A Project on

"Overview of Microemulsions: Novel Approach in Novel Drug Delivery Systems and comparative study with Nanoemulsions and Macroemulsions"

By

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Submitted to,

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In partial fulfillment of the requirements for the award of degree

of B Pharmacy

Under the Guidance of

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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. Lipid dosage forms are attractive delivery systems for hydrophobic drug molecules. Emulsion is one of the popular system since many decades. Pharmaceutical applications of emulsions widened especially after micro and nano-emulsion emergence aspects like definition, theories, types, methods of preparations, advantages, disadvantages and methods of analysis of microemulsion and comparision with macroemulsion and nanoemulsion.

Key words: Microemulsions, thermodynamically stable, amphiphile, solubilization, Macroemulsion, Nanoemulsion

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].

Emulsions are dispersions made up of two immiscible liquid phases which are mixed using mechanical shear and surfactant. Particle size of this conventional emulsion grows continuously with time and hence finally separation occurs at gravitational force thus these emulsions are thermodynamically unstable.

Surface tension theory- this theory assumes that, when surface tension between two phases lessens then emulsion can be formed.

Repulsion theory- this theory explains a phenomenon by which emul- sifying agent forms a film containing globules on one of the immiscible phases with ability to repel each other. Thus immiscible globules remain suspended in the dispersion medium due to these repulsive forces.

Viscosity modification- according to this theory emulsifying agents raises viscosity of the medium and thus miscible viscous suspension of globules is formed.

Advantages of Microemulsion system [6-11]

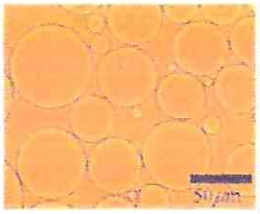
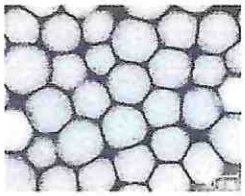
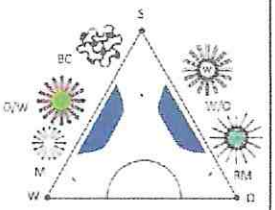
1. Microemulsions are easily prepared and require no energy contribution during preparation this is due to better thermodynamic stability.
2. The formation of microemulsion is reversible. They may become unstable at low or high temperature but when the temperature returns to the stability range, the microemulsion reforms.
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, NANOEMULSION 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 individualentities.	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.

	macroemulsions	nanoemulsions	microemulsions
			
size	1-100 µm	20-500 nm	10-100 nm
shape	spherical	spherical	spherical, lamellar
stability	thermodynamically unstable, weakly kinetically stable	thermodynamically unstable, kinetically stable	thermodynamically stable
method of preparation	high & low energy methods	high & low energy methods	low energy method
polydispersity	often high (>40%)	typically low (<10-20%)	typically low (<10%)

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. Bi continuous microemulsion or winsor III
4. Single phase homogeneous mixture or winsor IV

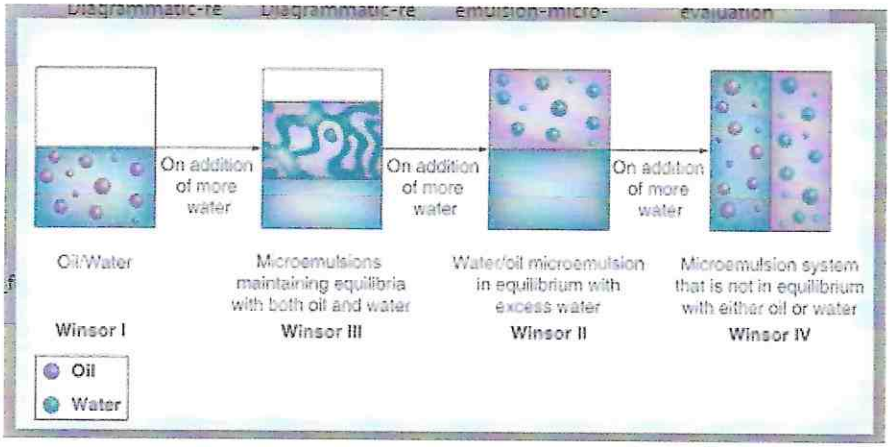


Fig.1: TYPES OF MICROEMULSIONS

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.

Bi continuous smicroemulsion or winsor III

In bi continuous microemulsion 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.

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

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 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 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 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.

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,

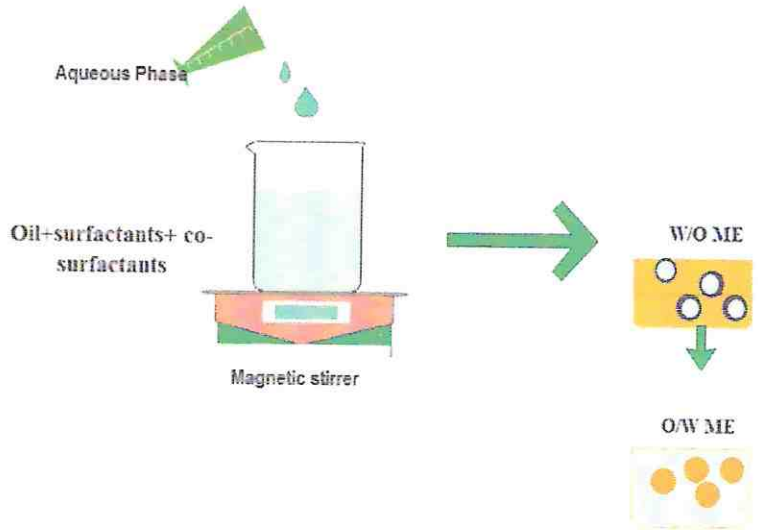


Fig.2: Phase Inversion Method

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.

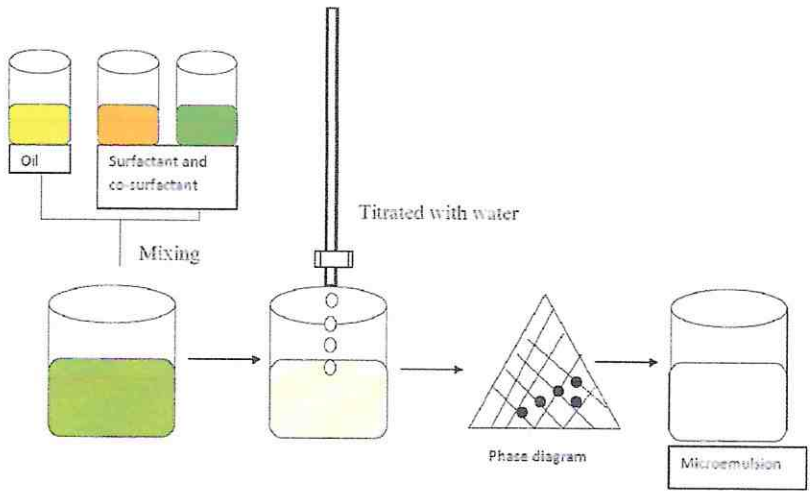


Fig.3: Phase Titration Method

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 OFMICROEMULSION [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

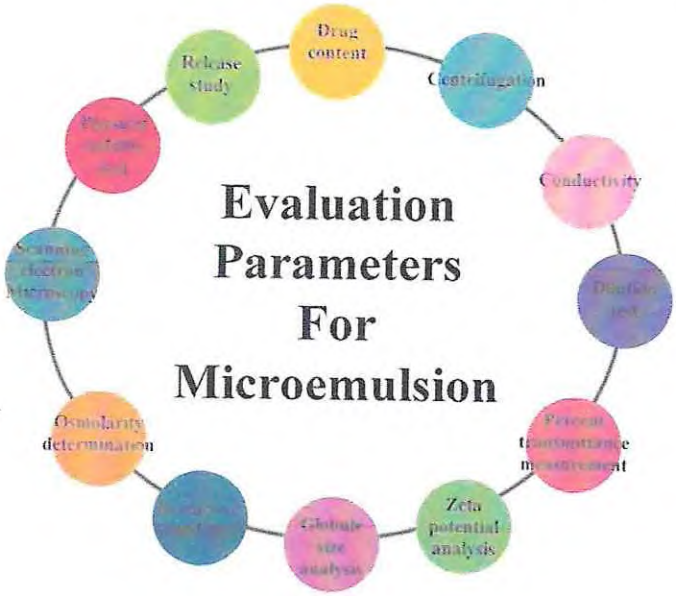


Fig.4: Evaluation of Microemulsion

Physical appearance

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

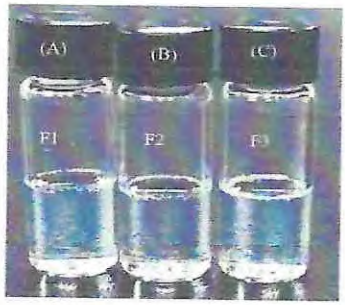


Fig.5: Physical appearance

Procedure: Optical transparency of the formulation was determined by inspecting the sample in clear and transparent container under the presence of good light against reflection into the eyes, and viewed against black and white illuminated.

Determination of pH

Procedure: pH is measured using a pH meter of a glass electrode. pH fundamentally represents the value of hydrogen ion activity in solutions. It is defined by the equation given below. This value well accords with the logarithm of the reciprocal of hydrogen ion concentration in dilute solutions. The pH was measured in microemulsion formulations using a ELICO LI120 pH meter that was calibrated before formulation use with buffered solutions at pH 4 and pH 9.2.

Background.Scattering Techniques [36]

Method: 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.

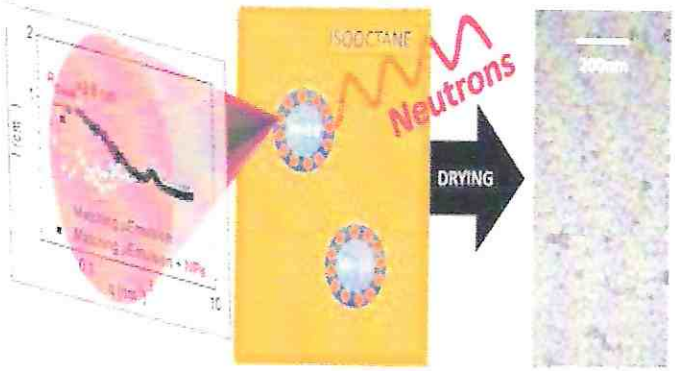


Fig.6: Scattering Techniques

Limpidity Test (Percent Transmittance) [37]

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

Fig.7: spectrophotometer.

Drug stability [38]

Procedure: 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.

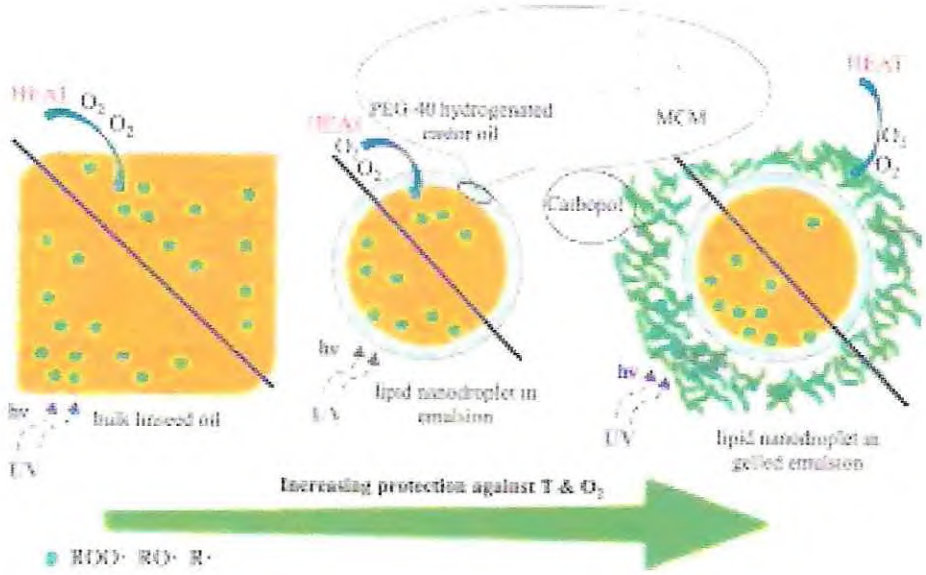


Fig.8: Drug stability oxidative study

Globule size and zeta potential measurements [39]

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

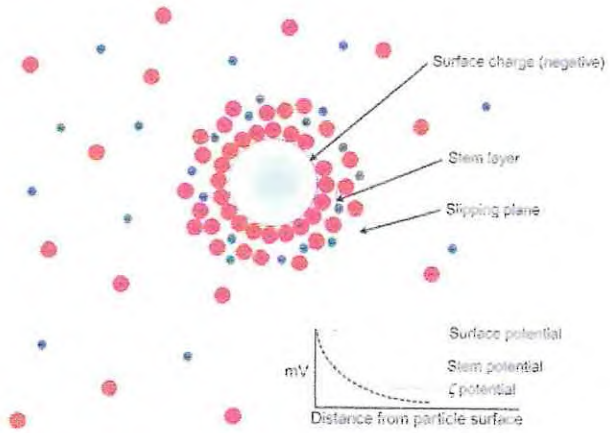


Fig.9: Globule size and zeta potential

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

Procedure: The rheological properties play an important role in stability. It can be determined by Brookfield digital viscometer. Change in the rheological characteristics

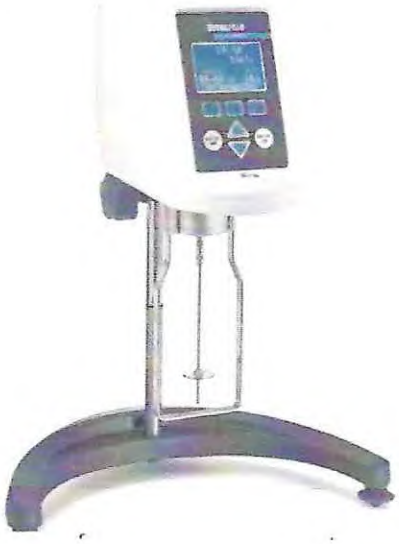


Fig.10: Brookfield digital viscometer

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.

- Check to confirm that the viscometer has been calibrated. If not, calibrate using software.
- The sample container and quantity should be approximately the same as for the Calibration Standard. Equilibrate the temperature of the sample to the temperature designated in the specification (±1°C).
- Confirm that the viscometer is level using the bubble level on the back of the instrument. For the Brookfield LV-II, the instrument with spindle attached and the speed set as designated in the product specification. The main display will flash 00.0 after 10 seconds.
- Immerse the spindle designated in the product specification into the sample to the groove on the spindle shaft. Do not allow air bubbles to be formed. Attach the spindle to the viscometer.
- The spindle should not touch the bottom or sides of the container and should be centered. Reconfirm that the viscometer in level.
- The spindle no: 64 were rotated at a speed of 60 rpm. Samples of microemulsions were allowed to settle over 30 min at room temperature before the measurements were taken.
- For the LV-II, choose the units by pressing the desired unit key (CPS for centipoises).
- Set the speed as designated in the product specification, start the viscometer and read at constant reading. For manual models, use the conversion chart to convert the dial readings to centipoises.
- When done, turn motor and power off. Clean spindle and place in spindle holder.

Electrical conductivity [41]

Procedure: 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.

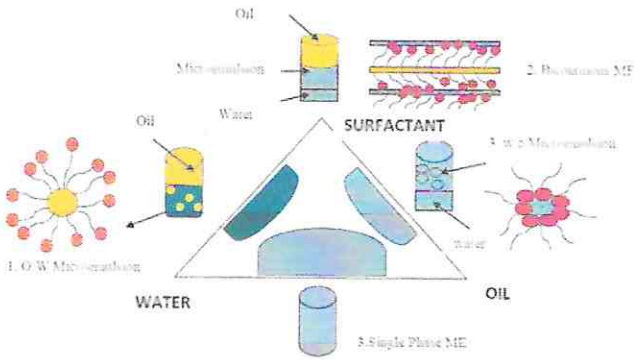


Fig.11: Conductivity method

Drug solubility [42]

Procedure: 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.

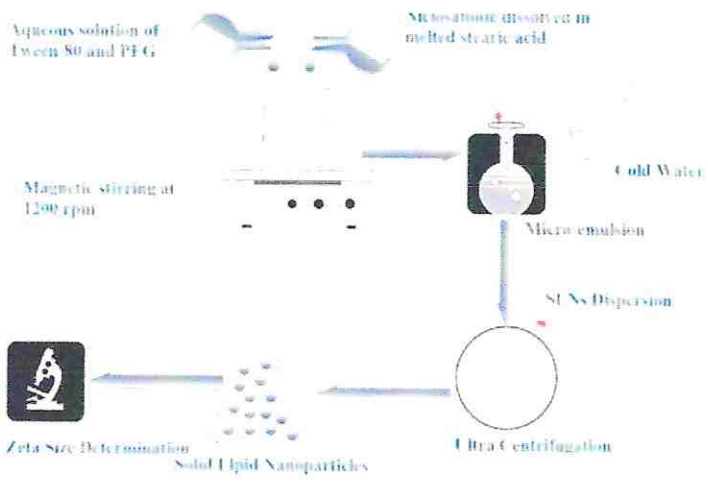


Fig.12: Drug Solubility

In-vitro drug release [43, 44]

Procedure: 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.

Fig.13: Franz diffusion cell

APPLICATION OF MICROEMULSION SYSTEM

Microemulsion in Pharmaceutical

From last two decades there has been a revolution in the 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.
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.

- ***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

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

Microemulsions are widely used in the field of analytical techniques such as chromatography etc. 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 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.

Marketed Microemulsion Products


Microemulsion Fungicidal
Wall Flush Solution

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