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MICROEMULSION SIGNIFICANCE IN THE ADVANCED DRUG DELIVERY FOR THERAPEUTIC APPLICATIONS

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ABSTRACT

Introduction: Microemulsions have attracted the interest of formulation scientists since their discovery, owing to their superior properties in terms of stability, solubility, simplicity, and formulation features. **Methods:** An extensive search was carried out in different databases viz. Scopus, Embase, Cochrane and PubMed**.** The keywords used in the search were microemulsions, formulation of the microemulsion, different types of microemulsions and advantages of microemulsions. All the studies published in English and studies researched microemulsion its therapeutic benefits. **Results:** A microemulsion is a thermodynamically stable, transparent mixture of two immiscible liquids stabilized by surfactant. Microemulsions have a number of advantages over conventional formulations, including increased drug solubility, thermodynamic stability, ease of manufacture, and penetration. **Conclusion**: This review aims to talk about how microemulsions are made and how they can be used in improved drug delivery.

Keywords: Microemulsion, Hydrophobic, Hydrophilic, Phase inversion, Phase titration, Surfactants, active drug

INTRODUCTIONS

Rodewald was the first to develop microemulsions in the form of liquid waxes in 1928. Hoar and Schulman coined the term microemulsion, which they characterized as a clear solution made by titrating a conventional coarse emulsion with medium-chain alcohols. Because of their thermodynamic stability and the ease with which they may be prepared, microemulsions are simple carrier systems **[1]**. A microemulsion is a transparent, single, optically isotropic, and thermodynamically stable liquid consisting of water, oil, and amphiphilic chemicals. Microemulsions are thermodynamically stable isotropic and transparent systems of oil, water, and a surfactant, usually combined with a cosurfactant. The size of the droplets might range from 10 to 200 nm **[1]**. Microemulsions have a unique mechanism of skin penetration because they react with lipids on the skin, causing the intercellular space to shift and the medicine to be delivered. The size of the dispersed phase droplets is the significant difference between an emulsion and a microemulsion. Microemulsions are potential delivery methods because they provide for both regulated and sustained drug release for various routes of administration **[3, 4]**. As a delivery mechanism, microemulsions have several distinct characteristics. The most notable is that they are less poisonous, facilitate increased drug absorption, and regulate drug distribution rates **[5, 6]**.

A vast number of novel compounds have been created due to recent advances in the detection of bioactive chemicals. Today, a vast percentage of these novel drugs and many established medications have poor solubilization behaviour, resulting in poor oral bioavailability with wide intra- and inter-subject variation and posing significant technical hurdles to formulators **[7]**. Because a dosage form with poor drug delivery might render a useful medicine useless, choosing the right dosage form is crucial. Because pharmacologic and toxic effects are proportional to both dose and bioavailability, bioavailability has substantial therapeutic consequences. A topical medication is a word used to describe formulations that have effects exclusively in a specific body location and are designed so that the medicament's systemic absorption is minimal **[8]**.

Microemulsion

A microemulsion is a colloidal dispersion of oil, aqueous phase, surfactant, and co-surfactant in proper ratios that form a single optically isotropic and thermodynamically stable liquid solution with droplet diameters ranging from 10 to 100 nanometers **[9]**. Microemulsions have

been extensively researched as a means of improving the bioavailability of poorly soluble medicines. In such circumstances, they provide a cost-effective solution. Microemulsions have low surface tension and small droplet size, resulting in excellent absorption and penetration **[10]**. The popularity of these adaptable carriers is growing, and their uses have expanded to include a variety of administration methods in addition to the traditional oral route. This is due to their unique solubilization capabilities and thermodynamic stability, which has sparked interest in their application as innovative drug delivery vehicles **[11, 12]**.

Microemulsions benefit colloidal systems under investigation, and conventional emulsions, suspensions, and micellar solutions could be used as drug carriers **[13]**. They promise drug delivery systems that allow for regulated or sustained drug release via percutaneous, peroral, topical, transdermal, ophthalmic, and parenteral routes. They benefit from spontaneous synthesis, ease of production and scale-up, thermodynamic stability, and increased drug solubilization and bioavailability for hydrophobic medicines. On the other hand, microemulsions with an inverse micellar structure may be less comedogenic than creams or solutions **[14, 15]**.

Microemulsions are quaternary systems that include an oil phase, a water phase, surfactants, and a cosurfactant. Transparency, optical isotropy, low viscosity, and thermal stability are among the physicochemical features of these spontaneously generated systems. The transparency of these systems is because the dispersed phases maximum droplet size is less than one-fourth of the wavelength of visible light, which is roughly 150 nm. Droplet diameter in stable microemulsions is typically between 10 and 100 nanometres, implying that the word microemulsion is deceptive and that these systems are essentially Nano-sized emulsions. Many in vitro and a few in vivo investigations have indicated that microemulsion formulations have better transdermal and dermal distribution qualities **[16-18]**.

Microemulsion structure and types

To generate a microemulsion, the interfacial tension between oil and water must be close to zero. Microemulsions are biphasic liquid dosage forms, which distinguishes them from molecular hydrocarbon and water solutions.

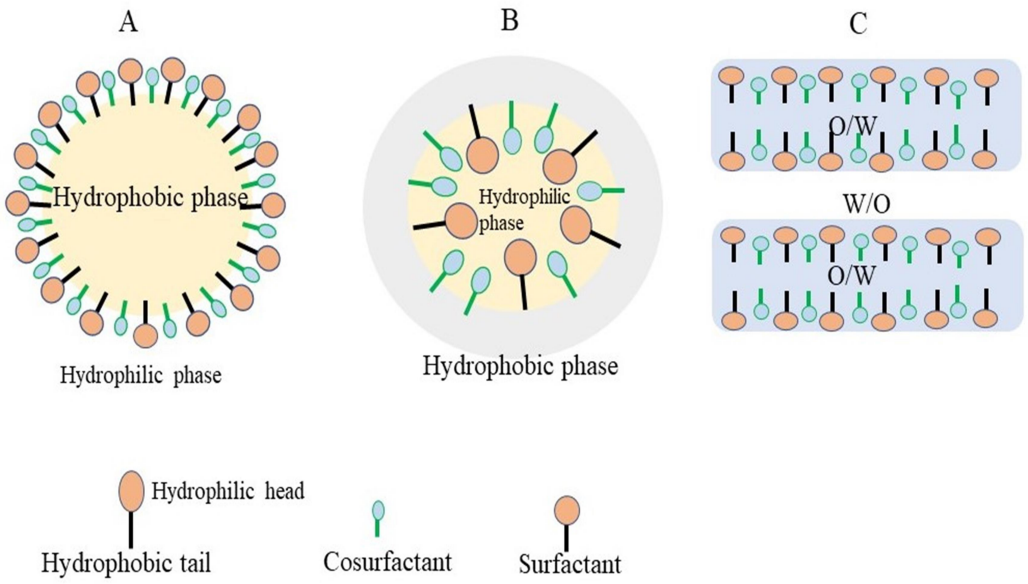

Figure 1

Figure 1 shows a schematic representation of the three types of microemulsions that are most likely to be designed based on the concentration of multiple components. Between the water and oil domains, the created three structures exhibit an interfacial monolayer of surfactants. However, the globules of oil-in-water (o/w) or water-in-oil (w/o) microemulsions do not have a spherical shape; instead, they have an asymmetric, frequent-adopting prolate ellipsoid shape. Furthermore, in microemulsions with low oil content, the presence of globules (o/w) is regarded as a critical feature **[19]**.

1. Microemulsions of oil in water (O/W), in which oil droplets are scattered in a continuous aqueous phase.
2. W/O microemulsions are water-in-oil microemulsions in which water droplets are spread in a continuous oil phase.
3. Bi-continuous microemulsions are those in which microdomains of oil and water are interspersed throughout the system.

Components of Microemulsion

Oil phase: The oil phase must be chosen appropriately, the solubilizing potential of the oil for the selected substance must be seen. And secondly, the chosen must be such that the microemulsion forming region is enhanced. Oils with shorter hydrocarbon chains are easier to micro emulsify as compared to oils with long hydrocarbon chains. Oil ability to solubilize lipophilic groups is directly proportional to the chain length of the oil **[20]**.

Water phase: Water may form water as a dispersion medium in micro-emulsion systems depending on the amount of water present **[21]**.

Surfactants: Surfactants with a hydrophilic-lipophilic balance of 3–6 are preferable for preparing W/O microemulsions; surfactants with a hydrophilic-lipophilic balance of 8–18 are preferred for the preparation of O/W microemulsions. Surfactants with hydrophilic-lipophilic balance values more significant than 20 frequently require the inclusion of a cosurfactant to bring them within the appropriate range. Surfactants **(Table 1)** can be changed by inserting groups of intermediate polarity such as polypropylene oxide or polyethene oxide between the hydrophilic head and the hydrophobic tail. They are capable of improved interaction with both oil and water phases due to their changed structure. As a result, microemulsions with extremely low interfacial tension and high solubility are formed **[21-23]**.

Table 1: Surfactants used for the formulation of microemulsions

S. No.	Surfactants
1	Cremophor RH 40
2	Tween 20
3	Tween 80
4	TPGS
5	Span 80
6	Labrafil M-1944CS
7	Labrasol
8	Gelucire 44/14

Cosurfactants

A cosurfactant, which is an amphiphilic molecule, is commonly seen in microemulsions. Along with the primary surfactant, it accumulates in the interfacial region. If the hydrophilic-lipophilic balance of the system needs to be changed, a combination of a low hydrophilic-lipophilic balance surfactant and a high hydrophilic-lipophilic balance surfactant is tried. The goal of using a cosurfactant is to change the system hydrophilic-lipophilic balance. In most cases, the amount of cosurfactant employed in the formulation is smaller than that of surfactant. Alcohols can behave as a cosurfactant, and nonionic surfactants can also be used as a cosurfactant. Single chain surfactants are frequently unable to lower the O/W interfacial tension to an acceptable level, necessitating introducing a cosurfactant. Phosphatidylcholine, phosphatidylethanolamine, phosphatidyl-glycerol, and their derivatives, synthetic ethanol, isopropanol, propanol, transcutol, polyethene glycol, propylene glycol, and others are examples of natural cosurfactants **[24, 25]**.

Single-chain surfactants cannot reduce the o/w interfacial tension sufficiently to generate a microemulsion. The inclusion of cosurfactants gives the interfacial layer enough flexibility to take on the various curvatures required to produce microemulsion throughout a wide range of compositions. Cosurfactants with short to medium chain lengths (C3-C8) are often used to lower interfacial tension and promote interface fluidity **[26]**.

Buffer

In the creation of microemulsions, phosphate and borate buffers and their combinations are used at low concentrations. Because they reduce the strength currently produced during migration, zwitterionic microemulsions are designed to allow greater voltages for speedier separation. Aminoethane sulfonic acid and N-cyclohexyl-3-aminopro-panesulfonic acid are examples of zwitterionic buffers. Buffers were primarily utilized in the pH range of 7 to 9. Low pH values below three are used to negate the negative voltages provided via the capillaries, allowing hydrophobic substances to be identified more easily. pH levels above 12 have two advantages: they prevent essential substances from ionizing and cause ionization in molecules like oestrogens, making them easier to detect **[27]**.

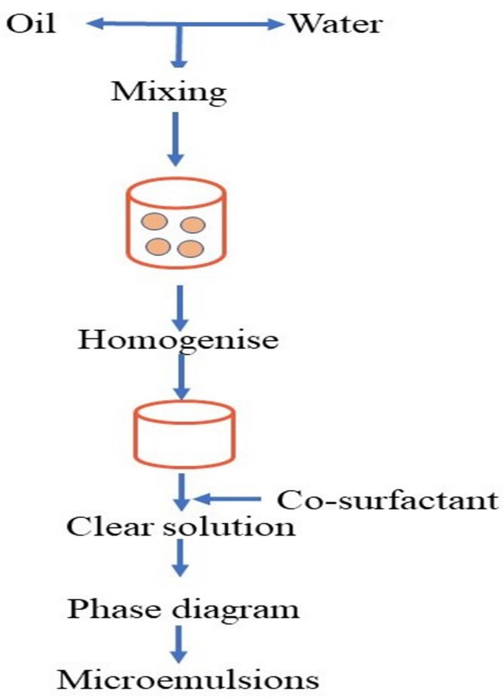

Figure 2: Schematic presentation of microemulsion preparation

Techniques for preparing microemulsions

The O/W kind of microemulsion is made by starting with a W/O emulsion containing a lipophilic surfactant. During the procedure, a hydrophilic surfactant is added with stirring, forming a cubical structure at first, but an O/W microemulsion is formed after more hydrophilic surfactant is applied. For the preparation of the W/O kind of microemulsion, use the exact opposite approach **[28]**.

Phase inversion

It's a technique for transforming a dispersed phase to a continuous phase and back. Surfactant configurations at the O/W interface very spontaneously, which is accompanied by phase inversion. The four methods can be used to achieve phase inversion.

• Changing the temperature of the system
• Adding salts
• Changing the volume fractions
• The introduction of certain flows, the morphology of the emulsion system changes dramatically when the experimental conditions change.

Phase titration

A triangle-shaped phase diagram can be used to demonstrate the phase titration method, which is one of the methods for preparing microemulsions. Ternary diagrams are three-dimensional phase diagrams that are triangular. They are simple to read and interpret, taking less time, and have three corners, each signifying 100% of the pure component. The materials are weighed into clean, dry vials, then titrated with water and swirled together. Visual inspection is used to determine if a monophasic or biphasic system has formed. If turbidity is followed by phase separation, the samples are assumed to be biphasic. After stirring monophasic systems, we can generate clear and transparent systems. In phase diagrams, these are referred to as points. The micro emulsification zone is the area occupied by these spots. Phase diagrams help describe the microemulsion system. The mixing of oil, water, and surfactant is depicted in a simple ternary diagram. Each triangle's corner symbolizes a pure compound. Each triangle's corner point indicates the composition of a two-component blend, whereas the point inside the figure represents a three-component blend. When the water content of the microemulsion is low, the localized structure consists of swelling inverse micelles near the oil corner of the phase diagram. The oil phase is continuous, while the dispersed phase is made up of water micellar droplets. Surfactant and cosurfactant are deposited at the water-oil interface. The shape and volume of the hydrophilic micelles' hydrophilic core expand as the water content rises. Because water is the

continuous phase, the microemulsion appears to be a natural micellar solution at the water corner. The system is a lamellar phase in the intermediate phase, when the water and oil phases are nearly identical in quality **[29, 30]**.

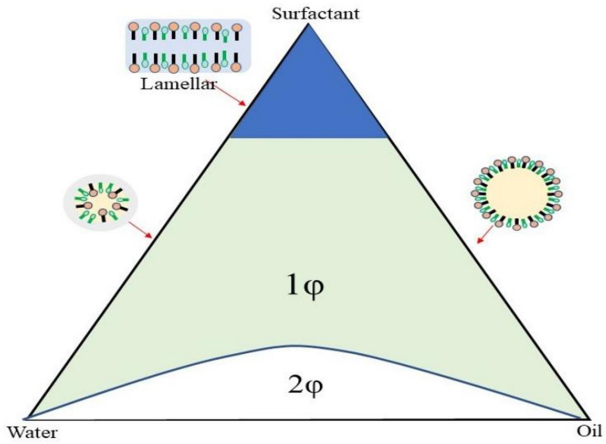

Figure 3: Microemulsion phase diagram

Microemulsion composition

The selection of emulsion components and their ratios is crucial in producing stable emulsion systems with acceptable particle sizes. A wide variety of components and combinations have been studied. Fatty acids (oleic acid), esters of fatty acids and alcohols (isopropyl myristate, isopropyl palmitate, ethyl oleate), medium-chain triglycerides, triacetin, terpenes (limonene, menthol, cineole), and other penetration enhancers are among the oil phase components. These can be used singly or in combination to create the oil phase. Preservatives and penetration enhancers and sodium chloride and buffer salts may be present in the aqueous phase **[31]**. Viscosity increasing agents (Gelatin) are added to the product to minimize fluidity and achieve the desired final consistency. Surfactants and cosurfactants have been made from a wide variety of materials. Combinations that successfully reduce interfacial tension and produce stable emulsions with adequate particle size while also ensuring minimal skin irritancy must be considered; consequently, non-ionic surfactants are preferred **[32]**. Because it is a natural chemical with a low skin irritancy profile, lecithin, an amphiphilic substance, has been widely explored as the "perfect" surfactant. Common cosurfactants are common for short and medium-chain alcohols and polyglycerol derivatives, such as ethanol, isopropanol, isopropyl myristate, and propylene glycol. Nonionic surfactants have also been utilized to create cosurfactants with reduced irritancy **[33]**.

Microemulsions have several merits over other dosing forms

- Microemulsions are used in a wide range of medication targeting and controlled drug release applications.
- Microemulsions can transport water-soluble medicines into the aqueous phase, demonstrating that they can transport both lipophilic and hydrophilic pharmaceuticals.
- Microemulsions have a broad range of applications since all major drug delivery routes can administer them.
- When compared to other biphasic dose forms, microemulsions have a longer shelf life.
- Microemulsions are created to maximize their distinctive qualities, such as minimizing hazardous side effects and reducing the amount of the transport vehicle.
- Because of their ease of use, they are significantly superior to conventional dosage forms.
- They offer resistance to hydrolysis and oxidation.
- They make it easier for patients to comply.

Pharmaceutical application of microemulsion

Topical application of microemulsions

Superficial fungal infections, such as deep skin mycoses, respond better to topical therapy than to other routes of administration. It mitigates the drug's adverse effects and enhances the effectiveness of its local action at the place of application. Antifungal drugs are predominantly lipophilic by nature, making them amenable to formulation in topical carriers. Because of their capacity for improved solubilization, microemulsions have a higher ability to carry large volumes of water and topical medications into the skin than water alone or other traditional carriers such as creams and lotions. They also operate as an ideal reservoir for poorly soluble pharmaceuticals. Microemulsions of antifungal drugs that are weakly soluble, such as miconazole nitrate, have been successfully created. In vitro methods were used to compare micro emulsion-based gels for vaginal administration of clotrimazole and fluconazole to a commercially available clotrimazole gel. Compared to traditional carriers such as pure oils, emulsions, and aqueous solutions, microemulsions have been shown to improve the cutaneous absorption of both hydrophilic and lipophilic medicaments. This microemulsion behaviour is usually linked to the high solubility of the medicament in the microemulsions, which results in a higher concentration gradient towards the skin. In terms of applications for transdermal medication administration, microemulsions have gained a lot of

traction. Curcumin has been widely used to treat various disorders, including skin cancer, psoriasis, and scleroderma. Microemulsions can be used as a carrier system for ascorbic acid, which can be used as a whitening agent **[34]**.

Furthermore, an excellent drug-in-drug transit could be interesting for the relative oxygen matrix damage. The optimal formulation for delivering the entire dose and improving skin penetration was a microemulsion comprising diethyl glycol monoethyl ether. The antifungal activity test against Candida albicans yielded the best results for this microemulsion. As a result, these microemulsions appear to be very promising for clinical testing. For the treatment of psoriasis, a microemulsion gel containing betamethasone dipropionate and salicylic acid shows good anti-inflammatory action **[35]**.

Ocular drug delivery

To treat eye problems, drugs are applied topically. O/W microemulsions have been used in ocular administration to dissolve poorly soluble medicines, enhance absorption, and extend the release profile. Lecithin, propylene glycol and PEG 200 were used as cosurfactants, while isopropyl myristate was used as the oil phase in pilocarpine microemulsions. Microemulsions have many benefits as ocular delivery carriers, including low surface tension, thermodynamic stability, a phase transition to liquid crystal state, and small particle size, all of which may contribute to improved ocular retention, high absorption, long duration of action, and enhanced permeation of loaded drugs. Microemulsions provide benefits such as sterilization ease, particular shapes, stability, and the ability to dissolve pharmaceuticals **[36]**.

Nasal delivery

Intranasal medication administration allows pharmaceuticals to skip the blood-brain briar and enter the brain directly, avoiding substantial hepatic and intestinal processing. This method is both convenient and trustworthy. Drugs are delivered to the brain via olfactory, neuronal, and trigeminal routes using various novel formulations **[37, 38]**. Microemulsions, an optically isotropic and thermodynamically stable system made of oil, water, and surfactant, are a promising and new formulation for delivering lipophilic medicines to the brain via the intranasal route. It offers the advantages of acceptability, biodegradability, and quick absorption by the brain because of its high solubilization of lipophilic medicines, stability, ease of manufacture, and handled stabilization of hydrolytically sensitive substances. The oil phase, which has propylene glycol and surfactant and co-surfactant, was used to create

nanoemulsions for a delivery system via the nasal route to treat depression. Compared to the oral paroxetine control groups, intranasal treatment of depressed rats with paroxetine microemulsion considerably increased behavioural activity **[39, 40]**.

Parenteral drug delivery

Parenteral delivery of medications with low solubility is a big issue since only a small amount is delivered to the intended site. When supplied parenterally, microemulsion formulations have significant advantages over macroemulsion systems because fine particle microemulsions clear more slowly than coarse particle emulsions and have a longer residence time in the body **[41, 42]**.

Cosmetics

Cosmetics are another essential application for microemulsions. Microemulsions have numerous applications in the cosmetics industry. The advantages of microemulsions are high solubilization power, thermodynamic stability, and ease of production. They can improve the penetration of laden substances through the skin. Microemulsion formulations decrease toxicity while increasing production efficiency **[43]**. Microemulsions could be used as aesthetic agents as well as pharmaceutical drug delivery systems. They boost the bioavailability of hydrophobic medicines due to their high oil content. There is evidence that microemulsions can regulate and control drug release patterns in a therapeutic setting. Microemulsions are also utilized in the development of new cosmetics and the preservation of products. It is claimed that the skin absorbs cosmetics based on microemulsions. Because some amphiphiles are not acceptable for personal healthcare goods, cost and safety are the most important requirements for microemulsion formulations in cosmetics **[44, 45]**.

CONCLUSION

Microemulsions are a widespread technology platform among pharmaceutical formulators because of their high transparency and straightforward formulation procedure. The importance of microemulsion systems in delivering unique solutions to tackle the difficulties of poor water solubility of highly lipophilic medicinal molecules and give high, consistent, and repeatable bioavailability is critical.

Acknowledgement

Conflict of Interest

Nil

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