal tract leading to multifarious effects.[14]

The nasolachrymal drainage system consists of three parts:

- The secretory system, The distributive system, The excretory system.

Conjunctivitis

Conjunctivitis, commonly known as pink eye as shown in Fig 1, is an the clear membrane that covers the white part of the eye and lines the inner surface of the eyelids. The inflamed conjunctiva will usually make the eye appear red or pink because the tiny blood vessels that are normally within the conjunctiva get irritated and enlarged.[15] It usually affects both eyes at the same time although it may start in one eye and spread to the other after a day or two days. It may be asymmetrical, affecting one eye more than the other. Pink eye can be infectious or non infectious.[16]

There are many causes for conjunctivitis, including –

- Bacterial conjunctivitis – staphylococci, streptococci.
- Viral conjunctivitis (often associated with the common cold) – adenovirus.
- Chlamydial conjunctivitis – Chlamydia trachomatis.
- Allergic conjunctivitis –allergic disease such as hay fever, asthma and eczema and by antigens like pollen, dust mites or cosmetics.
- Reactive conjunctivitis or irritant conjunctivitis – chemicals, smoke, fumes etc.

Corneal ulcers/ Keratitis

Inflammation of cornea (Keratitis) is characterized by corneal oedema, cellular infiltration & ciliary congestion. Being the most anterior part of eyeball, cornea is exposed to atmosphere & hence prone to get infected easily. Bacterial corneal ulcers are the most commonly caused by virulent organism. Common bacteria associated with corneal ulceration are Staphylococcus aureus, Pseudomonas pyocyanea, E.coli and Proteus etc.[17]

Endophthalmitis

It is severe form of intraocular inflammation (purulent uveitis) involving ocular cavities & inner coats of eyeball. Causative organisms include Streptococci, E.coli, Pseudomonas, etc.[18]

Accordingly, the armamentarium of available antimicrobials used in the prevention and treatment of these infections includes antivirals, antifungals, and antibacterials. Common topical antibacterials used in the treatment of ocular infectious diseases include sulfonamides, aminoglycosides, polymyxin-based combinations, and fluoroquinolones.[19]

MECHANISM OF OCULAR DRUG ABSORPTION

Drugs administered by instillation must penetrate the eye and do so primarily through the cornea followed by the non-corneal routes. These non-corneal routes involve drug diffusion across the conjunctiva and sclera and appear to be particularly important for drugs that are poorly absorbed across the cornea.[20]

CORNEAL PERMEATION

The permeation of drugs across the corneal membrane occurs from the precorneal space.[21]

NON-CORNEAL PERMEATION

Primary mechanism of drug permeation is the sclera is likely to be diffusion across the intercellular aqueous media in the case of structurally similar corneal stroma. Therefore the possibility of partitioning mechanism cannot be eliminated. Although like cornea, the conjunctiva is composed of an epithelial layer covering an underlying stroma, the conjunctival epithelium offers substantially less resistance than does the corneal epithelium.[22]

CLASSIFICATION OF OCULAR DRUG DELIVERY SYSTEMS

A multitude of ocular dosage forms are available for delivery of drugs to the eye. These can be classified on the basis of their physical forms as follows:[23]

1. Liquids: - Solutions, Suspensions, Sol to gel systems, Sprays
2. Solids: - Ocular inserts, Contact lenses, Corneal shield, Artificial tear inserts, Filter paper strips
3. Semi-solids: Ointments, Gels
4. Miscellaneous: Ocular iontophoresis, Vesicular systems, Muco-adhesive dosage forms, Particulates.

MICROEMULSIONS

Micro emulsions are a promising dosage form for the natural defense of the eye, due to their intrinsic properties and specific structure. Microemulaions are prepared by inexpensive processes through autoemulsification or supply of energy and can be easily sterilized, so they are stable and have high capacity of dissolving the drugs.[24] The *in vivo* results and preliminary studies on healthy volunteers have shown a delayed effect and an increase in the bioavailability of drug.[25]

2. SOLIDS: - The concept of using solids for the eye is based on providing sustained release characteristics.[26]

OCULAR INSERTS

Ocular inserts are solid dosage form and can overcome the disadvantage reported with traditional ophthalmic systems like aqueous solutions, suspensions and ointments. The typical pulse entry type drug release behavior observed with ocular aqueous solutions (eye drops), suspensions and ointments is replaced by more controlled, sustained and continuous drug delivery using a controlled release ocular drug delivery system.[27] The ocular inserts maintain an effective drug concentration in the target tissues and yet minimize the number of applications consonant with the function of controlled release systems.[28] Limited popularity of ocular inserts has been attributed to psychological factors, such as reluctance of patients to abandon the traditional liquid and semisolid medications, and to occasional therapeutic failures (e.g. unnoticed expulsion from the eye, membrane ruptures etc.).[29] A number of ocular inserts were prepared utilizing different techniques to make soluble, erodible, non-erodible, and hydrogel inserts.[30]

PARTICULATES (NANOPARTICLES/MICROPARTICLES)

Particulate polymeric drug delivery systems include micro- and nanoparticles. Particles in the micrometer size range >1mm are called Microparticles or microspheres, whereas those in the nanometer size range < 1mm (1000 nm) are called nanoparticles.[31] Microparticles with a capsule wall enclosing a liquid or solid core are called microcapsules. The upper size limit for Microparticles for ophthalmic administration is about 5-10 mm. above this size, a scratching feeling in the eye can result after ocular application. Microspheres and Nanoparticles represent promising drug carriers for ophthalmic application. The binding of the drug depends on the physicochemical properties of the drugs as well as of the nano or micro particle polymer. Particulates such as nanoparticles, nanocapsules, submicron emulsions, nanosuspensions improved the bioavailability of ocularly applied drugs.[32]

INTERESTS OF NOVEL OPHTHALMIC DRUG DELIVERY

Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientist. The landscape of ophthalmic drug delivery is highly competitive and rapidly evolving. New classes of pharmaceuticals and biologics are fueling the demand for novel drug delivery.[33]

The main aim of pharmacotherapeutics is the attainment of effective drug concentration at the site of action for the sufficient period of time to elicit a response. The challenge is to provide a system with improved ocular drug bioavailability and prolonged duration of activity, but still with a minimum risk of ocular complications. A major problem of ophthalmic drug delivery is not the lack of efficient drugs but the attainment of their optimal concentration at the site of their optimal concentration at the site of action.[34]

WHAT IS MICROEMULSION

The term "*microemulsion*" refers to a thermodynamically stable, isotropically clear dispersion of two immiscible liquids, such as oil and water, which is stabilized by an interfacial film of surfactant molecules. Surfactant molecules contain both a polar as well as a polar group. So they exhibit a very peculiar behavior, firstly, they get adsorbed at the interface, where they can fulfill their dual affinity with hydrophilic groups located in aqueous phase and hydrophobic groups in oil or air.

The dispersed phase typically comprises of small particles or droplets, with a size range of 5 nm-200 nm, and has very low oil/water interfacial tension. Because the droplet size is less than 25% of the wavelengths of visible light, microemulsions are transparent.[35]

STRUCTURE OF MICROEMULSION

Microemulsions are dynamic system in which the interface is constantly and spontaneously fluctuating. Structurally, microemulsions are divided into water in oil (w/o), oil in water (o/w) and bi-continuous microemulsions. In water in oil type, water droplets are dispersed in constant oil phase while oil in water type are formed when oil droplets are dispersed in the constant aqueous phase. The bi-continuous microemulsions may result wherever the amounts of oil and water are same in the system (Figure-2)[36]

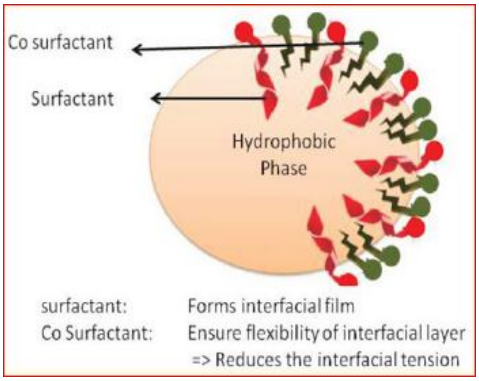

Figure No. 2 Structure of Microemulsion.

DIFFERENCE BETWEEN EMULSION AND MICROEMULSIONS[37]

CHARACTERSTICS	EMULSION	MICROEMULSION
Appearance	Cloudy	Transparent
Microstructure	Static	Dynamic
Droplet size	1-20 nm	10-100 nm
Stability	Thermodynamically unstable, kinetically stable	Thermodynamically stable and long shelf life
Phases	Biphasic	Monophasic
Formation	Energy input required	Spontaneous, no energy input required
Cost	Higher cost	Lower cost
Viscosity	High viscosity	Low viscosity with Newtonian behavior
Turbidity	Turbid	Transparent
Co-surfactant used	No	Yes
Surfactant concentration	1-20%	> 10%
Size range	0.5-5 μ	< 0.1 μ
Contact position	Direct oil/water contact at the interface	No direct oil in water contact at the interface
Optical property	Most emulsions are opaque (white) because the bulk of their droplets is greater than the wavelength of light and many oils have higher refractive indices than water.	They are transparent or translucent as their droplet diameter are less than ¼ of the wavelength of light, they scatter little light.

THEORIES OF MICROEMULSION FORMULATION [38-40]

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

THERMODYNAMIC THEORY

Formation and stability of microemulsion can be expressed on the basis of a simplified thermodynamic mechanism. The free energy of microemulsion formation can be dependent on the level to which surfactant reduces the surface tension of the water-oil interface and the change in entropy of the system, thus

DG f = γ DA - TDS

Where,

DG f = Free Energy of formation

γ =Surface Tension of the oil-water interface

DA = Change in interfacial area on microemulsification

T = Temperature

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

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

The interface mixed film theory, i.e., a negative interfacial tension theory, according to this theory the microemulsion 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 co-surfactant 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 γ T is given by the following expression:

γ T = γ (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.

INGREDIENTS OF MICROEMULSION[41]

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

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 drugs 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, toluene, & vegetable oil etc.

AQUEOUS PHASE

Water is most commonly used as aqueous phase. The pH of aqueous phase always needs to be adjusted due to its considerable impact on phase behavior of

microemulsions. As in case of microemulsions used for parenteral administration aqueous phase should be isoosmotic to blood which is adjusted by sodium chloride, glycerol, dextrose and sorbitol. Generally the aqueous phase contains hydrophilic active ingredients and preservatives. Sometimes Buffer solutions are used as aqueous phase.

SURFACTANT

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 an 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 the surfactant is mixed with oil and water, they accumulate at the oil/water interface, because it is ther-modynamically favourable. The surfactant molecules can arrange themselves in a variety of shapes. They can form spherical micelles, a hexagonal phase, lamellar (sheet) phases, rod-shaped 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 resembles to nitrogen compounds like 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 of the cationic surfactant class are hexadecyltrimethylammonium 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, that 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 sulphate 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 don't ionize in aqueous solution, as their hydrophilic group is for non-dissociable type, such as phenol, alcohol, ester, or amide. A large amount of these non-ionic surfactants are made hydrophilic by the occurrence 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 diacylphosphatidylcholine as the major constituent show excellent biocompatibility. Another important class of zwitterionic surfactants is the buttons, such as alkyl betaines, and heterocyclic batons.

It has been observed that single-chain surfactants are unable to reduce the oil in water interfacial tension necessarily to form a microemulsion. The addition of co-surfactants allows the interfacial film to be flexible to take up different curvatures necessary to form a microemulsion over a wide range of excipients.

METHODS OF PREPARATION OF MICROEMULSION[42-44]

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

Phase inversion of microemulsion take place upon addition of excess of dispersed phase or in response to temperature. In phase inversion, drastic physical changes take place, comprising changes in particle size which can distress drug release both *in-vitro* and *in-vivo*. These methods make use of altering the spontaneous curvature of surfactant. For non-ionic surfactants, this can be accomplished by altering the temperature of system, forcing a conversion from oil in water microemulsion at low temperature to a water in oil microemulsion at high temperature. During cooling, the system crosses a point of zero spontaneous curvature and negligible surface tension, supporting the development of finely dispersed oil droplets. This method is discussed to as phase inversion temperature method. Rather than the temperature, other parameters like pH value or salt

concentration may be considered as well rather than the temperature alone. Moreover, a transition in spontaneous radius of curvature may be obtained by altering the water volume fraction. By consecutively adding water into oil, primarily water droplets are formed in continuous oil phase. Increasing the water volume portion changes the spontaneous curvature of surfactant from primarily stabilizing water in oil microemulsion to oil in water microemulsion at the inversion locus. Short chain surfactant form flexible monolayers at o/w interface resulting in bicontineousmicroemulsion at the inversion point.

PHASE TITRATION METHOD (SPONTANEOUS EMULSIFICATION METHOD)

Microemulsions are prepared by phase titration method and can be described through phase diagrams. Construction of phase diagram is a beneficial method to study the complex series of interfaces which can take place when the different constituents are mixed. Microemulsions are formed together with several association structures depending on the concentration and chemical composition of each constituent. The appreciative of their phase equilibrium and demarcation of phase boundaries are essential aspects of study. As quaternary phase diagram is time consuming and tough to understand, the pseudoternary phase diagram is frequently constructed to find the different zones comprising microemulsion zone, in which each corner of diagram represents 100% of the particular constituent (Figure 6). The region may be separated into O/W or W/O microemulsion by only bearing in mind the composition, that is, whether it is water rich or oil rich. Observations should be made cautiously so that metastable systems are not included.

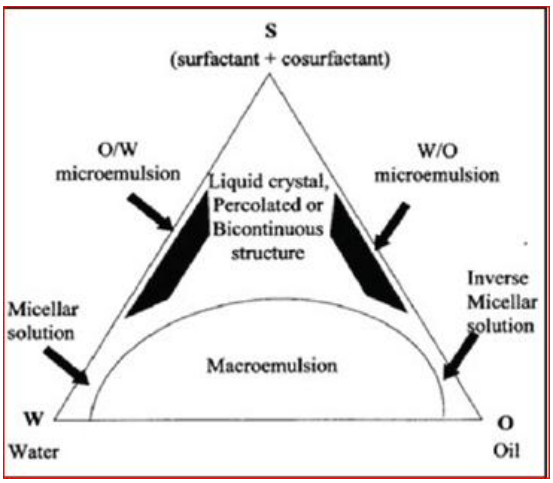

Figure no. 6: Pseudo ternary phase diagram of oil, water and surfactant.

CHARACTERIZATION OF MICROEMULSION[45]

The droplet size, viscosity, density, turbidity, refractive index, phase separation and pH measurements shall be performed to characterize the microemulsion. This technique has been advocated as the best method for predicting microemulsion stability.

DROPLET SIZE MEASUREMENTS[46]

Size analysis of microemulsion was carried out by dynamic light scattering experiments or electron microscopy. The polydispersity index of the formulation was determined by the same instrument**.**

ZETA POTENTIAL MEASUREMENTS[47]

Zeta potential for microemulsion was determined using zetasizer Dilution test: It is confirmatory test of microemulsion to know which type of microemulsion was formed. The prepared optimized microemulsion was diluted with water (as external phase)**.**

PHASE ANALYSIS[48]

To determine the type if microemulsion that has formed the phase system (o/w or w/o) of the microemulsions is determined by measuring the electrical conductivity using a conductometer. The measurement of electrical conductivity gives the quantitative idea of the solubilization of water phase in the selected mixture containing oil phase, surfactant and cosurfactant. It also gives the idea about the types of microemulsion**.**

VISCOSITY MEASUREMENT[49]

The viscosity of microemulsions of several compositions can be measured at different shear rates at different temperatures using Brookfield type rotary viscometer. The sample room of the instrument must be maintained at 37 ± 0.2°C by a thermobath, and the samples for the measurement are to be immersed in it before testing**.**

DRUG CONTENT DETERMINATION[50]

Itraconazole content in microemulsion based gel was measured by dissolving known quantity of microemulsion based gel in solvent (methanol) by Sonication. Absorbance was measured after suitable dilution at 280 nm using UV/VIS spectrophotometer**.**

***IN VITRO* DRUG PERMEATION STUDIES[51]**

Franz diffusion cells with a cellulose membrane are utilized to determine the Release rate of drug from different microemulsion formulations. The cellulose (molecular weight G12 000) membrane is first hydrated in the distilled water solution at 25^0C for 24 hours. The membrane is then clamped between the donor and receptor compartments of the cells Diffusion cell was filled with 25 ml of phosphate buffer (pH = 7.4) and methanol (1:2). The receptor fluid was constantly stirred by externallydriven magnetic bars at 600 rpm throughout the experiment. The Microemulsion (5 g) is accurately weighted and placed in donor compartment. At 0.5, 1, 2, 3, 4, 5, 6, 7, 8 and 24 h time intervals, 2ml sample is removed from receptor for spectrophotometric determination and replaced immediately with an equal volume of fresh receptor solution. Samples are analyzed using UV visible spectrophotometer. The results are plotted as cumulative released drug percent versus time.

STABILITY STUDIES[52]

The physical stability of the microemulsion must be determined under different storage conditions (4, 25 and 40 $^{\circ}C$) during 12 months. Fresh preparations as well as those that have been kept 1under various stress conditions for extended period of time were subjected to droplet size distribution analysis. Effect of surfactant and their concentration on size of droplet is also to bestudied.

FACTOR AFFECTING FORMULATION OF MICROEMULSION SYSTEM PROPERTY OF SURFACTANT[53]

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 the presence of salt or when a high concentration of surfactant is used, degree of dissociation of polar groups becomes lesser and resulting system may be water in oil type.

PROPERTY OF OIL PHASE[54]

Oil phase also influences curvature by its capability to penetrate and swell the tail group region of surfactant monolayer, swelling of tail results in an increased negative curvature to water in oil microemulsion.

PACKING RATIO[55]

Hydrophilic-lipophilic balance of surfactant defines the type of microemulsion by its effect on film curvature and packing. The analysis of film curvature for surfactant associations leading to the formation of microemulsion.

TEMPERATURE[56]

The temperature is very important in defining the effective head group size of non-ionic surfactants. They are hydrophilic and form normal oil in water system at low temperature. They are lipophilic and form water in oil systems at higher temperature. Microemulsion coexists with excess oil and water phases and form bicontineous structure at an intermediate temperature.

APPLICATION OF MICROEMULSION IN VARIOUS DELIVERY OF DRUG

Microemulsions are promising delivery systems which allow controlled or sustained drug release for peroral, percutaneous, transdermal, topical, parenteral and ocular administration. Modulation of the kinetics of the drug release, enhanced absorption of drugs and decreased toxicity are numerous advantages in the delivery practice. The role of microemulsion as a drug delivery system shall be discussed here below:

ORAL DELIVERY[57]

The development of effective oral delivery systems has always been challenging to researchers because drug efficacy can be restricted by poor solubility or instability in the gastrointestinal fluid. Microemulsions have the probable to improve the solubilization of poorly soluble drugs and solve the dissolution related bioavailability problems. Due to the presence of polar, nonpolar and interfacial domains, hydrophilic drugs, including macromolecules can be encapsulated with varying solubility.

PARENTERAL DELIVERY[58]

The formulation of parenteral dosage form of hydrophilic and lipophilic drugs has proven to be difficult. Oil in water microemulsions is advantageous in parenteral delivery of sparingly soluble drugs wherever the administration of suspension is not mandatory. They provide a means of attaining relatively high concentration of these drugs that generally requires repeated administration. Numerous sparingly soluble drugs have been developed into oil in water microemulsion for parenteral delivery.

TOPICAL DELIVERY[59]

Topical administration of drugs can have benefits over other methods for some reasons, one of which is the anticipation of hepatic first-pass metabolism of drug and related toxicity. Additional is the targetability and direct delivery of drug to the affected areas of eyes or skin. They are able to incorporate both hydrophilic and lipophilic drugs and enhance their permeation.

OPHTHALMIC DELIVERY[60]

In conventional ophthalmic dosage forms, water soluble drugs are delivered in aqueous solution while water insoluble drugs are formulated as a suspension or ointments. Low corneal bioavailability and lack of efficacy in posterior section of ocular tissue are some of the severe problem of these systems. For ocular use, microemulsions have emerged as promising dosage form.

NASAL DELIVERY[61]

Recently, microemulsions have been studied as a delivery system to improve uptake of drug by the nasal mucosa. In addition to mucoadhesive polymer helps in extending residence time on the mucosa.

EVALUATION PARAMETERS OF MICROEMULSION BASED SYSTEMS DRUG STABILITY[62]

The 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 analysed for globule size, % transmittance, phase separation and % assay.

PHYSICAL APPEARANCE[63]

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

SCATTERING TECHNIQUES[64]

Scattering techniques like small angle X-ray scattering, small angle neutron scattering and light scattering have found uses in studies of microemulsion structure.

MEASUREMENT OF PH[65]

The pH values of Microemulsions were determined using a digital pH meter standardized using pH 4 and 7 buffers before use.

VISCOSITY MEASUREMENT[66]

The rheological properties play an important role in stability. It can be determined by Brookfield digital Viscometer. Change in the rheological characteristics helps in determining the region of microemulsion and its separation from other region. Bicontineousmicroemulsions are dynamic structures with continuous fluctuations taking place between the bicontineous structure, swollen reverse micelle, and swollen micelles.

ELECTRICAL CONDUCTIVITY[67]

Water phase was added to a mixture of oil, surfactant and co-surfactant. The electrical conductivity can be measured using a conductometer at ambient temperature and at a constant frequency (1 Hz).

GLOBULE SIZE AND ZETA POTENTIAL MEASUREMENTS[68]

They can be measured by dynamic light scattering, using a Zetasizer**.**

DRUG SOLUBILITY[69]

The drug was added in excess to the microemulsion formulation and also each individual ingredient of the formulation. After constant stirring for 24 hrs at room temperature, samples were withdrawn and centrifuged for 10 min at 6000 revolutions per minute. The quantity of soluble drug in the formulation and also each individual ingredient of the formulation were considered by subtracting the drug present in the sediment from the total amount of drug added. The solubility of the drug in formulation was matched with respect to its individual ingredients.

***IN-VITRO* PERMEABILITY STUDY**

The diffusion study can be carried out in a modified Franz diffusion cell, within volume of 20 ml. The receptor compartment was filled with of buffer. Donor compartment was fixed with cellophane membrane, containing the microemulsion and the plain drug solution, distinctly. Samples were withdrawn from receptor compartment at predetermined time and analysed for drug content, by using a UV spectrophotometer at specific wavelength.[70]

RESEARCH WORK ON MICROEMULSIONS

During the last one decade much research work has been carried out on microemulsions for various routes of drug administration.[71] Research work on microemulsions is summarized in **Table 2**:

Table 2: Research work on microemulsions.

S No.	Drug	Route	Benefit
1	Itraconazole	Parenteral	For better absorption
2	Diclofenac	Transdermal	Permeability enhancement
3	Chloramphenicol	Ocular	Increase the solubility
4	Sumatriptan	Intranasal	Enhance the bioavailability
5	Amphotericin	Parenteral	For better absorption
6	Flurbiprofen	Parenteral	Increased the solubility
7	Apormorphine HCL	Transdermal	Increased the permeability
8	Ketoprofen	Transdermal	Enhancement of permeability
9	Prilocainne-HCL	Transdermal	Increased the solubility
10	Estradiol	Transdermal	Improvement in solubilization
11	Aceclofenac	Dermatological	Increased the solubility
12	Piroxicam	Oral	Increased the solubility
13	Diclofenac	Transdermal	Permeability enhancement
14	Dexamethasone	Topical	Ocular Enhanced the Bioavailability
15	Chloramphenicol	Parenteral	Increased the solubility
16	Ibuprofen	Ocular	Increased the solubility
17	Sumatriptan	Intranasal	Enhanced the Bioavailability
18	Ibuprofen	Topical	Increasing the solubility
19	Doxorubicin	-	Increasing the Stability

CONCLUSION

An ideal system should be able to achieve an effectivedrug concentration at the target tissue, while minimizingsystemic exposure. In addition, the system should becomfortable and easy to use An ideal system should be able to achieve an effectivedrug concentration at the target tissue, while minimizingsystemic exposure. In addition, the system should becomfortable and easy to use. In present microemulsions able to control drug release, increase drug solubility, increase the rate ofabsorption, increasebioavailability, reduce patient variability, helps solublize lipophilic drug, MANY routes

liketropical, oral and intravenous can be used to deliver the product, helpful in mask the bitter taste, and increases patientcompliance. It is most attractive drug delivery system and suitable area of research.

REFERENCES

1. Hoar TP and Schulman JH. "Transparent water-in-oil dispersions, the oleopathichydromicelle". *Nature*, 1943; 152: 102-103.
2. Schulman JH., et al. "Mechanism of formation and structure of micro emulsions by electron microscopy". *The Journal of Physical Chemistry*, 1959; 63.10: 1677-1680.
3. Gennaro AR and Remington. "The Science and Practice of Pharmacy". 2001: 313.
4. Lippincott Williams and Wilkins. "Ansel's pharmaceutical dosage forms and drug delivery systems". 2011: 403.
5. J. Barar, M. Asadi, S. A. Mortazavi-Tabatabaei, and Y. Omidi, "Ocular drug delivery, impact of *in vitro* cell culture models," *Journal of Ophthalmic and Vision Research*, 2009; 4(4): 238–252.
6. Attwood D., Microemulsions in Colloidal drug delivery systems (J. Kreuter ed.), Marcel Dekker, New York, 1994.
7. Shinoda K and Lindman B. "Organized surfactant systems microemulsions". *Langmuir*, 1987; 3.2: 135-149.
8. Prince LM. "A theory of aqueous emulsion I: Negative interfacial tension at the oil/water interface". *Journal of Colloid and Interface Science*, 1967; 23.2: 165-173.
9. M. Hornof, E. Toropainen, A. Urtti, Cell culture models of the ocular barriers, Eur. J. Pharm. Biopharm, 2005; 60: 207–225.
10. A.L. Gomes dos Santos, A. Bochot, A. Doyle, N. Tsapis, J. Siepmann, F. Siepmann, J. Schmaler, M. Besnard, F. BeharCohen, E. Fattal, Sustained release of nanosized complexes of polyethylenimine and anti-TGF-beta 2 oligonucleotide improves the outcome of glaucoma surgery, J. Control. Release, 2006; 112: 369–381.
11. L. Pitkänen, M. Ruponen, J. Nieminen, A. Urtti, Vitreous is a barrier in non-viral gene transfer by cationic lipids and polymers, Pharm. Res., 2003; 20: 576–583.
12. Jtirvinena K, Tomi J, Urttia SA. Ocular absorption following topical delivery. *Adv Drug Deliv Rev*, 1995; 16: 3-19.
13. Nanjawade BK, Manvi FV, Manjappa AS. In situ-forming hydrogels for sustained ophthalmic drug delivery. *J Control Release*, 2007; 122: 119–34.
14. Meqi SA, Deshpande SG. Ocular drug delivery: Controlled and novel drug delivery. New delhi:CBS Publishers, 2002; 82-84.
15. Eva M, Amo D, Urtti A. Current and future ophthalmic drug delivery systems. A shift to the posterior segment. *Drug Discov Today*, 2004; 13: 2004, 135-143.
16. Blondeau JM. Fluoroquinolones: Mechanism of Action, Classification, and Development of Resistance. *Surv Ophthalmol*., 2004; 49: S73-S78.
17. Martinez M¸ McDermott P, Walker R. Pharmacology of the fluoroquinolones: A perspective for the use in domestic animals. *The Veterinary Journal*, 2006; 172: 10– 28.
18. Gupta P, Vermani K and Garg S. Hydrogels: from controlled release to pHresponsive drug delivery. *Drug Discov Today*, 2002; 7: 569-79.
19. Desai PN. Synthesis and characterization of polyionic hydrogels, Bachelors of Homoeopathic Medicine and Surgery, LMF's Homoeopathic Medical College, India, 2005.
20. He C, Kim SW, Lee DS. In situ gelling stimuli-sensitive block copolymer hydrogels for drug delivery. *J Control Release*, 2008; 127: 189–207.
21. Lawrence MJ, Rees GD. Microemulsion-based media as noveldrug delivery systems. Advanced Drug Delivery Reviews, 2000; 45(1): 89-121.
22. Tenjarla S. Microemulsions: An Overview and Pharmaceutical Applications. Crit Rev Ther Drug Carrier Syst, 1999; 16(5): 62.
23. Lawrence M. Surfactant systems: Microemulsions and vesicles asvehicles for drug delivery. European Journal of Drug Metabolism and Pharmacokinetics, 1994; 19(3): 257-269.
24. Remington JP, Beringer P.20, Remington: the science and practice of pharmacy, Philadelphia, Lippincott Williams & Wilkins, 2006; 280-292.
25. Lv FF., et al. "Phase behaviour of the microemulsions and stability of the chloramphenicol in microemulsions based ocular drug delivery system". International Journal of Pharmaceutics, 2005; 14.1-2: 237-246.
26. Vyas TK., et al. "Preliminary brain targeting studies on intranasal mucoadhesivemicroemulsions of Sumatriptan". AAPS Pharmaceutical Science Technology, 2006; 7.1: E49-E57.
27. Pradnya S., et al. "Formulation and evaluation of Microemulsions based delivery system for amphotericin". AAPS Pharmaceutical Science Technology, 2008; 9: 122-128.
28. Peltola S., Saarinen SP., Kiesavaara J and Urttia STM., Microemulsions for topical delivery of estradiol. Int. J.Pharm., 2003; 254: 99-107.
29. Yang JH., Kim YI and Kim KM., Preparation andevaluation of aceclofenacmicroemulsions for transdermaldelivery system, Arch. Pharm. Res., 2002; 25: 534-540.
30. Andrade SM and Costa SM., Fluorescence quenching ofacridine orange in microemulsions induced by the nonsteroidalanti inflammatory drug piroxicam, Photochem. Photobiol. Sci., 2003; 2: 605-610.
31. Kweon JH., Chi SC and Park ES., Transdermal delivery ofdiclofenac using microemulsions. Arch. Pharm. Res., 2004; 27: 351-356.
32. Fialho SL and Cunha DS., New vehicle based on amicroemulsion for topical ocular administration

ofdexamethasone, Clin. Experiment Ophthalmol, 2004; 32: 626-632.
33. Lv FF., Zheng LQ and Tung CH., Phase behavior of themicroemulsions and stability of the chloramphenicol inmicroemulsion based ocular drug delivery system, Int. J.Pharm., 2005; 14: 237-246.
34. Zhao X., Chen D., Gao P., Ding P and Li K., Synthesis ofibuprofeneugenol ester and its microemulsion formulation for parental delivery, Chem. Pharm. Bull., 2005; 53: 1246-1250.
35. Vyas TK., Babbar AK., Sharma RK., Singh S and MisraA., Preliminary brain targeting studies on intranasalmucoadhesivemicroemulsions of sumatriptan, AAPSPharm. Sci. Tech., 2006; 20: E8.
36. Chen H., Chang X., Du D., Li J., Xu H and Yang X.Microemulsion based hydrogel formulation of ibuprofen for topical delivery, Int. J. Pharm., 2006; 315: 52-58.
37. Formariz TP., Sarmento VH., Silva JAA., Scarpa MV., Santilli CV and Oliveira AG., 2006, Doxorubicinbiocompatible o/w emulsion stabilized by mixed surfactantcontaining soya phosphotidyl choline, Colloids Surf. B.Biointerfaces, 2006; 51: 54-61.
38. Rhee Y.S., Park CW., Nam TY., Shin YS., Chi SC and Park ES., Formulation of parental microemulsioncontainingitraconazole, Arch Pharm. Res., 2007; 30: 114-123.
39. Ali Y, Lehmussaari K. Industrialperspective in ocular drug delivery. Advanced Drug Delivery Reviews, 2006; 58(11): 1258-1268.
40. Jiao J. Polyoxyethylatednonionicsurfactants and their applications intopical ocular drug delivery. Advanced Drug Delivery Reviews, 2008; 60(15): 1663-1673.
41. Taha MO, Al-Ghazawi M, Abu-AmaraH, Khalil E. Development of quantitative structure-propertyrelationship models for pseudoternarymicroemulsions formulated withnonionicsurfactants andcosurfactants: application of datamining and molecular modeling. European Journal of Pharmaceutical Sciences, 2002; 15(5): 461-478.
42. Sznitowska M, Janicki S, DabrowskaE, Zurowska-PryczkowskaK.Submicron emulsions as drug carriers: Studies on destabilization potential ofvarious drugs. European Journal of Pharmaceutical Sciences, 2001; 12(3): 175-179.
43. Michael G. Recent developments inthe characterisation of microemulsions. Current Opinion in Colloid & amp; Interface Science, 2008; 13(4): 263-269.
44. Aboofazeli R, Barlow D, Lawrence M.Particle size analysis of concentratedphospholipidmicroemulsions: I. Totalintensity light scattering. The AAPS Journal, 2000; 2(2): 27-39.
45. Hasse A, Keipert S. Development andcharacterization of microemulsionsforocular application. European Journal of Pharmaceutics and Biopharmaceutics, 1997; 43(2): 179-183.
46. Peira E. and Transdermal permeation ofapomorphine through hairless mouse skin frommicroemulsions. International Journal of Pharmaceutics, 2001; 226: 47-51.
47. Rhee Y S. et al. Transdermal delivery ofketoprofen using Microemulsions. International Journal of Pharmaceutics, 2001; 226: 161-170.1994; p495.
48. Tomsic M., et al. "Water-Tween 40®/Imwitor 308®-isopropyl myristatemicroemulsions as delivery systems for ketoprofen: Smallangle Xray scattering study". International Journal of Pharmaceutics, 2006; 327.1-2: 170-177.
49. Martin A. "Coarse Dispersions In: Physical Pharmacy". New Delhi, 1994: 495.
50. Giustini M. "Microstructure and dynamics of the water-in-oil CTAB/n-pentanol/nhexane/ water microemulsion: spectroscopicand conductivity study". Journal Physical Chemistry, 1996; 100: 3190-3198.
51. Rhee YS., et al. "Formulation of parental microemulsions containing Itraconazole". Archives of Pharmaceutical Research, 2007; 30: 114-123.
52. Ashok Patel and Pradeepvavia R. Preparationand In-vivo Evaluation of Self-Microemulsifying Drug Delivery System Containing fenofibrate. The AAPS Journal, 2007; 226: 344-352.
53. Peltola S. et al. Microemulsions for topicaldelivery of estradiol. International Journal of Pharmaceutics, 2003; 254: 99-107.
54. Constantinides PP. et al. Formulation andintestinal absorption enhancement evaluation of water-in-oil microemulsionsincorporatingmedium-chain glycerides. Pharmaceutical Research, 1994; 11: 1385–90.
55. Constantinides PP. et al. Water-in-oilmicroemulsions containing medium-chain fattyacids/salts: formulation and intestinalabsorption enhancement evaluation. Pharmaceutical Research, 1996; 13(2): 205–105.
56. 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.
57. oil-waterlecithin-based microemulsions: formulation and toxicity evaluation. Journal Pharmaceutical Sciences, 2002; 91(4): 1178–85.
58. 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.
59. Shaikh I M. et al. Topical delivery ofaceclofenac from lecithin organogels:preformulation study. Current Drug Delivery, 2006; 3(4): 1727.
60. Tomsic M. et al. Water–Tween 40®/Imwitor308®–isopropyl myristatemicroemulsionsasdelivery systems for ketoprofen: Smallangle Xrayscattering study. International Journal of Pharmaceutics, 2006; 327: 170– 177.

61. Martin A. Coarse Dispersions In: Physical Pharmacy. Fourth Edition. B.I. Waverly Pvt.Ltd. New Delhi.
62. Kweon JH., et al. "Transdermal delivery of diclofenac using microemulsions". Archives of Pharmacal Research, 2004; 27.3: 351-356.
63. Li CC., Abrahamson M., Kapoor Y and Chauhan A., Timolol transport from microemulsions trapped in HEMAgels, J. Colloid Interface Sci., 2007; 315: 297-306.
64. Baboota S., AL-Azaki A., Kohli K., Ali J., Dixit N and Shakeel F., Development and evaluation of a microemulsion formulation for transdermal delivery of terbinafine, PDA J.Pharm. Sci. Technol, 2007; 61: 276-285.
65. Kunieda H., et al. "Two types of surfactant phases and four coexisting liquid phases in a water/nonionic surfactant/triglyceride/ hydrocarbon system". *The Journal of Physical Chemistry*, 1988; 92.1: 185-189.
66. Mukherjee K., *et al*. "Thermodynamics of Microemulsion Formation". *Journal of Colloid and Interface Science*, 1997; 187.2: 327-333.
67. Aboofazeli R and Lawrence MJ. "Investigations into the formation and characterization of phospholipid microemulsions. I. Pseudoternary phase diagrams of systems containing water- lecithin-alcohol-isopropyl myristate". *International Journal of Pharmaceutics*, 1993; 93.1-3: 161-175.
68. Jha SK., *et al*. "Microemulsions-Potential Carrier for Improved Drug Delivery". *Internationale Pharmaceutica Sciencia*, 2011; 1.1: 25-31.
69. Talegaonkar S., *et al*. "Microemulsions: A Novel approach to enhanced drug delivery". *Recent patents on drug delivery and formulation*, 2008; 2.3: 238-257.
70. Bagwe RP., *et al*. "Improved drug delivery using Microemulsions: Rationale, recent progress and new horizons". *Critical reviews in therapeutic drug carrier systems*, 2001; 18.1: 77-140.