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A Promising Approach To Deliver Lipophilic Drug Candidate: Microemulsion Based Drug Delivery

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ABSTRACT

Microemulsions are isotropic mixtures which are thermodynamically stable containing oil, water, surfactants, and co-surfactants that form spontaneously with droplet sizes ranging from 5–100 nm. These systems have gained significant attention as efficient drug delivery carriers for lipophilic and poorly water-soluble drugs. Their ability to enhance solubility, improve bioavailability, and provide controlled and targeted delivery makes them suitable for a broader range of pharmaceutical applications. This review discusses the types, classification (Winsor I–IV), formulation theories (thermodynamic, interfacial, and solubilization), excipients used, and various preparation methods such as phase inversion and titration techniques. Applications across oral, topical, ocular, nasal, parenteral, and cosmetic routes are explored, highlighting microemulsions' versatility. Characterization methods, including droplet size analysis, viscosity, and stability testing, are also covered. Overall, microemulsion-based systems offer an effective and reliable approach for delivering lipophilic drugs and therapeutic agents.

1. INTRODUCTION

A dispersion system is a heterogeneous mixture where one phase is distributed within another. The classification of a system as a foam, emulsion, or suspension depends on the physical form of the dispersed phase—be it gas, liquid, or soli. Depending on the particle size of the dispersed phase, such systems are further divided into categories like colloids, suspensions, macroemulsions, and microemulsions(1). One innovative approach for masking the taste of bitter drugs is using multiple emulsion systems. Such formulations often involve loading the drug into the innermost water phase of a water-in-oil-in-water (w/o/w) emulsion, which helps maintain overall stability. This structure allows the drug to be gradually released through the oil layer in the gastrointestinal tract, thereby enhancing solubility, dissolution, and overall bioavailability (2).

2. MICRO EMULSION

Hydrophobic medicinal compounds are attractively delivered in lipid dosage formulations. Emulsion has been a widely used system for many years (3). In actuality, oil and water do not mix. This is a harsh reality in a number of applications, and it is quite disheartening that water and oil, two distinct macroscopic phases, cohabit and only interact through a tiny interface. Of course, stirring the liquid will break the both phases in the droplets and enhance the interfacial area, but without other tactics, the combination of two variables would make this strategy fail. Chemicals that settle down at the interface and stop collision and coalescence must be added to the dispersion to increase its stability. When appropriate surfactants are added, water and oil dispersions can be given kinetic stability as macro emulsions or just emulsion droplets (4).

Thanks to the efforts of Jack H. Schulman and colleagues at Columbia University, the word "micro emulsion" first appeared in the scientific lexicon in 1959 (5). Microemulsions are clear, thermodynamically stable systems composed of water, oil, a surfactant, and occasionally a cosurfactant. Since the droplet sizes in microemulsions range from 5 to 100 nm, they are optically transparent solutions (6). We can now accept Attwood's definition, which states that "a microemulsion is a mixture of oil, water, and amphiphilic compounds (Co-surfactant and surfactant), which is thermodynamically stable, single optically isotropic and transparent liquid." The presence of this structure was subsequently confirmed using a range of analytical

techniques(7)

Types of microemulsions

Microemulsions are primarily classified into three types based on their composition:

Oil-in-water (O/W) microemulsions, where oil droplets are finely dispersed within a continuous water phase.

Water-in-oil (W/O) microemulsions, where water droplets are distributed throughout an oil phase.

Bi-continuous microemulsions, in which oil and water form interwoven microdomains within the system.

In each of these types, the interface is stabilized by an appropriate blend of surfactants and, in some cases, co-surfactants. Winsor further introduced a classification system involving four types of phase behavior, categorized based on the properties and arrangement of the phases present. Using his framework, microemulsions can be grouped into four distinct types(8)

Type I: This category of microemulsion results in the formation of an oil-in-water (O/W) system(9). A surfactant (and may including a co-surfactant) coating envelops the oil droplets in these microemulsions, which form the continuous phase that is dispersed throughout the water (10)

Type II: In this type of microemulsion, water-in-oil (W/O) microemulsion is formed.(9) This kind of microemulsion features a continuous oil phase around water droplets. These structures, often referred to as “reverse micelles,” have their hydrophobic tails oriented toward the surrounding oil, while the polar head groups of the surfactant align inward, surrounding the water droplets(10).

Type III: A middle phase loaded with surfactants generates a three-phase microemulsion by combining with both phases. Both the oil and the water in this microemulsion are phases lacking surfactants. Another name for this is "Winsor III." In bi-continuous microemulsion systems, both water and oil act as continuous phases. When water mixes with oil, it forms a complex, irregular network often referred to as a "sponge phase." This unique structure can evolve as the system transitions between oil-in-water (O/W) and water-in-oil (W/O) types. Bi-continuous microemulsions often exhibit plasticity and non-Newtonian flow behaviour, which makes them especially suitable for drug delivery via intravenous injection or topical application(10).

Type IV: Alcohol (amphiphile) plus a suitable amount of surfactant is added to create an isotropic (single micellar) solution (Winsor IV). The middle phase of a Winsor Type III micro emulsion extends and unifies to form a Winsor Type IV micro emulsion at greater surfactant concentrations. In a single-phase homogeneous system, also known as Winsor IV, the surfactants, oil, and water are uniformly blended to form a stable mixture(10).

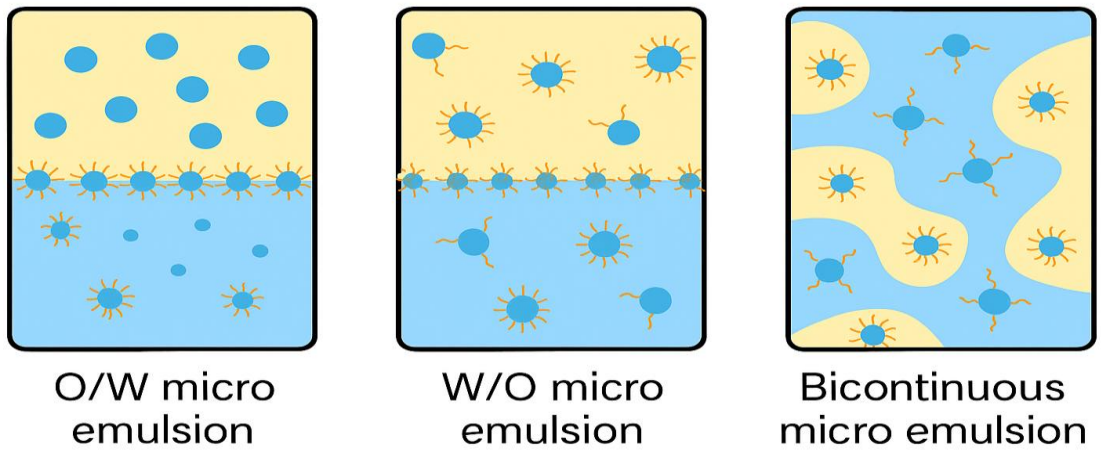

Figure 1: O/W, W/O and Bi-continuous Micro emulsions.

Advantages & disadvantages of microemulsion(11–14)

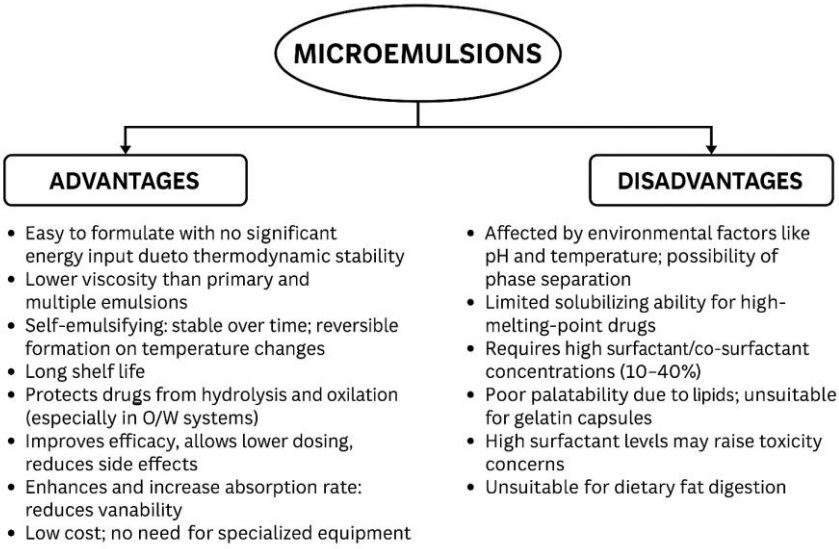

Figure 3: Advantages & disadvantages of microemulsion

Various Applications of Microemulsions

The production of microemulsions is quicker and more spontaneous; thus, thermosensitive medications can be added straight away without running the risk of degrading. Since microemulsions appear isotopically clear, spectroscopic analysis of them is simple. Phase separation is not possible due to their indefinite stability.

4.1. Oral Delivery

Microemulsions have the potential to overcome dissolution-related bioavailability issues and enhance the solubilization of poorly soluble medications. Hydrophilic pharmaceuticals, which include macromolecules, having the capacity to be encapsulated with different levels of solubility due to the existence of interfacial domains, polar and nonpolar. (10)

4.2. Proteins and Peptides

Proteins and peptides are poorly absorbed orally due to degradation in the acidic GI tract, leading to less bioavailability. As a result, they are usually given by injection, but their short half-life requires frequent dosing. Microemulsions offer a promising solution by enabling controlled release of drugs like diuretics, steroids, hormones, and antibiotics reducing the need for frequent administration(15,16).

4.3. SMEDDS

By formulating self-microemulsifying drug delivery systems, bioavailability & solubility of many drugs have been improved compared to other conventional drug formulations. As SMEDDS is the preconcentrate mixture of oil, surfactant & co-surfactant ready to form microemulsion upon gentle shaking with aqueous media. (10)

4.4. Topical Delivery

One key benefit of using topical medications is that it bypasses hepatic first-pass metabolism, reducing the risk of liver-related drug toxicity. Additionally, it allows for direct delivery of the drug to affected areas such as the skin or eyes. This approach can improve the therapeutic performance of both lipophilic and hydrophilic drugs(17,18).

4.5. Ocular Delivery

In conventional ocular formulations, water-soluble active pharmaceutical ingredients (APIs) are delivered through aqueous solutions, while poorly water-soluble drugs are typically prepared as suspensions or ointments. Among the serious issues with these methods are less corneal bioavailability and less effectiveness on the posterior area of ocular tissue. Microemulsions have become a viable dosage form for ocular usage(19,20).

4.6. Nasal Delivery

Microemulsions are now recognized as effective carriers for improving drug absorption through the nasal mucosa. Additionally, the use of mucoadhesive polymers helps extend the retention time of the formulation on the mucosal surface(10).

4.7. Intravaginal Delivery

Gel-micro emulsions have been employed as intravaginal drug delivery systems and vaginal spermicides. According to reports, the new gel-micro emulsions are nontoxic, dual-purpose intravaginal spermicides that can be utilised to deliver lipophilic chemical compounds that target STDs (6).

4.8. Parental Delivery

Microemulsions offer key benefits over macroemulsions for parenteral use, as their smaller particle size allows slower clearance and longer circulation time. Both oil-in-water (O/W) and water-in-oil (W/O) microemulsions are considered appropriate for drug delivery applications. Since protein and peptide drugs have low oral bioavailability, they are typically administered via injection(21,22).

4.9. Buccal Delivery

Drugs can be delivered via the buccal route to have both local and systemic effects. For medications that experience quick biotransformation, this pathway appears to be a promising one(10).

4.10. Tumour Targeting.

Microemulsions offer a promising approach for delivering chemotherapeutic or diagnostic agents directly to cancer cells, minimizing exposure and potential damage to healthy tissues. Since cancer cells often overexpress LDL receptors, microemulsions composed of cholesterol esters, triglycerides (≤20%), phospholipids, and a drug can target these cells. The microemulsion enters via LDL receptors, allowing higher drug concentrations in tumour cells while reducing toxicity to healthy tissues(23,24).

4.11. Cosmetic Application

Microemulsions are extensively utilized in cosmetic formulations for skin, hair, and personal care products because of their transparency, excellent solubilizing capacity, stability, and ease of preparation. They enhance product efficiency and stability, especially for poorly soluble ingredients. Oil-in-water microemulsions have been used as transparent carriers for sunscreens, offering benefits like a smooth feel, water resistance, non-stickiness, and easy application. Ingredients like lycopene, which are difficult to dissolve in water or oil, can also be effectively formulated using microemulsions(24–26).

Theory of micro-emulsion formulation

Several theories have been proposed to explain and control the stability and phase behaviour of microemulsions, which serve as the foundation for their formulation. These theories are

5.1. Thermodynamic Theory

The formation and stability of microemulsions can be understood through basic thermodynamic principles. The reduction in interfacial tension by surfactants and the accompanying increase in system entropy contribute to lowering the free energy required for microemulsion formation; thus,

$DG_f = \gamma DA - T\,DS$

γ represents the surface tension at the oil–water interface,

DG_f is the free energy required for microemulsion formation,DA denotes the change in interfacial area during emulsification,DS refers to the change in entropy of the system—primarily the entropy of dispersion,and T is the absolute temperature.

It has been observed that the interfacial area (DA) undergoes a significant increase during microemulsion formation due to the generation of numerous tiny droplets. Although the surface tension (γ) remains a positive value, it is typically very low and is effectively offset by the entropy contribution. The major entropic gain, known as dispersion entropy, results from the thorough mixing of one phase into another as fine droplets, which plays a crucial role in driving the formation of microemulsions.(27). Additionally, dynamic processes such as surfactant monomer-micelle exchange and diffusion of surfactants within the interfacial layer also contribute positively to the system's entropy. When these entropic effects are strong enough to substantially lower the surface tension, the free energy of formation becomes negative. This leads to a thermodynamically stable system and allows microemulsification to occur spontaneously(28).

5.2 Solubilization Theory

The solubilization hypothesis relies on the assumption that micelles exist in two distinct forms: normal and reverse. Normal micelles are capable of solubilizing oil, whereas reverse micelles can encapsulate water. There is a strong relationship between micelle formation (micellization) and solubilization, with the micelle concentration playing a critical role in influencing the critical micelle concentration (CMC) and the extent of solubilization. One of the many important factors influencing solubilization is temperature. Generally speaking, solubility increases with temperature. The solubilising power increases when electrolytes and non-electrolytes, such as alcohols, are added because they increase the size of the micelles(29,30).

In the micellization process, reverse micelles or standard micelles gradually expand and swell to a certain size, ultimately forming a microemulsion that incorporates both oil-soluble and water-soluble phases. The dispersions seem transparent because the water droplets are smaller than 1000 A. (%A of light)(31,32). These transparent formulations containing equal proportions of oil and water require high concentrations of soap, along with a non-ionized amphipathic compound—such as an aliphatic alcohol, cresol, or amine—present in at least the same concentration as the soap. When water is added to non-conducting systems, these droplets appear to enlarge to an observable size (the Tyndall effect), maintaining the non-conducting nature of the system. The system became an oil-in-water opaque emulsion when more water was added. It was proposed that an interfacial mixed monolayer of alcohol and soap stabilised the droplets(33).

Two main approaches are commonly considered when explaining microemulsion systems: one views them as highly swollen micelles, while the other focuses on structural changes occurring at the oil–water interface. Microemulsion droplets can be formed by either of the following mechanisms (34):

The breakdown of larger droplets due to a reduction in interfacial tension.

The swelling of micelles as a result of molecular diffusion of the internal medium, leading to the release of most of the dispersed phase.

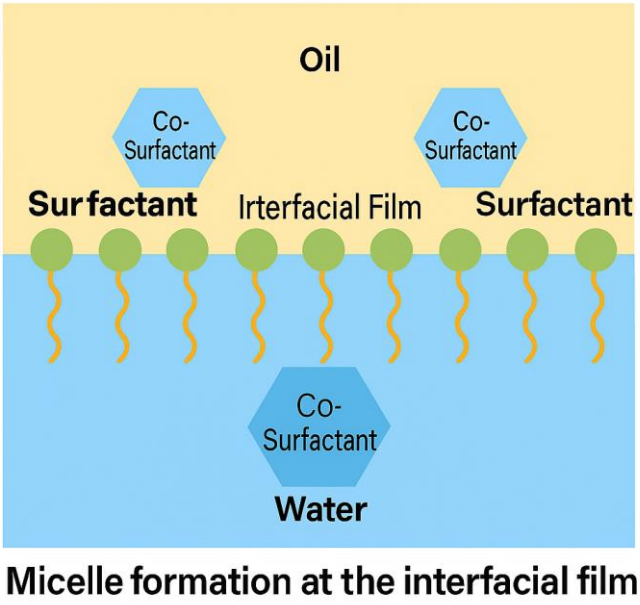

Figure 2: Arrangement of surfactant & co-surfactant at the interfacial film.

5.3 Interfacial theory

According to the interface mixed-film theory, microemulsions can form quickly and spontaneously when surfactants and co-surfactants interact at the interface. The duplex film theory further explains this phenomenon by providing an expression for the interfacial tension (γ_T) as follows(35,36):

$\gamma_T = \gamma(O/W)$ --- π

Where,

γ (O/W) a = Interfacial Tension

Excipients used to prepare microemulsion

A microemulsion is a type of colloidal dispersion composed of an oil phase, an aqueous phase, a surfactant, and a co-surfactant, all combined in specific ratios. Excipients are present in almost all pharmaceuticals and are added to improve manufacturing, patient acceptability, stability, release control, and other factors. A drug product's main ingredients are usually excipients, with the active molecule appearing in comparatively minor levels. Generally, excipient grades and quality might change during the course of a pharmaceutical product's life. Supply security should be a primary consideration when choosing excipients, especially for less widely used excipients like stock kipping.

6.1. Oil/Lipid Phase

The oil phase plays a crucial role in microemulsion formulation, as it influences the selection of other components. Two key factors must be considered when selecting an appropriate oil. The first is its ability to effectively dissolve the active pharmaceutical ingredient (API). Second, the selection must be such that the microemulsion can have a large existence area(37,38). In comparison to oils with large hydrocarbon chains, those with smaller chains are easier to generate a microemulsion. In contrast, an oil's capacity to dissolve lipophilic groups is straight correlated with its chain length. The oil serves as a key excipient in the formulation, largely depending on the molecular structure of its triglycerides. It not only helps solubilize the necessary drug dose but also enhances the transport of lipophilic drugs through the intestinal lymphatic pathway, thereby improving gastrointestinal absorption. The oil component affects curvature by attaching to the surfactant monolayer's tail group region and causing it to swell. Short-chain oils penetrate deeper into the tail region of surfactant molecules compared to long-chain alkenes, leading to greater expansion of this region. This results in increased negative curvature and a reduced effective hydrophilic-lipophilic balance (HLB)(39).

A variety of oils are commonly used in microemulsion formulations.

Saturated fatty acids such as lauric acid, capric acid, and myristic acid are frequently employed.

Unsaturated fatty acids include linolenic acid and oleic acid.

Fatty acid esters such as methyl or ethyl esters of lauric, myristic, and oleic acids are also utilized.

Both saturated and unsaturated fatty acids have gained significant attention due to their exceptional ability to enhance skin and membrane penetration. Fatty acid esters are also commonly employed as the oil phase in microemulsion systems. Lipophilic drugs are preferably incorporated into oil-in-water (O/W) microemulsions, where they dissolve effectively. When selecting an appropriate oil, the solubility of the drug is a key factor, as it allows for a more compact formulation capable of delivering the therapeutic dose in an encapsulated form.(40,41).

6.2. Surfactant

Microemulsions can be formulated using both single-chain and double-chain surfactants. However, co-surfactants are often required because single-chain surfactants alone may not sufficiently reduce the oil–water interfacial tension. To form a stable monolayer surfactant film, the surfactant’s lipophilic chains should either be relatively short or include fluidizing elements such as unsaturated bonds. The primary role of surfactants is to significantly lower interfacial tension, enabling efficient dispersion. In microemulsion systems, surfactants also help form a flexible interfacial film with optimal lipophilic characteristics that can easily wrap around droplets, providing the necessary curvature for stability(42,43). To stabilise a microemulsion system, surfactants can be

Non-ionic,

Zwitterionic,

Cationic, or

Anionic surfactants.

The ionic or non-ionic nature of a surfactant plays a crucial role in determining how its hydrophilic end interacts with the aqueous phase during microemulsion formation. In the case of ionic surfactants, stabilization is primarily achieved through the formation of an electrical double layer. For non-ionic surfactants, stability arises from dipole interactions and hydrogen bonding with water molecules in the hydration shell around the hydrophilic region. As a result, ionic surfactants are more sensitive to changes in salt concentration, which can affect the stability of emulsions or microemulsions. However, due to safety and toxicity concerns, ionic surfactants are generally avoided in pharmaceutical formulations. In contrast, non-ionic surfactants are considered safer for oral use and are commonly found in commercially available solubilized drug products. Examples include polyethylene glycol 1000 succinate, Solutol HS-15, d-α-tocopherol, polyoxyl 40 stearate, sorbitan monooleate (Span 80), polyoxyl 35 and polyoxyl 40 hydrogenated castor oil (Cremophor RH 40), castor oil derivatives (Cremophor EL), polysorbate 20 (Tween 20), polysorbate 80 (Tween 80), and polyglycolyzed glycerides such as Labrafil M-2125CS, Labrafil M-1944CS, and Gellucire 44/14(44,45).

It is widely accepted that the solubilization process in microemulsions relies primarily on surfactant molecules situated at the water–oil interface. To accurately assess the net solubilization capability of the surfactant, the portion of surfactant molecules dissolved individually (monomerically) in the oil phase must be subtracted from the total surfactant initially introduced into the system. This approach has proven effective in studying the phase behaviour of different mixed surfactant systems.

6.2.1 Method of Selection of Surfactant

6.2.1.1 HLB Method

When choosing a surfactant that will generate a microemulsion, one can start by looking at its hydrophilic-lipophilic balance

(HLB). Surfactants with hydrophilic-lipophilic balance (HLB) values in the range of 3–6 generally favour the formation of water-in-oil (W/O) microemulsions, while those with higher HLB values (typically between 8–18) are more suitable for oil-in-water (O/W) microemulsions.(46).

6.2.1.2 CPP Method

The preferred geometry of the surfactant is measured by CPP, which can be used to forecast the kind of structure that would emerge. The Critical Packing Parameter (CPP) is calculated by dividing the partial molar volume of the surfactant's hydrophobic portion by the product of its tail length and the optimal surface area occupied by the surfactant's head group. Micelles or lamellar structures resembling worms are typically formed with CPP values near one. Head groups are substantially larger when the CPP value is more than one, leading to w/o microemulsion systems. For CPP values below one, the inverse is true. Lamellar phase development may be indicated by CPP values close to one. The amount of surfactant needed can be determined based on the surfactant molecules' cross-sectional area and the total surface area of the droplets(47,48).

6.3 Co Surfactant

Single-chain surfactants typically do not reduce the oil–water interfacial tension enough to form stable microemulsions effectively. Co-surfactants provide the necessary flexibility to the interfacial film, allowing it to adjust to different curvatures and facilitating the formation of stable microemulsions over a broad range of compositions. When creating a monolayer surfactant film, surfactants should have relatively short lipophilic chains or incorporate fluidizing groups, such as unsaturated bonds. Additionally, short- to medium-chain alcohols (C3–C8) are frequently used as co-surfactants to further reduce interfacial tension and enhance film flexibility. Typical examples of co-surfactants include amines, acids, short-chain alcohols (ethanol to butanol), medium-chain alcohols, and glycols such as propylene glycol(49,50). In the majority of systems, a microemulsion phase can be replaced by liquid crystalline or gel structures, and co-surfactant-free microemulsion can only be produced at high temperatures. (51).

A co-surfactant's function is as follows:

Enhance the interface's evenness.

Destroy the gel or liquid crystalline structure that would stop a microemulsion from forming.

Modify the surfactant partitioning property to alter the HLB value and the interface's spontaneous curvature.

6.4 Aqueous Phase

The water phase may hold hydrophilic drugs and preservatives. Buffer solutions are used as the aqueous phase by certain researchers.

3. METHOD OF PREPARATION

An isotropic, thermodynamically stable single phase made up of at least three components—two of which are immiscible, while the third, known as the surfactant, exhibits amphiphilic behaviour—is known as a microemulsion. In contrast to regular emulsions, microemulsions are created by combining the right amounts of materials at the right temperature. The formation of an oil-in-water (O/W) microemulsion typically begins with the development of a water-in-oil (W/O) emulsion, using a surfactant that favours oil solubility. A hydrophilic surfactant is introduced during the procedure while being stirred, first forming a cubical structure, but an O/W microemulsion is created when a hydrophilic surfactant is added further. To prepare the W/O type of microemulsion, the exact opposite process can be used(52). Water-in-oil (W/O) microemulsions are characterized by the presence of free water droplets at their core, often referred to as "micro-pools." Structurally, they resemble reverse micelles, where the polar head groups of the amphiphiles face inward toward the water, and the hydrophobic tails extend into the surrounding oil phase. Typically, a specific ratio of surfactant and co-surfactant is used to achieve a stable formulation. Lower-chain alcohols—such as butanol, pentanol, and hexanol—and certain amines like butylamine and hexylamine are commonly utilized as co-surfactants. These compounds not only help reduce interfacial tension, enabling the formation of thermodynamically favourable dispersions, but also impart flexibility to the interfacial film, supporting efficient curvature at the oil–water boundary(53,54).

7.1 Phase Inversion Method

Microemulsions can undergo phase inversion when there is an excessive amount of the dispersed phase or due to changes in temperature. This inversion leads to notable physical alterations, including shifts in droplet size, which can influence drug release behaviour in both in vitro and in vivo settings. Such transitions are primarily driven by modifications in the surfactant's spontaneous curvature. In systems containing non-ionic surfactants, phase inversion from an oil-in-water (O/W) to a water-in-oil (W/O) microemulsion can be induced by increasing the temperature. Conversely, cooling the formulation allows the system to pass through a zone characterized by minimal interfacial tension and zero spontaneous curvature, favouring the formation of finely dispersed oil droplets(55,56). This approach is referred to as the Phase Inversion Temperature (PIT) method. While temperature is the primary factor, other parameters such as salt concentration and pH can

also influence phase behaviour. Additionally, adjusting the water volume fraction can impact the surfactant's spontaneous radius of curvature. For instance, when water is gradually added to an oil phase, initial formation of water droplets occurs within the oil, creating a water-in-oil (W/O) microemulsion. As the proportion of water increases, the surfactant's spontaneous curvature shifts, leading to the transition from a W/O to an oil-in-water (O/W) microemulsion at a specific inversion point(57,58).

When there is a high oil content, surfactants can create reverse micelles, which will solubilize more water molecules in their hydrophilic centre. When the water content is low, the initially clear and isotropic region becomes turbid and exhibits birefringence. With the further addition of water, the system may evolve into a water-in-oil (W/O) microemulsion, where water exists as dispersed droplets encapsulated and stabilized by a surfactant and co-surfactant interfacial film. With increasing water content, the lamellar structure breaks down, giving rise to a continuous aqueous phase in which oil droplets are dispersed and stabilized by surfactants or co-surfactants, resulting in the formation of an oil-in-water (O/W) microemulsion(59,60).

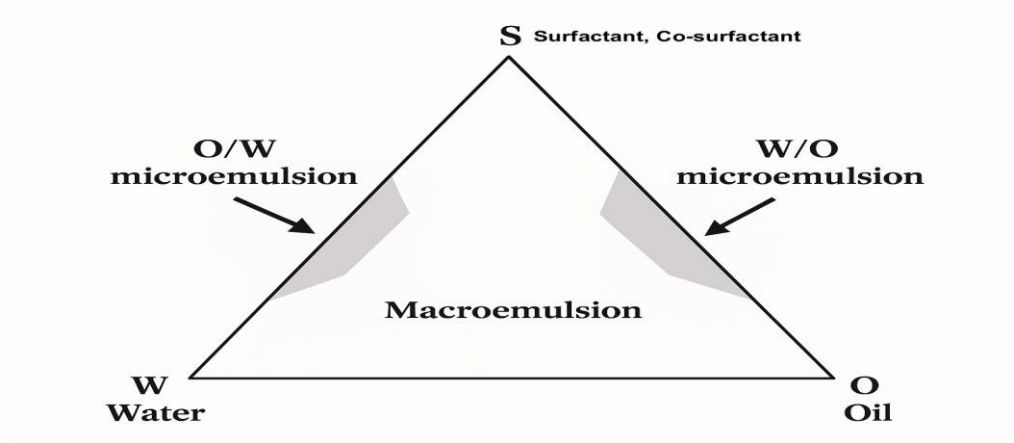

Figure 3: Hypothetical Phase region of Micro micro-emulsion system

7.2 Phase Titration Method

Microemulsions created by the phase titration method can be described using phase diagrams. A helpful method for studying the complex series of interfaces that might happen when many elements are joined is the creation of phase diagrams. To make microemulsions, the phase titration method is employed. This technique is also known as spontaneous emulsification. Microemulsions can be described using phase diagrams. Four-compartment systems are difficult to intercept and take a lot of time. Consequently, when creating microemulsions, the pseudo-ternary phase diagram is employed. Both separate zones and microemulsion zones are present in these.(61,62). These show every individual component at 100%. The phase titration technique involves combining oil, water, surfactants, and co-surfactants in predetermined weight ratios. A phase diagram is then used to guide the mixing of these components. Each mixture is stirred at room temperature and visually examined to determine whether it forms a monophasic or biphasic system. While some turbidity may occur during phase separation, only mixtures that remain clear and transparent after continuous stirring are considered monophasic; turbid samples are classified as biphasic. The results are then plotted on a pseudoternary phase diagram to identify the phase boundaries(63,64).

4. CHARACTERIZATION OF MICRO EMULSION

Appearance

One-phase systems are microemulsions. It is translucent or transparent. It is a homogenous, monophasic system with a distinct isotropic look. For this, freeze fracture transmission electron microscopy, phase contrast microscopy, and visual measurements can all be employed(65).

Dye Solubility Test for Microemulsion

Methylene blue solution, a water-soluble dye, is added to the emulsion. The dye will dissolve evenly throughout the system if water (o/w emulsion) is the continuous phase. The dye will stay in a cluster on the system's surface if the continuous phase is oil(66).

Viscosity measurement

The Brookfield viscometer can be used to measure it. Rotating spindles of various sizes are employed and submerged in test material. For repeatable results, this process is carried out three times. The microemulsion area can be identified and distinguished from other comparable structures, such as liquid crystals, with the aid of changes in rheological properties(67).

Conductivity measurement for Microemulsion

Conductivity measurements provide a simple and effective way to identify whether a microemulsion system is continuous in water or oil. By evaluating the electrical conductivity (σ), the extent to which the aqueous phase has been incorporated into the oil phase can be quantitatively assessed(68,69).

Light Scattering by Microemulsion

Techniques such as light scattering, small-angle X-ray scattering (SAXS), and small-angle neutron scattering (SANS) have been widely employed to investigate the structural characteristics of microemulsions(70,71).

Thermodynamic stability

The ideal microemulsion is maintained at room temperature, at a temperature of 50 ± 2 °C, and at a cold temperature (4–8°C). Microemulsions can be evaluated bi-monthly for parameters such as phase separation, percent transmittance, globule size, and drug content. An ideal formulation should demonstrate long-term shelf stability and maintain thermodynamic equilibrium(72).

Droplet size distribution and zeta-potential analysis

Dynamic light scattering, performed using instruments such as the Zeta Sizer HSA 3000 and laser particle size analyzers, is commonly used to measure the zeta potential and droplet size of microemulsions. Ideally, the droplet size should be below 100 nanometers(73,74).

pH measurement

It is measured at room temperature, pH indicator are used to measure pH. When creating microemulsions, pH is monitored(75).

Assay

The microemulsion assay provides information on the medication content. Assays are performed using spectrophotometry. The drug's standard calibration curve is used to determine the concentration(76).

Differential scanning colourimetry

An essential evaluation method for identifying any potential interactions between the medicine and excipients is thermal analysis. Any change in the thermogram can be used to identify such an interaction(77).

In Vitro Drug Release Study

A modified Franz diffusion cell is commonly employed to perform diffusion studies. The donor compartment, which clearly contains the microemulsion and the simple medication solution, is sealed with a cellophane membrane. the receptor compartment is filled with the buffer. At specified time intervals, samples are withdrawn from the receptor compartment and analyzed using a UV spectrophotometer set to a specific wavelength to quantify the drug content. In vitro drug release testing plays a vital role in the quality control of drug delivery systems and also serves as a predictive tool for estimating in vivo drug behaviour. USP apparatus II and the membrane diffusion method are used to measure this *In Vitro* Drug Release Study (78,79)

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