



## Review Article

# Microemulsion-Based Topical Therapies: Exploring New Potential

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### ARTICLE INFO

Received: 13 Aug 2024

Accepted: 17 Aug 2024

Published: 18 Aug 2024

#### Keywords:

Topical drug delivery,  
Microemulsion, Colloidal  
system

#### DOI:

10.5281/zenodo.13337270

### ABSTRACT

Lipid-based pharmaceutical systems called microemulsions have a great deal of promise for improving medication absorption via the skin. Stable oil-in-water emulsions with droplet sizes between approximately 100 and 400 nm are known as microemulsions. These systems' internal oil phase aids in the solubilization of lipophilic medications, resulting in high encapsulation. When administering poorly soluble medications topically, there are several advantages over oral delivery, chief among them being the avoidance of first-pass metabolism. By applying the medication directly to the problematic area, this method minimizes the amount of medication required and lowers the possibility of adverse effects, making it very helpful for treating skin diseases. Lipophilic barriers can be effectively overcome by microemulsions, which have been successfully used in the formulation of synthetic and natural chemicals to improve therapeutic stability, delivery, and efficacy.

### INTRODUCTION

In order to maintain homeostasis, the skin acts as a vital barrier, shielding the body from external chemicals and germs while also limiting excessive water loss. The stratum corneum (Figure no. 1), which is distinguished by its distinct structure of layers of flattened corneocytes surrounded by lipid bilayers mainly formed of ceramides, is where the skin's principal barrier function is found. The majority of compounds given topically pass through the stratum corneum's complex lipid bilayers through the intercellular pathway, while in some circumstances the transcellular pathway

via the corneocytes may also be involved. Hair follicles (and their related sebaceous glands) and sweat glands give possible entrance routes into the skin, while making up just around 0.1% of the total skin surface area. This may be especially important for nanotechnology-based systems [1]. Usually, compounds that can successfully pass through the stratum corneum are water-soluble, lipophilic, and tiny (up to 500 Da). This restricts the delivery of numerous potentially helpful treatment drugs that don't fit these requirements. In response, a number of micro- and nanoscale systems have been investigated as means of

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



enhancing the skin penetration of tiny and macromolecules that would not otherwise be able to reach the stratum corneum in sufficient quantities to be therapeutically effective. With a focus on microemulsions in particular, which are an improvement over conventional topical formulations used in medicines, cosmeceuticals, and personal care products.

#### **MICROEMUSION:**

The word "microemulsions" first appeared in 1959 after Schulman et al. observed tiny emulsion-like formations using electron microscopy. Microemulsions are clear, translucent, isotropic, thermodynamically stable mixtures of water, oil, and surfactant—often with a cosurfactant added for additional stability. Droplet diameters range from 20 to 200 nm on average. These homogeneous systems typically have low viscosities and can be produced with variable oil-to-water ratios and surfactant concentrations [2].

Two immiscible liquids, such as water and oil, are mixed into a single phase using an appropriate surfactant or a mixture of surfactants to generate stable isotropic systems known as microemulsions. In several of these systems, co-surfactants with short to medium chains are utilized. Microemulsions with droplet sizes ranging from 10 to 140 nm can form spontaneously when surfactants and co-surfactants are added, as they significantly decrease the interfacial tension.[3]. Due to these benefits, microemulsions have attracted a lot of interest as possible medication delivery systems [4]. These formulations are renowned for their superior thermodynamic stability, improved drug solubilization, and simplicity of manufacture. Due to their flexibility, microemulsions can be used for a wide range of medication delivery methods, with a significant emphasis on topical uses. They provide a number of ways to enhance systemic or local medication delivery. Both water- and oil-soluble materials can be dissolved when there are

microdomains with different polarity present in a single-phase solution. Moreover, the composition of microemulsions can alter the drug's thermodynamic activity and change the skin's diffusional barrier, which may enhance the drug's skin partitioning [5-8].

#### **ADVANTAGES: [9-10]**

1. Drugs can be effectively dissolved in aqueous or hydrophobic solvents by using microemulsions, which can dissolve both hydrophilic and lipophilic compounds, even those with limited solubility.
2. They can transport both hydrophilic and lipophilic drugs.
3. The broad applicability of these systems in colloidal drug delivery, which improves drug targeting and enables controlled release, makes them desirable.
4. Because microemulsions have fundamental thermodynamic stability, they are easy to manufacture and require little energy.
5. Drug efficacy can be improved by using microemulsions as delivery vehicles, which may result in a lower dosage requirement and less side effects.
6. They have the ability to accelerate medication absorption.
7. They contribute in decreasing absorption variability.

#### **DISADVANTAGES: [11-13]**

1. The stabilization of the droplets requires a significant amount of surfactants.
2. The stability of microemulsions is influenced by external influences, including temperature and pH.
3. They have a limited capacity to solubilize materials with high melting points.

#### **STRUCTURE OF MICROEMULSION:**

Micro emulsion are dynamic systems in which the interface varies continually and on its own. Based on their structural characteristics, they can be divided into three types: bicontinuous



microemulsions, water-in-oil (w/o), and oil-in-water (o/w). Water droplets are distributed across a continuous oil phase in w/o microemulsions, while oil droplets are distributed throughout a continuous aqueous phase in o/w microemulsions. Bicontinuous microemulsions can develop when the amounts of oil and water are approximately equal. Depending on the ratios of each ingredient, the mixture of oil, water, and surfactants can result in a vast range of structures and phases. The nature of a colloidal system is also influenced by the characteristics of the continuous and discontinuous phases. Both water and oil (w/o) and oil and water (o/w) can form a colloidal dispersion as shown in (figure no.2). Oil-in-water (o/w) emulsions, which facilitate the transport of lipophilic compounds within the internal phase, are the most widely utilized emulsions in the pharmaceutical industry [14]. Because these emulsions make it easier for hydrophilic substances to pass through the stratum corneum of the skin, they are especially well suited for topical treatments. However, o/w emulsions usually do not form spontaneously because of their thermodynamic instability. Rather, they are often created by homogenizing the two immiscible phases using mechanical stirring. The stability of the emulsion may be threatened when the external force is removed, which could result in phase separation and ultimate characteristic degradation [15]. The phenomenon indicated is the consequence of interphase tension, which is the difference in the forces of attraction between the molecules in the two liquid phases. These interactions can be classified into three categories: (i) stable particle collisions form a film, which may lead to flocculation; (ii) dominant attractive forces between droplets cause the film to break and become unstable, which may lead to foaming or coalescence; (iii) stronger repulsive forces cause the colliding particles to repel one another, preventing aggregation and phase separation and

improving system stability. Therefore, droplet interactions cause emulsions to exhibit metastable colloid behaviour, which is typified by flocculation, creaming, and separation. A number of techniques, such as solid particle stabilization or electrostatic and steric stabilization, can be used to reduce these effects and preserve emulsion stability. Surfactants, on the other hand, are largely responsible for the stability of the majority of pharmaceutical formulations [16].

#### **TYPES OF MICROEMULSION: [17]**

Water and oil can naturally generate translucent or transparent systems when combined with a considerable number of surfactants and co-surfactants. Microemulsions were classified into Winsor I, Winsor II, and Winsor III varieties as study on them developed, as shown in Figure no. 3). An oil-in-water (O/W) microemulsion of the Winsor I type occurs when surfactants help a small amount of oil dissolve in water. This is known as a lower phase microemulsion; in this case, water serves as the continuous phase and oil as the dispersed phase. The Winsor II type, on the other hand, is a water-in-oil (W/O) microemulsion in which surfactants solubilize a little amount of water in oil, forming an upper phase microemulsion where the oil is the continuous phase and the water is the dispersed phase. Because of the action of surfactants, the Winsor III type has a unique structure in which a third phase forms a "bicontinuous" network structure between the phases of excess oil and water. In this kind, known as the middle-phase microemulsion, water and oil operate as continuous phases and usually involve equal amounts of each.

#### **COMPONENTS OF MICROEMULSION: [18-24]**

The formulation of microemulsions include the use of a variety of substances, the main ones being oils and surfactants. Clinically acceptable, non-toxic, and biocompatible substances are required.



Some of a microemulsion's main ingredients include:

1. Oil phase
2. Aqueous phase
3. Surfactant
4. Co-surfactant

#### **Oil phase:**

Oil selection is based on the desired method of administration as well as the properties of the medication. The medicine needs to be well-dissolved by the chosen oil. Oils can cause the surfactant tail groups to enlarge and have a major effect on the system's curvature. Immersion-improving qualities are innate to both unsaturated and saturated fatty acids. Through their ability to break up dense lipid packing and fill extracellular gaps in the stratum corneum, these fatty acids improve permeability.

#### **Aqueous phase:**

An aqueous phase containing hydrophilic active ingredients such as preservatives and buffers may be included.

#### **Surfactant:**

The selected surfactant should have the ability to significantly decrease interfacial tension, which facilitates the dispersion process when preparing microemulsions. Together with having the right lipophilic properties to provide the required curvature at the interface, it should also form a flexible film that is easily bendable around the droplets. Surfactants with a low HLB (hydrophilic-lipophilic balance) are generally favored for w/o (water-in-oil) microemulsions, whereas surfactants with a high HLB (>12) are best for o/w (oil-in-water) microemulsions. Co-surfactants are frequently required to reduce the effective HLB of surfactants with an HLB greater than 20 to a range that is appropriate for the generation of microemulsions. Four types of surfactants are commonly identified as cationic, non-ionic, zwitterionic, and anionic surfactants.

- **Anionic surfactants:**

These are the most frequently utilized surfactants, with a negative charge, which make up almost half of global production.

- **Cationic surfactants:**

These surfactants are usually more expensive and contain a positive charge as compared to anionic surfactants.

- **Non-ionic surfactants:**

They are stabilized by hydrogen bonding and dipole interactions made possible by their hydrophilic surface hydration layer. Because the hydrophilic group of non-ionic surfactants does not dissolve, they do not ionize in aqueous solutions. Two examples are phenols and alcohols.

- **Zwitterionic surfactants:**

These surfactants have both positive and negative charges. In most instances, they require a cosurfactant to produce microemulsions. Lecithin is one of the most commonly used zwitterionic surfactants.

#### **Co-surfactant:**

Usually, single-chain surfactants are insufficient on their own to create a microemulsion by reducing the oil-water interfacial tension. The interfacial film gains the flexibility it needs to adopt different curvatures for microemulsion production in a wide variety of compositions by the inclusion of cosurfactants.

#### **METHOD OF PREPARATION: [25]**

##### **1. Phase Titration Method:**

Phase titration, usually referred to as spontaneous emulsification, is a regularly used technique to prepare microemulsions. Phase diagrams are useful for illustrating the behavior of these materials. Designing these schematics is an effective way to investigate the complicated interactions that emerge when different parts are assembled together. Depending on the concentration and chemical composition of the constituents, microemulsions can form a variety of association structures, including gels, oily



dispersions, lamellar phases, hexagonal phases, cubic phases, emulsions, and micelles. Studying these systems involves determining the phase boundaries and determining the phase equilibrium. Pseudo-ternary phase diagrams are usually used to replace of quaternary phase diagrams, which are complicated and difficult to read because they comprise four components. Each corner of a pseudo-ternary phase diagram indicates 100% of a specific component, and the various zones including the microemulsion zone are indicated. These diagrams aid in determining the composition of the microemulsion, or whether it is mostly made of water or oil, and thus assist determine if it is water-in-oil (w/o) or oil-in-water (o/w). To make sure that metastable systems are not included, it is crucial to closely examine these diagrams shown in (figure no. 4).

## **2. Phase Inversion Method:**

While additional dispersed phase is incorporated into microemulsions, phase inversion may result from temperature variations or by spontaneously. Drug release can be affected by this phase inversion in both in vitro and in vivo settings due to the substantial physical changes it includes, including changing particle sizes. It is based on altering the surfactant's spontaneous curvature. Phase inversion for non-ionic surfactants can be accomplished simply changing the temperature. The system can create an oil-in-water (o/w) microemulsion at low temperatures and change to a water-in-oil (w/o) microemulsion at higher temperatures. The Phase Inversion Temperature (PIT) method is the name given to this temperature-induced phase inversion. As the system cools, it approaches a state of zero spontaneous curvature and low surface tension, which makes it easier for finely distributed oil droplets to form. Phase inversion can also be influenced by variables like pH or salt concentration in addition to temperature. Furthermore, changing the water volume fraction

might cause phase inversion. Water droplets are first distributed in the continuous oil phase by gradually adding water to an oil phase. The surfactant's spontaneous curvature shifts as the water volume percentage increases, going from stabilizing a w/o microemulsion to generating an o/w microemulsion at the inversion point. Using short-chain surfactants results in the formation of flexible monolayers at the o/w interface, which at the inversion locus creates a bicontinuous microemulsion.

## **CHARACTERIZATION OF MICROEMULSION: [26-30]**

An experiments process is frequently used to produce microemulsion formulation, utilizing characterisation techniques such as conductivity, viscosity, zeta potential, droplet size, and turbidity. Even while these methods might not give a whole depiction, they do give formulators important information about the characteristics of the microemulsion system, which helps in the development process.

### **Droplet size:**

Microemulsion droplet sizes typically range between 10 and 100 nm, though this may vary depending on a variety of factors. These factors have been thoroughly discussed in previous conversations. However, research has documented droplet sizes below 100 nm and approximately 200 nm in an attempt to improve the administration of two well-known medications incorporated into SMEDDs: saquinavir, an HIV protease inhibitor, and cyclosporine A, an immunosuppressant.

### **Zeta potential**

Zeta potential is a measurement of the surface charge of emulsion droplets and gives important details about the charge interactions (attractive or repulsive) that could occur between droplets in an emulsion system. Phase separation is mostly avoided by delaying processes like flocculation and coalescence, which are facilitated by this type of electrostatic repulsion. As a result, zeta



potential is frequently taken of as a measure of emulsion stability. It is a common misconception, however, that zeta potential values especially those above  $\pm 30$  mV are the only reliable indications of stability. Monitoring the zeta potential of droplets over time or calculating the rate of change in zeta potential yields a more precise measure of stability.

### **Electrical conductivity**

The type of microemulsion that has formed can frequently be confirmed using electrical conductivity. Hydrogen is a powerful ion conductor, hence microemulsions containing more water generally have greater conductivity values. Several broad patterns can be observed, even if the particular conductivity values might change depending on the oil or surfactant employed. Water-in-oil microemulsions, or inverse microemulsions, are recognized for their extremely low electrical conductivity, which is typically between  $10^{-5}$  and  $10^{-2}$  S/m. More recent research has found even lower electrical conductivity values, ranging from  $10^{-7}$  to  $10^{-9}$  V<sup>-1</sup> cm<sup>-1</sup>. On the different hand, oil-in-water microemulsions can have electrical conductivity values that are  $10^4$ – $10^3$  times greater. Noting that the particular components of the microemulsion have an impact on these values is significant. This characteristic is especially clear for microemulsions that contain ionic surfactants. To obtain measurable electrical conductivity, a salt such sodium chloride must be added to those containing non-ionic surfactants.

The lipophilicity of microemulsions increases when they go from Type I to Type III and finally to Type II as a result of rising temperatures or concentrations of salt. Conductivity is an excellent tool to track this change because it typically decreases gradually, with notable drops at each transition point. Formulators are able to identify these important breaking moments during a change due to this.

### **Viscosity**

Due to viscosity influences both the diffusion constant and droplet interactions, it is essential to understanding the stability of a microemulsion system. The diffusion constant of the system is directly correlated with the viscosity of the continuous phase. Phase separation can occur as a result of droplet collisions, however as viscosity increases, the diffusion constant decreases. Higher viscosity thus improves stability by lowering the frequency of these impacts. The composition of the emulsion can affect individual viscosity values, but typically, surfactant concentration increases cause different micellar structures to develop, which raise viscosity overall.

### **Turbidity**

Turbidity can frequently be a measure of droplet size; larger droplets scatter light more readily, which causes more turbidity. Because of their smaller droplets' reduced ability to scatter light, microemulsions tend to be transparent or very slightly turbid, which are usually opaque and turbid. But there's a significant distinction between W/O (water-in-oil) and O/W (oil-in-water) microemulsions. In O/W microemulsions, a layer of surfactant surrounds the oil droplets, while in W/O microemulsions, the surfactant surrounds the water droplets. Because of this difference, O/W microemulsions frequently have an opaque color as opposed to W/O microemulsions' typically clear appearance.

### **APPLICATION OF MICROEMULSION: [31-34]**

The pharmaceutical industry has extensively investigated microemulsions due to their unique properties and their applications in drug delivery. They are an appropriate choice for improving drug delivery because of their ability to distribute both hydrophilic and hydrophobic medicines, as well as their optical clarity and thermodynamic stability. Microemulsions demonstrate great promise in improving medication delivery over time and



resolving bioavailability problems. They have been used in oral, topical, and parenteral medication delivery techniques, among others. Drugs that are poorly soluble can have their bioavailability increased by oral microemulsions. Using topical microemulsions to improve drug distribution via the skin performs effectively. Parenteral microemulsions are used to target the lymphatic system and provide lipophilic medications.

The potential of microemulsions to improve topical medication administration is the main topic of this review. Studies indicate that microemulsions can greatly increase the drug's skin penetration and retention, as the method shown in (Figure no. 5). medicines such as antifungal therapies, anti-inflammatory drugs, and anti-cancer medication. have been all successfully applied topically using them. Because they can pass through the lipid bilayers of the skin thanks to their small droplet size typically less than 100 nm microemulsions are particularly effective in transdermal medication administration.

#### **FUTURE PERSPECTIVES: [35]**

As lipid-based drug delivery systems, microemulsions (MEs) have attracted a lot of attention. This is especially because of their potential use in topical and systemic drug delivery via the skin. For improving the stability and attaining a prolonged release of encapsulated herbal compounds, these technologies hold particular promise. MEs have demonstrated promise in topical applications for enhancing skin penetration, which may boost the potency of the chemicals they contain. Research has shown that MEs are generally safe for topical application, even if they contain high amounts of nonionic surfactants. Their usefulness for such uses has been supported by studies that consistently indicate no skin discomfort even after long-term application. Another of the appeal of ME formulations is that the components are often

permitted for use in topical medicines and cosmetics. MEs are also beneficial in terms of production because they are simple to make using basic agitation techniques and use little energy. According to this data, MEs may develop into efficient topical medication delivery systems, especially for herbal cosmeceuticals. In comparison to conventional formulations, microemulsions may provide better therapeutic results by improving the transport of active components through the stratum corneum.

#### **CONCLUSION:**

A particularly promising delivery and administration route for drugs is through the skin. Its benefits include avoiding the first-pass effect, having a broad application surface area, maintaining consistent medication concentrations in the bloodstream, and overall convenience. Because of their special qualities, which aid in overcoming the stratum corneum barrier, microemulsions are useful carriers for improving medication absorption and penetration into the skin. Through the incorporation of nonpolar chains into their more polar structures, these systems can also address bioavailability difficulties by improving the solubility of hydrophilic medicines. Similar to this, the addition of polar chains to nonpolar components of lipophilic compounds increases their efficacy. Microemulsions, which can be composed of various oils, surfactants, co-surfactants, and water-based components, offer several benefits as drug delivery systems. These include their ability to dissolve both hydrophilic and hydrophobic drugs effectively, their thermodynamic stability, ease of formulation, and cost-effectiveness. In some instances, microemulsions can enhance drug accumulation at the target site, improving drug targeting while minimizing systemic side effects. When applied topically, microemulsions have been found to significantly boost the skin absorption of drugs. These systems often function as penetration



enhancers, though this effect can vary depending on the specific oil and surfactant used, which may sometimes lead to local skin irritation. The process of drug permeation through the skin is intricate, but recent research has shed light on the mechanisms involved, helping to better understand and control skin permeability. This growing knowledge at the molecular level is crucial for the development of more effective topical formulations that enhance drug bioavailability while reducing potential side effects

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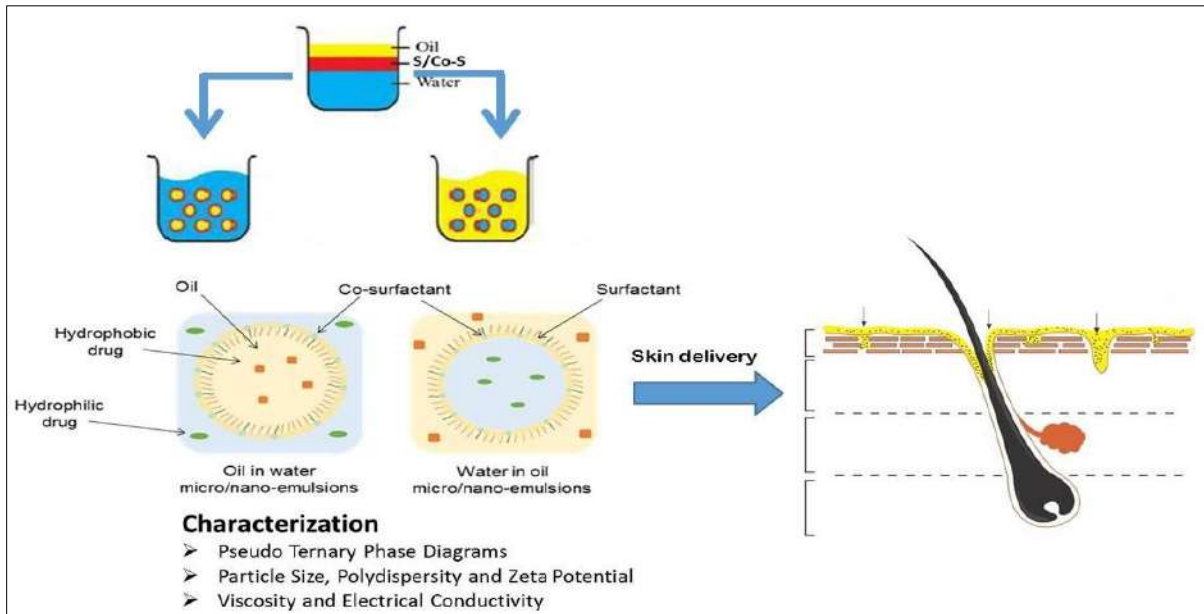


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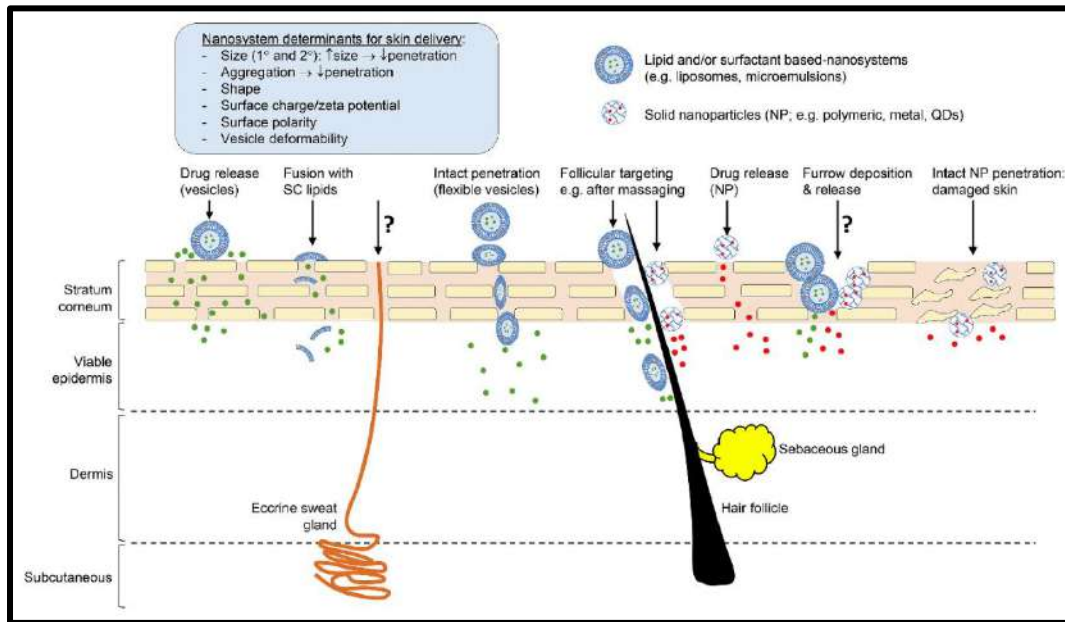
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**HOW TO CITE:** Mayuri Mhatre , Gangotri Yadav, Ashish Jain, Microemulsion-Based Topical Therapies: Exploring New Potential, *Int. J. of Pharm. Sci.*, 2024, Vol 2, Issue 8, 3347-3359. <https://doi.org/10.5281/zenodo.13337270>





**GRAPHICAL ABSTRACT**



**Figure No. 1 Characteristics of nanosystems influencing skin absorption and possible penetration pathways**

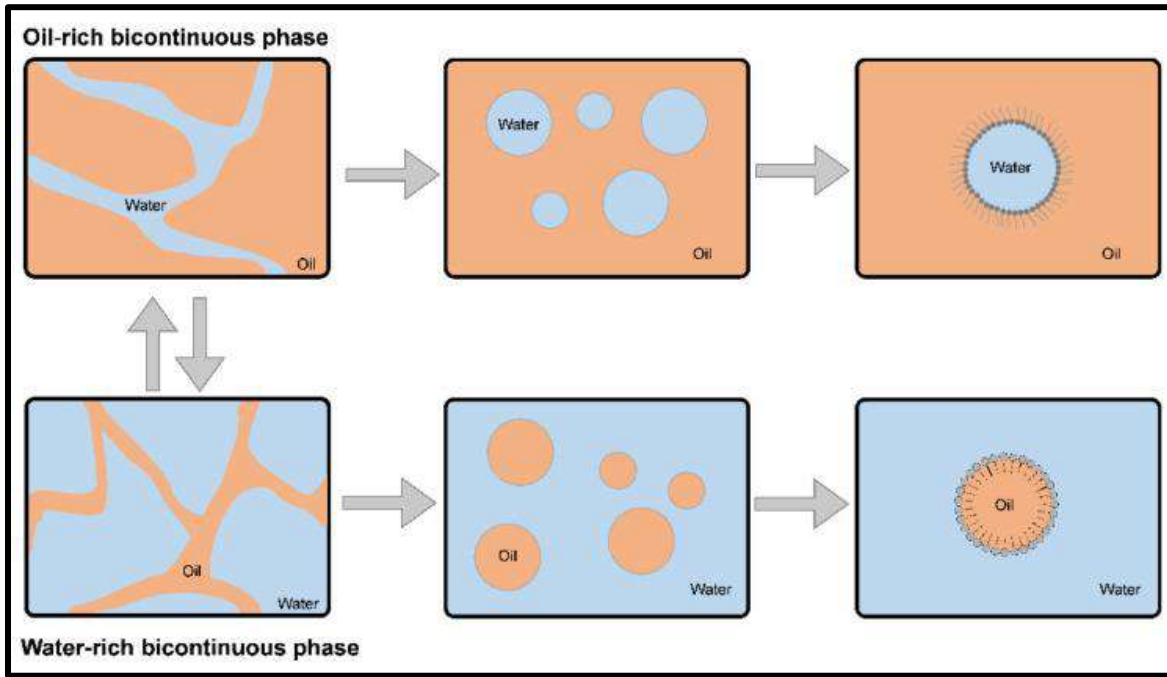


Figure No. 2 Illustration of o/w and w/o colloidal dispersions

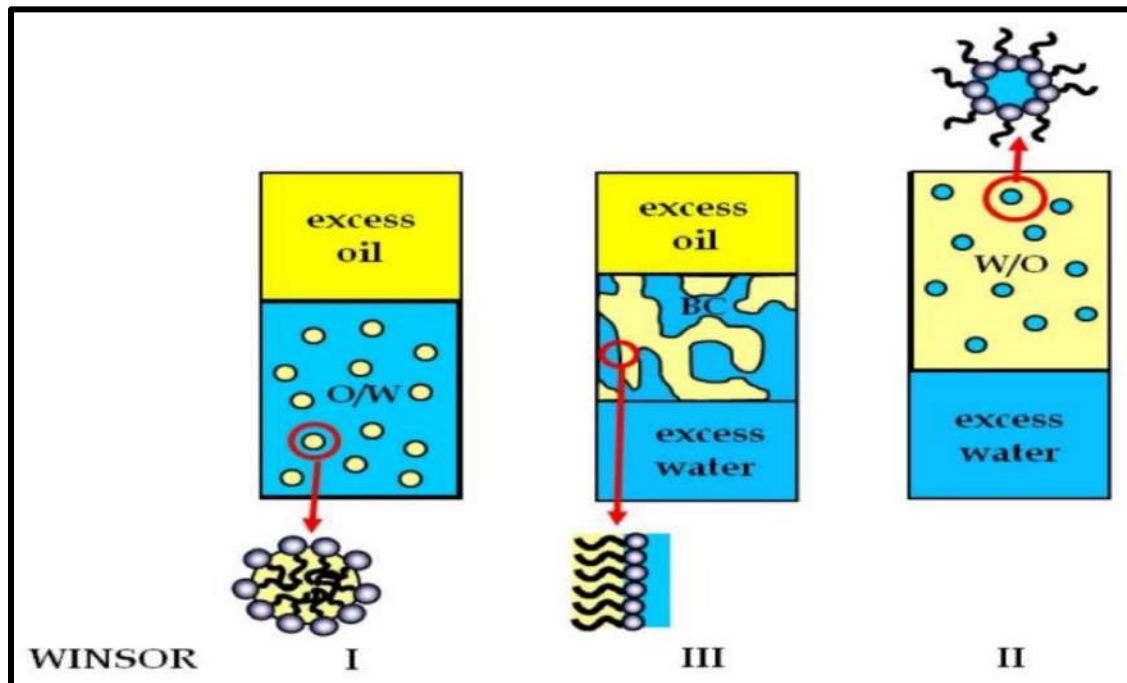


Figure No. 3 Winsor Classification of Microemulsion

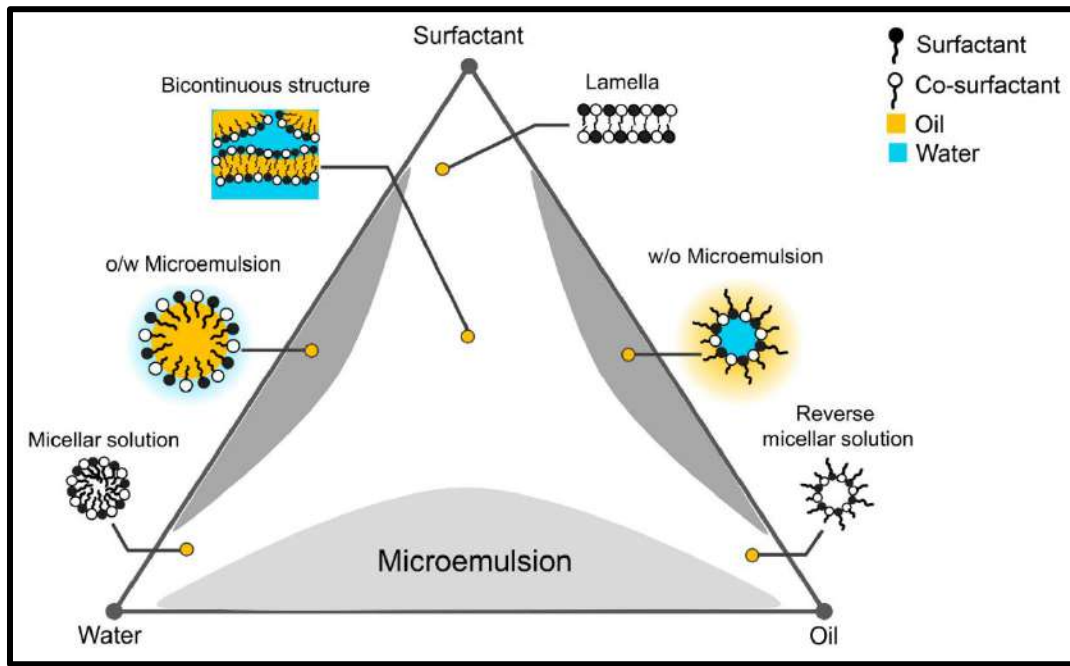


Figure No. 4 A pseudoternary phase diagram displaying the microemulsion region for oil, water, and surfactant

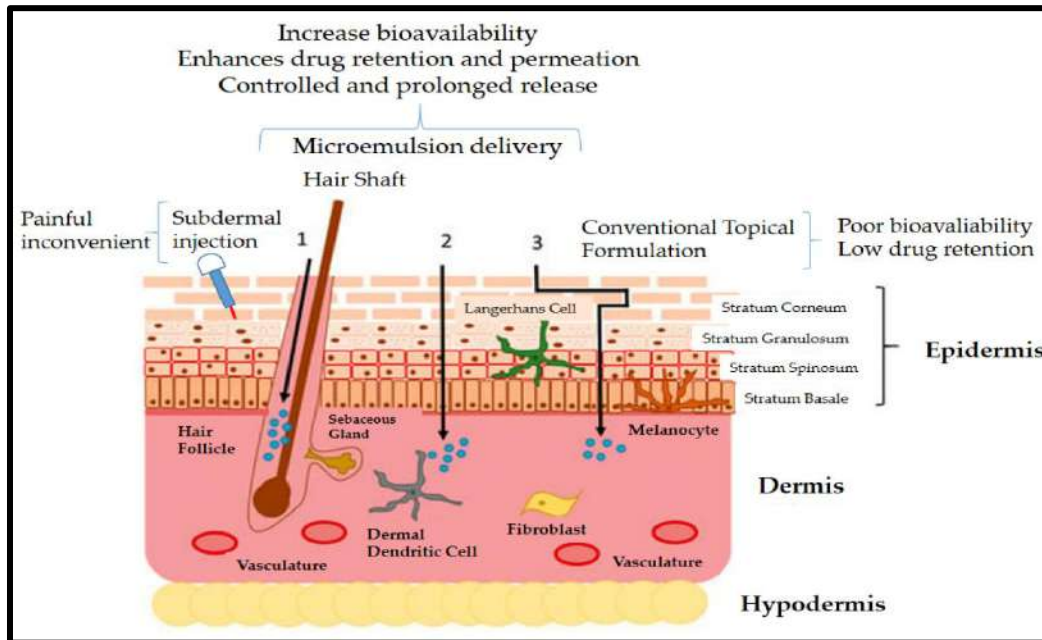


Figure No. 5 Illustration of the several skin penetration pathways used by microemulsions