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Review Article

Microemulsion: A Verasatile Platform for Drug Delivery

Vyshnavi R. Nath*, Dr. Biji P. A., Hendrieta Mary Bivera

Department Of Pharmaceutics, St. Joseph's College of Pharmacy Cherthala, Alappuzha, 688524.

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ABSTRACT

Microemulsions are thermodynamically stable, optically isotropic colloidal dispersions of oil, water, surfactant, and cosurfactant with droplet sizes typically ranging from 5-100nm. They have emerged as versatile platforms for drug delivery due to their unique ability to solubilize both hydrophilic and lipophilic drugs, enhance bioavailability, and provide controlled release profiles. Their spontaneous formation, low viscosity, and large interfacial area facilitate rapid drug release and absorption, making them suitable for multiple administration routes including oral, parenteral, topical, ocular, and pulmonary. Theories such as interfacial film theory, solubilization theory, and thermodynamic theory explain their formation and stability. Various formulation components, including oil phase, surfactants, cosurfactants and cosolvents are selected based on drug solubility, safety and desired release characteristics. Characterization techniques like droplet size analysis, zeta potential, viscosity, conductivity, and refractive index evaluation ensure optimized formulation performance. Microemulsions have demonstrates significant potential in improving the therapeutic efficacy of poorly water-soluble drugs, reducing required dosages, and minimizing side effects. They are also explored in pharmaceuticals, biotechnology, cosmetics, agrochemicals, and enhanced oil recovery. Despite these advantages, limitations include high surfactants or cosurfactants requirements, sensitivity to environmental conditions and toxicity concerns for certain excipients. With the growing demand for more efficient drug delivery systems, microemulsions represent a promising bridge between formulation science and clinical application.

INTRODUCTION

Emulsions are heterogenous system comprising of one immiscible liquid, dispersed as droplets across another liquid. These unstable system in thermodynamics is kinetically stabilized by adding an additional ingredient or a combination of ingredients with emulsifying qualities. Double emulsion, multiple emulsion or emulsified emulsion are terms used to describe one emulsion

***Corresponding Author:** Vyshnavi R. Nath
Address: *Department Of Pharmaceutics, St. Joseph's College of Pharmacy Cherthala, Alappuzha, 688524.*
Email ✉: vyshnavirnath8822@gmail.com

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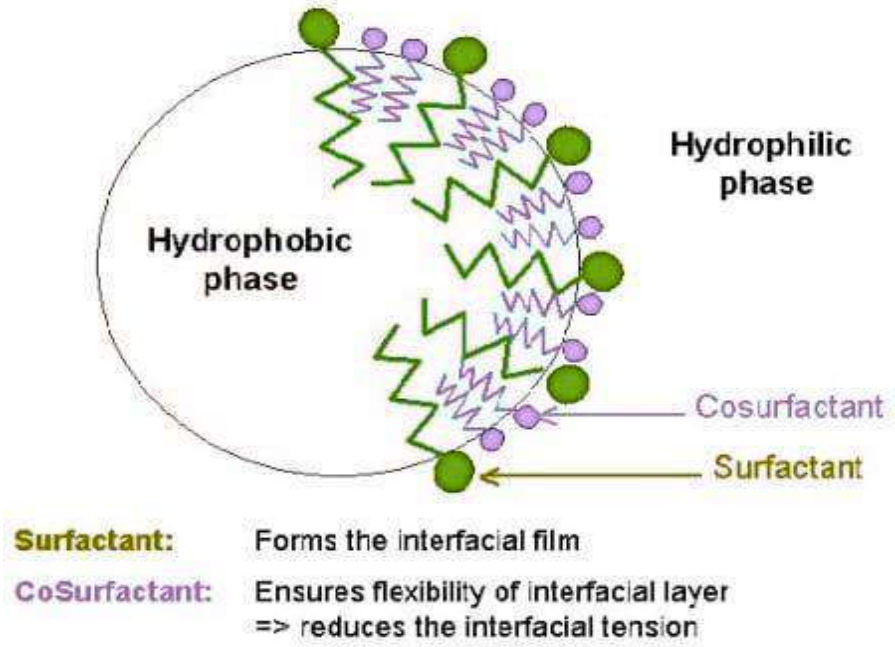
that is further disseminated in to another continuous phase.[1]

Emulsions are of two types based on the dispersed phase: oil I n water (O/W) where oil is the dispersed phase and water is the continuous phase; another one is water in oil (W/O) where water is the dispersed phase and oil is the continuous phase.

On the basis of size of dispersed phase emulsion is again divided into three distinct categories: macroemulsion, nanoemulsion and microemulsion with droplet size ranging from 1.5-100µm, 50-500nm and 3-50nm.[2] Microemulsions are sophisticated drug delivery systems that have drawn a lot of interest in the field of pharmaceutical sciences because of their special physicochemical characteristics and capacity to improve oral drug absorption. When Hoar and Schulman titrated a milky emulsion with hexanol in the 1940s, they produced a clear, single-phase solution that give rise to the idea of microemulsion. They made a stable, clear mixture by mixing oil with a water-based surfactant solution and adding alcohol, which was the first microemulsion ever created. The term "microemulsion" has since been used to refer to a transparent, thermodynamically stable, and optically isotropic system made up of water, oil, and surfactants and cosurfactants that form droplets with a typical size of 5 to 100 nanometers.[3] IUPAC defines microemulsion as dispersion made of water, oil and surfactant(s) that is an isotropic and thermodynamically stable system with dispersed domain diameter varying approximately from 1 to 100nm, usually 10 to 50 nm. The stability and small droplet size of microemulsion result in high surface area, which enhances drug solubilization and absorption, especially for lipophilic or poorly water-soluble drugs. In contrast to conventional microemulsions, microemulsions form spontaneously upon gentle mixing of their components and require no high-energy input. Different structural forms, such as oil-in-water (o/w), water in oil (w/o), or bicontinous systems, depend on the composition and the relative proportions of oil, water, surfactants, and cosurfactants. [4] Emulsion comprises of three components oil, surfactant and water, while in microemulsion apart from these a fourth component is present that is cosurfactants consist of linear alcohols of medium chain length that is miscible with water. Both surfactants and cosurfactants combinedly induce the development of extensive interfaces through the spontaneous dispersion of oil in water, or vice-versa. [1]

Structure of Microemulsions [5]



Microemulsions are dynamic systems with interfaces that fluctuate naturally and continuously. They are generally classified into three types: water-in-oil (w/o), oil-in-water (o/w), and bicontinuous microemulsions. In the o/w type, water droplets are dispersed in the continuous aqueous phase, while in the w/o type, water droplets are dispersed in a continuous oil phase. Bicontinuous microemulsions occur when the amount of water and oil in the system are same. [6]

Theories of Microemulsion [7,8]

Interfacial Theory

Also known as the mixed film or dual film theory, it states that the surfactant and the cosurfactant together form a complex film at the oil water interface, leading to the formation of microemulsion droplets.[7]

Solubilization Theory

This theory suggests that microemulsions are essentially swollen micellar systems. Oil is solubilized through normal micelle formation, while water is solubilized via reverse micelle formation.[8]

Thermodynamic Theory

The formation and stability of a microemulsions can be explained using a simplified thermodynamic approach. The free energy of formation depends on how much the surfactant reduces the surface tension at the oil-water interface and the change in system entropy:

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

Where:

ΔG_f = free energy of formation
γ = surface tension at the oil water interface
ΔA= change in interfacial area during microemulsion
T= temperature
ΔS=change in entropy

During the formation of microemulsion, ΔA increases greatly because many tiny droplets are developed. Although γ is always positive, it is small and outweighed by the entropy term. The largest entropy contributions come from the

mixing of two phases into numerous small droplets.[8]

Types of Microemulsions [6,9]

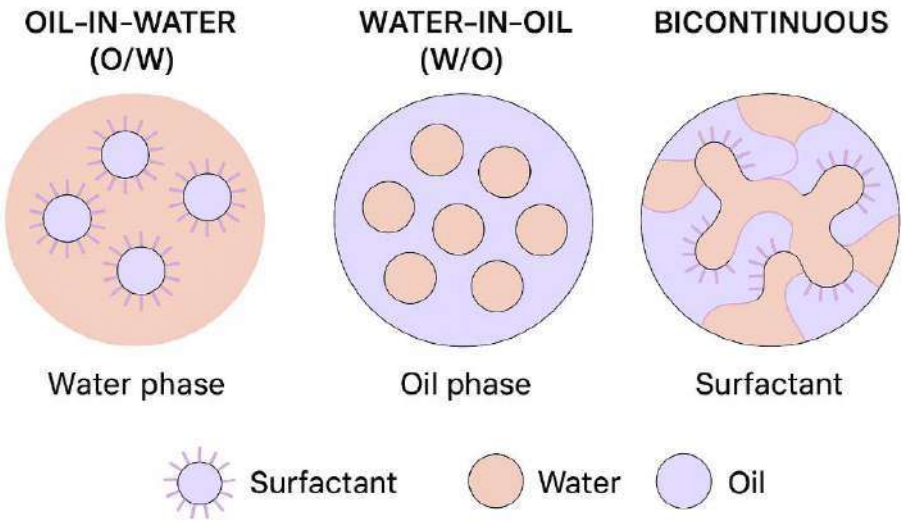
Three distinct categories of microemulsion arise by categorizing the system based on whether the domains are continuous or in droplets:

Oil-in water microemulsion

Oil in water microemulsion consist of droplets of oil dispersed in the continuous aqueous phase where the oil droplets are surrounded by a surfactant and a cosurfactant. The surfactant monolayer builds a interfacial film that exhibits a positive curve indicating that the lipophilic tails face into the oil droplets and the polar head group face the continuous phase. These microemulsion generally contains a larger interaction volume than the w/o microemulsion.

Water in oil microemulsion

Water in oil microemulsion consist of droplets of water dispersed in the continuous oil phase. These are commonly referred as reverse micelles where the polar headgroups of the surfactant are facing into the water droplets, with the fatty acid tails into the oil phase. when these microemulsion are administered orally or parenterally they may be destabilized by the aqueous biological system by increasing the phase volume of the internal phase, which ultimately results in a percolation phenomenon where phase separation or phase inversion occurs.



Bicontinuous microemulsion

Bicontinuous microemulsion in which water and oil microdomains are inter-dispersed throughout the system. Both water and oil exist in this instance as a continuous phase. An irregular tangle of oil and water channels occurs, which seems to be appear as a sponge-phase. These microemulsion are particularly beneficial for intravenous administration or for topical delivery of drugs, because they may show characteristics such as non-Newtonian flow and plasticity and upon dilution with aqueous biological fluids, form an o/w microemulsion.

Components of Microemulsion

Microemulsion is a system which contains oil, surfactant, cosurfactant and water as the major elements. A large abundant quantity of oils and

surfactants can be used for the development of microemulsion, but due to their toxicity, irritation potential and unclear mechanism of action their uses are limited. The materials used in the formulation of emulsion should be biocompatible, nonhazardous and clinically acceptable. With an emphasis on safety, every component used in the formulation of a microemulsion must be recognized as generally regarded as safe (GRAS). [1,8]

Oil Phase

Oil phase is one of the most important excipients in the formulation of microemulsion. Oil phase significantly solubilizes lipophilic drug molecules and enhances absorption through the body's lipid layer. Unique ability of the oil to penetrate the cell walls, makes it very useful for lipophilic active drug delivery. Due to the penetration capacity of the oil phase, it alters the curvature, causing the surfactant's tail group area to swell. Short chain oils have more ability to get through the surfactant's tail group compared to long chain oils. [1,8] The rationale for the selection of desired oil depends on the solubility of drug in the oil.

Surfactants

Surfactants facilitate dispersion, generates the proper curvature at the interfacial, and reduces interfacial tension to a very low value during the microemulsion formulation. Low HLB value surfactants (HLB<10) are appropriate for water in oil (w/o) microemulsions, whereas high HLB value surfactants (HLB>10) are appropriate for oil in water (o/w) microemulsions. Surfactants are mainly used to stabilize the system. These are molecules containing a polar head group and a polar tail. Because of numerous intramolecular and intermolecular forces together with entropy consideration, causes the surfactant molecules to self-associate. [1,5]

The several kinds of surfactants that support the microemulsion system's ongoing development are:

Cationic surfactants

Cationic surfactants, which are often of halogen type, turns into amphiphilic cations and anion forms when comes in contact with water. Most well-known examples of these surfactants are Hexadecyltrimethyl-ammonium bromide (CTAB) and Didodcecylammonium bromide (DDAB). At the time of synthesis of these surfactants, high pressure hydrogenation reaction are executed which results these surfactants to be more expensive than anionics.[5,6]

Anionic Surfactants

Anionic surfactants are the most frequently used surfactants. An amphiphilic anion and a cation typically an alkaline metal (Na, K) or quaternary ammonium compound are generated upon dissociation of anionic surfactant into the water. The ionized carboxyl group in these surfactants is what gives them their anionic charge. Soaps a different term for Alkali alkanoates are most often used anionic surfactants. Approximately half of the global production is made up of these surfactants. In accordance of their shape and function, this is the most well known surfactants. The carboxylate, sulfonate and sulphate groups are the three most major anionic groups found in all of these surfactants. [5,6]

Non-Ionic Surfactants

Non-ionic surfactants accounts for roughly 45% of entire industrial production. Since their hydrophilic group is of a non-dissociable kind, like that of alcohol, phenol, ether, ester, or amide, these surfactants do not ionize in aqueous solution. Dipole and the hydrogen bond interaction with the water hydration layer on the hydrophilic surface of

a non-ionic surfactant stabilizes it. The presence of a polyethylene glycol chain renders a significant portion of these non-ionic surfactants hydrophilic. [5,6]

Zwitterionic Surfactants

Zwitterionic surfactants consists of both positively and negatively charged groups, which when blended with cosurfactants an microemulsion is produced. Lecithin along with other phospholipid that are naturally found in soybeans and eggs are the examples under this surfactant. Lecithin, which has diacyl phosphatidylcholine as it primary constituent, demonstrates remarkable biocompatibility in contrast to other ionic surfactants, which can be rather hazardous. Another significant class of zwitterionic surfactants are alkylbetaines, amidoalkylbetaines and heterocyclic betaines. [5,6]

Cosurfactants

For the microemulsion production, majority of times surfactants by themselves are incapable of achieving lower interfacial tension. So, for this cosurfactants are crucial because they offer a great deal of flexibility in commencing the different curvatures required to create a microemulsion. These cosurfactants generally increase the microemulsion region and decrease the interfacial tension. Due to the presence of fluidizing groups such as unsaturated bonds, cosurfactants increase the fluidity of the interface. They subsequently breakdown the liquid crystalline or gel structure and change the HLB value in a way that causes microemulsions to develop spontaneously. Cosurfactants also aids in further lowering of the surface tension and fluidizing the surfactant film, which raises the entropy of the system and results in thermodynamic stability. [1,6,8]

Aqueous phase

Preservatives and active substances that are hydrophilic may be present in the aqueous phase. Some researchers utilize buffer solutions as an aqueous phase. [7]

Cosolvents

Cosolvents especially plays a critical role in microemulsion systems, particularly for oral drug delivery. These organic solvents enhance the solubility of both hydrophilic surfactants and lipid-soluble drugs, enabling the use of high surfactant concentrations necessary for stable microemulsion formulation. Apart from their ability to dissolve, cosolvents can also act fuction as cosurfactants, contributing to the interfacial film's flexibility and promoting the development of microemulsion by disrupting the rigid liquid crystalline or gel phases. Their dual functionality makes them essential components in the development of effective and stable microemulsion based drug delivery system.[5,7,8]

Solubility Analysis for Microemulsion Preparation

Around 10 grams of oil were precisely weighed in a glass beaker to these, 100 milligrams of drug was added. The drug was then dissolved by stirring on a magnetic stirrer at a moderate speed, adding another 10 milligrams of drug and continuedly stirring until saturated solution was obtained. Finally the total amount of drug consumed was measured using a UV spectrophotometer at specified nm and in similar way the solubility of drug was examined in various surfactants and cosurfactants.[10]

Ternary Diagram

Pseudo ternary phase is not a new concept. Mostly using this technique microemulsion region were mapped. The ideal composition range for three important excipients (oil, surfactant and

cosurfactant) is mapped using a pseudo ternary phase diagram based on the resulting droplet size, stability after dilution, viscosity and self-emulsification.[11]

Construction of Ternary Phase Diagrams

To outline the microemulsion region and for determining the best mix of excipients (oil, surfactant and cosurfactant) for the formulation of microemulsion, pseudo ternary diagrams were established. The aqueous titration method was used to create pseudo ternary phase diagrams consisting of oil, smix and water. A certain ratio of smix and oil was placed in a vail and vortexed for five minutes. To this water was added using micropipette or burette were used. And this process was repeated until turbidity was produced until addition of one drop. Then they were visually examined for flowability and phase clarity. Aqueous phase volume was recorded. Phase diagram can be constructed using various software such as sigma plot application software, Chemex school software, ternaryplot.com. Apart from water titration, cosurfactant titration can be employed.[7,12]

Preparation of Microemulsion

Phase Titration Method

The spontaneous emulsification method also known as the phase titration method results in microemulsions, which can be explained with the support of a phase diagram. In order to comprehend the complexity of interactions between various components that arise from mixing, it is highly suggested to construct a phase diagram for this purpose. Microemulsion was developed by dispersing a sufficient quantity of drug in a appropriate amount of oil, which is necessary for the solubilization of the drug. The mixture was homogenized, and precisely weighed quantities of surfactants: cosurfactants blends were added in small portions while being stirred. The blends were thoroughly mixed using a magnetic stirrer, and dropwise double distilled water was added to it with continuous stirring for approximately 10 minutes, with the rate of stirring being adjusted to meet particle size requirements.[1,8]

Phase Inversion Method

When too much of dispersed phase is added or when the temperature changes, phase inversion occurs. During this process, particle size changes a lot and these changes affect drug release both *in-vitro* and *in-vivo.* Phase inversion works by changing the spontaneous curvature of surfactants. For non-ionic surfactants, temperature changes can alter their curvature. At low temperatures, the system usually forms an oil in water (o/w) microemulsion. When the temperature increases, it can change to a water in oil (w/o) microemulsions. As the system cools down, it passes through a point where the surfactant has no curvature and the surface tension is very low. At this point, very small oil droplets can form easily. This method is called the phase inversion temperature (PIT) method. Not only temperature, but also other factors like pH or salt concentration can cause phase inversion.[5]

Factors Influencing Microemulsion Formation and Phase Behavior [5,6,7]

1. **Factors affecting formation of microemulsion system**

- **Packing ratio**

For determining the type of microemulsion formed, the hydrophilic-lipophilic balance (HLB) of a surfactants plays a crucial role by influencing molecular packing and interfacial film curvature.

This association is explained through the Critical Packing Parameter (CPP), that is defined as
Critical Packing Parameter (CPP) = v/(a*l)

Where,

v = partial molar volume of the hydrophobic tail
a = optimal head group area
l = length of surfactant tail
According to studies by Israelachvili et al. (1976) and Mitchell and Ninham (1977),

When,

- CPP is between 0 and 1, the interface curves towards water (positive curvature), favoring oil in water (o/w) microemulsions.
- If CPP exceeds 1, the interface curves towards oil (negative curvature), leading to water in oil (w/o) systems.
- At CPP~1, corresponding to balanced HLB and zero curvature, bicontinuous or lamellar phases may form, depending on the rigidity of the surfactant film.

➢ **Role of surfactant**

Surfactant consist of two main parts: lipophilic tail group and hydrophilic head group. The nature and equilibrium of these groups influence the type of microemulsion formed. In diluted solutions, hydrophilic single chain surfactants have a tendency to dissociate entirely, which promotes the creation of oil in water microemulsions. The degree of polar group dissociation, however diminishes in the presence of salts or at high concentration of surfactants, frequently leading to water in oil (w/o) microemulsions. The effective areas of hydrophilic and lipophilic parts, which reflect their respective tendencies to interact with water and oil, are essential for estimating the surfactant's hydrophilic-lipophilic balance (HLB) in specific formulations. Dilution with water can accelerate dissociation, shifting system toward o/w type, while ionic surfactants are particularly sensitive to temperature, which can increase counter-ion dissociation and further influence microemulsion behavior.

➢ **Property of oil phase**

Oil phase also affects the curvature by its capacity to permeate and swell the surfactant monolayer's tail group region. This tail swelling leads to a higher negative curvature to the water in oil (w/o) microemulsion.

➢ **Temperature**

The temperature plays a crucial role in determining the effective head group size of non-ionic surfactants. They are hydrophilic, at low temperatures, produce normal oil in water systems and at high temperature produce water in oil systems. And during the intermediate temperature, the microemulsions forms a bicontinuous structure by coexisting with surplus oil and water phases.

➢ **Chain length, Type and nature of cosurfactant**

Alcohols are frequently utilized as cosurfactants in microemulsion production. Since alcohol results in the head region to swell more than the tail region, adding a shorter chain cosurfactant results in a favorable curvature effect. Longer chain cosurfactant favors w/o type by alcohol swelling more in the chain region than in the head region. Whereas the tail region makes it more hydrophilic and favors o/w type.

2. Factors affecting phase behavior

➢ **pH**

Microemulsions containing pH sensitive surfactants are affected by the change in pH. These effects are more noticeable while using alkaline or acidic surfactants. Also during the rase in pH,

carboxylic acids and amines alter the phase from o/w to w/o type microemulsion.

- **Ionic strength**

Increase in ionic strength cause the system to pass from o/w microemulsion in equilibrium with excess oil to the middle phase and finally to w/o microemulsion in equilibrium with excess water.

- **Nature of oil**

When increase in oil aromaticity occurs, it leads to phase transition from o/w to w/o microemulsion and it is opposite to that of increase in oil alkane carbon number.

- **Salinity**

At low salinity, the droplet size of the o/w microemulsion increases, which correlates to an increase in solubilization of the oil. As salinity further rises, the system becomes bicontinuous over an intermediate salinity range. During high salinity, a continuous microemulsion is formed with reduction in globule size and further increase in salinity leads to a complete phase transition.

- **Alcohol concentration**

The phase shift from w/o to bicontinuous and eventually to o/w type microemulsion occurs when the concentration of low molecular weight alcohol as a cosurfactant is increased. The exact opposite phase shift occurs in case of high molecular weight alcohol.

- **Surfactant hydrophobic chain length**

Increase in the surfactant hydrophobic chain length indicates the change of o/w microemulsion to w/o via bicontinuous phase.

Characterization of Microemulsion Systems

Appearance

Formulated microemulsions were visually examined for clarity or for any signs of precipitation or settling. The formulation was evaluated by observing them under light against alternative white and black backgrounds in order to assess their appearance. Turbidity was also assessed during the examination.[12,13]

pH Measurements

pH of the microemulsions were determined by immersing the electrode directly into the dispersion using a calibrated digital pH meter. The excipients employed in the formulation decide the pH of final formulation. According to the suggestion of some literatures a shift in the pH could alter the zeta potential of the microemulsion. Therefore, pH is also a factor in case of stability of the microemulsion.[14,15]

Percentage Transmittance

Also referred to as Limpidity Test or Optical Clarity. In this method spectrophotometer is used to evaluate the percentage transmittance of the formulation. Homogenous nature and formulation clarity can be determined using percentage transmittance. Also, higher transmittance percentage denotes the clarity of microemulsion because it should be more transparent and visually clear than the conventional emulsions.[13]

Dynamic Laser Scattering Spectroscopy (DLS)

DLS, provides the particle size distribution as a polydispersity index (PDI) used for droplet size measurement. A 90plus Brookhaven zetasizer can be used to perform DLS. It operates at a constant fixe angle of 90˚ and 25˚C. In order to operate the microemulsion needs to be diluted using ethanol (1

in 100). The results will be obtained in form of average diameter (Z-average) and PDI.[15]

Zeta Potential

Zetasizer can be employed for the determination of zeta potential of the microemulsion. Clear disposable zeta cells are used to hold the samples and the outcomes are noted. Zeta potential must be negative or neutral which indicates that the system is stable since the microemulsion droplets are charge free. Since electrical charges on the particle affects the rate of flocculation, zeta potential helpful for evaluating the flocculation.[7,16]

Viscosity

Brookfield viscometer is used to asses the rheological characteristics of microemulsions. Viscosity measurements verifies whether the system is o/w or w/o. If the system has low viscosity, then it is o/w type and if the system has high viscosity, then it is w/o microemulsions.[17,18]

Electrical Conductivity

Various conductivity meters such as Elico CM 180, WPA CM 35 can be used to measure the conductivity of microemulsions, which is equipped with platinum electrode cells and, in some cases inbuilt magnetic stirrers. Water was added dropwise to the oil phase, and conductivity was recorded after each addition. This study ascertains the type of system that is whether it is oil-continuous, water-continuous or bi-continuous and also assess the amount of water in the microemulsion. Conductivity increases when the water is the continuous phase and decreases when the oil is continuous.[19,20]

Drug Content

Accurate quantity of microemulsion was weighed and dissolved in suitable solvent in a volumetric flask. The above solution was diluted and analyzed spectrometrically or by using HPLC. The drug content was assessed in triplicate.[20,21]

Specific Gravity

For the determination of specific gravity, a capillary gravity bottle is employed. These gravity bottles must be thoroughly cleaned and dried before its use since even a small bit of moisture could cause errors in the data of the specific gravity of the samples.[22,23]

Refractive Index

Refractive index measurements were conducted to confirm the transparency of the formulation. Abbe's refractometer were used for the determination of refractive indices by placing a single drop of microemulsion on the refractometer slide.[24,25]

SEM

Electron microscopy is the most significant method for studying the microstructures of the microemulsions due to their ability to generate high-resolution images and can detect any co-existing structure. One essential feature of the particle in the microemulsion is its surface shape that is microemulsion ought to have an spherical shape and the particle without tail, due to the tailing of the particle microemulsion shows hazy appearance. The surface morphology of the microemulsion formulation can be done using scanni9ng electron microscopy.[26,27]

Accelerated Stability Studies [7,28]

Accelerated stability studies are more preferred because stability studies are often time-consuming. Physical instabilities such as phase separation, phase inversion, aggregation, creaming and cracking can be assessed.

- **Centrifuge stress test**

Samples are centrifuged for 30 minutes at 5000-10000 rpm. Formulations subjected to thermal testing previously are placed in centrifuge tubes and positioned in a well-balanced manner in the centrifuge basket under ambient conditions. After centrifugation, samples are examined visually for signs of incompatibility.

- **Freeze-Thaw cycles (FTC)**

Samples are subjected to three complete cycles that is 25˚C for 24 h followed by 24 h at 5˚C and the change is noted.

- **Long term stability**

Microemulsions stored for 6 months under ambient conditions and the system were periodically examined after 1,3 and 6 months by visual inspection, specific gravity, pH, measurement of percent transmittance and rheological evaluation.

Polarizing Microscopy [29]

Samples were analyzed using cross-polarized light microscopy to confirm the isotropic nature of microemulsion. Between the glass slide and the cover slip a drop of microemulsion were placed and then observed under the cross-polarized light. Staining Test [30] Also referred to as Dye solubility. To the microemulsion, methylene blue solution were added and if the dye will uniformly dissolve throughout the system, then it is an oil in water microemulsion where the water is the continuous phase and if the dye remains as cluster on the surface of system then it is water in oil microemulsion that is the oil is the continuous phase.

***In Vitro* Drug Release [31 32]**

In vitro drug release were performed using Franz diffusion cell. Suitable membrane was used and formulation placed in the donor compartment. Buffer is placed in the receptor compartment. At one hour intervals, 5ml of the sample was withdrawn from the receiver compartment through a side tube and the withdrawn samples were analyzed spectrophotometrically.

ADVANTAGES [33]

Microemulsions are thermodynamically stable systems, and this stability enables their self-emulsification. They act as a super solvent for drugs, capable of dissolving both hydrophilic and lipophilic compounds, even those with poor solubility in either aqueous or hydrophobic solvents. The dispersed phase whether lipophilic or hydrophilic can serve as a reservoir for corresponding drugs. By adjusting the dispersed phase volume, drug partitioning, and transport rate, drug release can be achieved with pseudo zero order kinetics. The mean droplet diameter in microemulsions is typically less than 0.22mm. when the droplets are extremely small, they provide a very large interfacial area, enabling rapid drug release into external phase. During both *in vitro* and *in vivo* absorption, this helps maintain drug concentration in the external phase near the initial phase. Microemulsions can encapsulate both hydrophilic and lipophilic drugs. Their thermodynamic stability makes them simple to prepare without requiring significant energy input, and they generally have lower viscosity than primary or multiple emulsions. Using microemulsions as drug delivery systems can enhance drug efficacy, allowing for a reduced overall dose and, consequently fewer side effects.

DISADVANTAGES [34]

A high concentration of surfactant and cosurfactant is required to stabilize the droplets in

a microemulsion. The system has limited ability to solubilize substances with high melting points.
For pharmaceutical use, the surfactant must be non-toxic. The stability of a microemulsion can be affected by environmental factors such as temperature and pH, which may vary once the formulation is administered to patients.

Applications of Microemulsions

Microemulsions are versatile delivery systems capable of providing sustained or controlled drug release for various route of administration, including percutaneous, peroral, topical, transdermal, ocular and parenteral. They offer advantages such as improved drug absorption, controlled release kinetics, and reduced toxicity. [6]

Pharmaceutical Application

Parenteral delivery

Administrating drugs with poor solubility through injections, especially into the veins is difficult because only a small amount reaches the target site. For this purpose microemulsions works better than the macroemulsion since their tiny particle stays within the body for longer time. Due to the toxicity effects of some surfactants, certain oil in water and water in oil microemulsions are only suitable. To make them safer, Von Corsewant and Thoren replaced harmful C3-C4 alcohols with safe co-surfactants like PEG 400, PEG 660 and ethanol. This created a middle phase microemulsion that could hold large amounts of oil and water with very little surfactant. [9]

Oral drug delivery

Researchers have always faced problems in developing efficient oral delivery systems since therapeutic efficacy may be limited by instability or low solubility in the gastrointestinal fluids. Microemulsions can improve the solubilization of poorly soluble drugs, and solve issues associated with dissolution related bioavailability.[7]

Topical drug delivery

One of the benefits of topical delivery over the other route is avoidance of hepatic first pass metabolism of the drug and associated side effects. Another is the direct administration and targetability of the drug to the affected areas of eyes or skin. [1,24]

Ocular and pulmonary drug delivery

In the treatment of eye diseases, drugs are generally applied topically. Oil in water microemulsions have been explored for ocular use to enhance the solubility of poorly soluble drugs, improve their absorption, and achieve sustained release.[7]

Microemulsions in biotechnology

For conducting a variety of biocatalytic and enzymatic reactions, aquo-organic or pure organic media, as well as biphasic media are employed. Due to ability to denature or inactivate the biocatalysts, their use is restricted. Microemulsions have recently drawn attention for a number of biotechnological uses, including bio separation, protein immobilization and enzymatic reactions. [6]

Other applications include [9,25]

- Microemulsions can be used to enhance the skin penetration of lycopene.
- Microemulsions as carriers for transdermal delivery of nimesulide.
- Applications in enhanced oil recovery, detergents, cosmetics, agrochemicals, food products, environmental remediation and detoxification.

- Applications in microporous media synthesis and in analytical methods.
- Use as liquid membranes and in the development of novel crystalline colloidal arrays for chemical sensing.

Future Prospectives

The future of microemulsion-based drug delivery lies in developing biocompatible, non-toxic surfactants from natural sources, tailoring formulations for targeted drug delivery and integrating stimuli-responsive systems for precision therapy. Advances in nanotechnology, green chemistry, and in silico modeling are expected to streamline formulation design, reduce surfactant load, and enhance stability under physiological conditions. Exploration into protein, peptide and gene delivery using microemulsions could further expand their therapeutic potential.

CONCLUSION

Microemulsions offer a robust and adaptable platform for enhancing the solubility, stability and bioavailability of diverse therapeutic agents. Their thermodynamic stability, ability to encapsulate both hydrophilic and lipophilic drugs, ease of preparation make them highly attractive for pharmaceutical applications. By optimizing the selection of oils, surfactants and cosurfactants, microemulsion can be tailored to achieve desired release kinetics and targeting profiles for wide range of administration routes. Despite certain limitations such as high surfactant requirements and sensitivity to environmental changes, ongoing research into compatible excipients and sensitivity to environmental changes, ongoing research into biocompatible excipients and novel formulation strategies is steadily overcoming these challenges. The integration of microemulsion technology with nanocarriers, targeted ligands and stimuli-responsive systems has the potential to revolutionize drug delivery. As formulation science advances, microemulsion are expected to play avital role in bridging the gap between poorly soluble drugs and their successful clinical application, paving the way for safer, more effective and patient friendly therapeutic solutions.

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