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Microemulsion-Based Drug Delivery Systems: Harnessing Nanostructures for Enhanced Therapeutic Efficacy

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ABSTRACT

Microemulsions represent a unique class of dispersions characterized by their transparent or translucent appearance. These systems have garnered significant attention as promising drug delivery vehicles due to several advantageous properties. Notably, microemulsions offer prolonged shelf life, enhanced drug solubilization, and ease of preparation and administration. Comprising thermodynamically stable and optically isotropic liquid solutions of oil, water, and amphiphile, they maintain constant droplet sizes typically ranging from 10 to 100 nm, along with minimal oil/water interfacial tension. As such, microemulsions serve as versatile carriers for controlled or sustained drug release across various administration routes including ocular, percutaneous, topical, transdermal, and parenteral applications. Importantly, they effectively enhance drug therapeutic efficacy while minimizing toxic side effects by reducing the volume of the drug delivery vehicle. Moreover, microemulsions facilitate the absorption of lipophilic drugs by aiding in their solubilization within cell membranes, further underscoring their potential as valuable tools in pharmaceutical formulations

Keywords: Microemulsion; surfactants; co-surfactants; Drug Delivery; Dispersions: Nanotehchbology

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1. Introduction

In the realm of pharmaceuticals, the quest for advanced drug delivery systems has led to the exploration of various innovative technologies. Among these, microemulsions have emerged as a particularly promising approach due to their unique properties and versatile applications. Microemulsions represent a distinct class of dispersions characterized by their transparent or translucent appearance, comprising thermodynamically stable liquid solutions of oil, water, and amphiphile. These systems offer several advantages that make them highly attractive for drug delivery purposes. With prolonged shelf life, improved drug solubilization, and ease of preparation and administration, microemulsions present a compelling option for enhancing therapeutic efficacy while minimizing adverse effects. One of the key features of microemulsions is their ability to maintain constant droplet sizes within the nanometer range (10-100 nm), along with minimal oil/water interfacial tension. This stability and uniformity contribute to their effectiveness as drug carriers, allowing for controlled or sustained release across a range of administration routes. From ocular to percutaneous, topical, transdermal, and parenteral applications, microemulsions offer versatile delivery platforms that can accommodate various therapeutic needs. Moreover, the unique properties of microemulsions extend beyond simple drug delivery. By reducing the volume of the drug delivery vehicle, these systems help minimize toxic side effects associated with conventional formulations. Additionally, in the case of lipophilic drug administration, microemulsions facilitate absorption by aiding in the solubilization of lipophilic components within cell membranes. In light of these advantages, the exploration of microemulsions as drug delivery systems holds significant promise for advancing pharmaceutical science and improving patient outcomes. This review aims to provide a comprehensive overview of microemulsion-based drug delivery, highlighting their formulation principles, applications, and potential impact on therapeutic efficacy. By delving into the intricacies of microemulsion technology, we hope to shed light on its role as a transformative tool in modern pharmacotherapy [1].

2. Structure of Microemulsion

The structure of microemulsions, also known as micellar emulsions, is characterized by dynamicity, with the interface continuously and spontaneously fluctuating. Structurally, microemulsions can be categorized into three main types: oil in water (o/w), water in oil (w/o), and bi-continuous microemulsions. In w/o microemulsions, water droplets are dispersed within the continuous oil phase. Conversely, o/w microemulsions form when oil droplets are dispersed within the continuous aqueous phase. Bi-continuous microemulsions occur when the amounts of water and oil are balanced, resulting in a system where both phases are interconnected and continuous.

The combination of oil, water, and surfactants in microemulsions can lead to a wide variety of structures and phases, depending on the proportions of each component. These structures play a crucial role in determining the properties and behavior of microemulsions, influencing factors such as stability, drug solubilization, and release kinetics. Understanding the structural characteristics of microemulsions is essential for optimizing their formulation and application in drug delivery and other industrial processes [2].

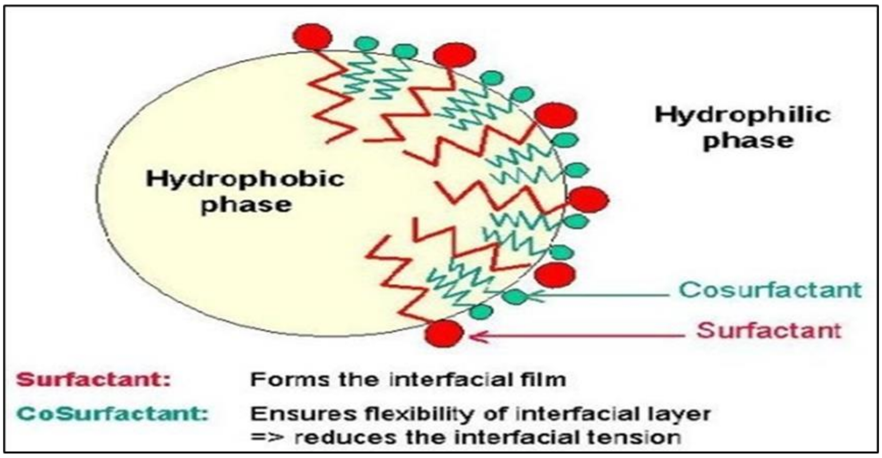


Fig.1: Structure of microemulsion

Advantages

Microemulsions offer a myriad of advantages as drug delivery systems. Firstly, they exhibit thermodynamic stability, ensuring self-medication and prolonged shelf life without the need for constant monitoring. Secondly, their versatility in solubilizing both hydrophilic and lipophilic drugs expands the scope of therapeutic compounds that can be effectively delivered. Additionally, microemulsions possess low viscosity compared to primary and multiple emulsions, facilitating ease of administration and patient compliance. Their straightforward preparation process, coupled with their inherent thermodynamic stability, eliminates the need for additional energy input during formulation. Moreover, microemulsions act as super solvents for drugs, with the capacity to solubilize compounds insoluble in both aqueous and hydrophobic solvents, thereby broadening the range of drugs that can be incorporated. Furthermore, they enhance drug bioavailability by promoting partitioning into the skin and facilitating drug diffusion, particularly beneficial for topical and transdermal applications. Overall, microemulsions serve as effective vehicles for poorly water-soluble drugs, offering enhanced solubilization and bioavailability while providing a versatile platform for drug delivery [3].

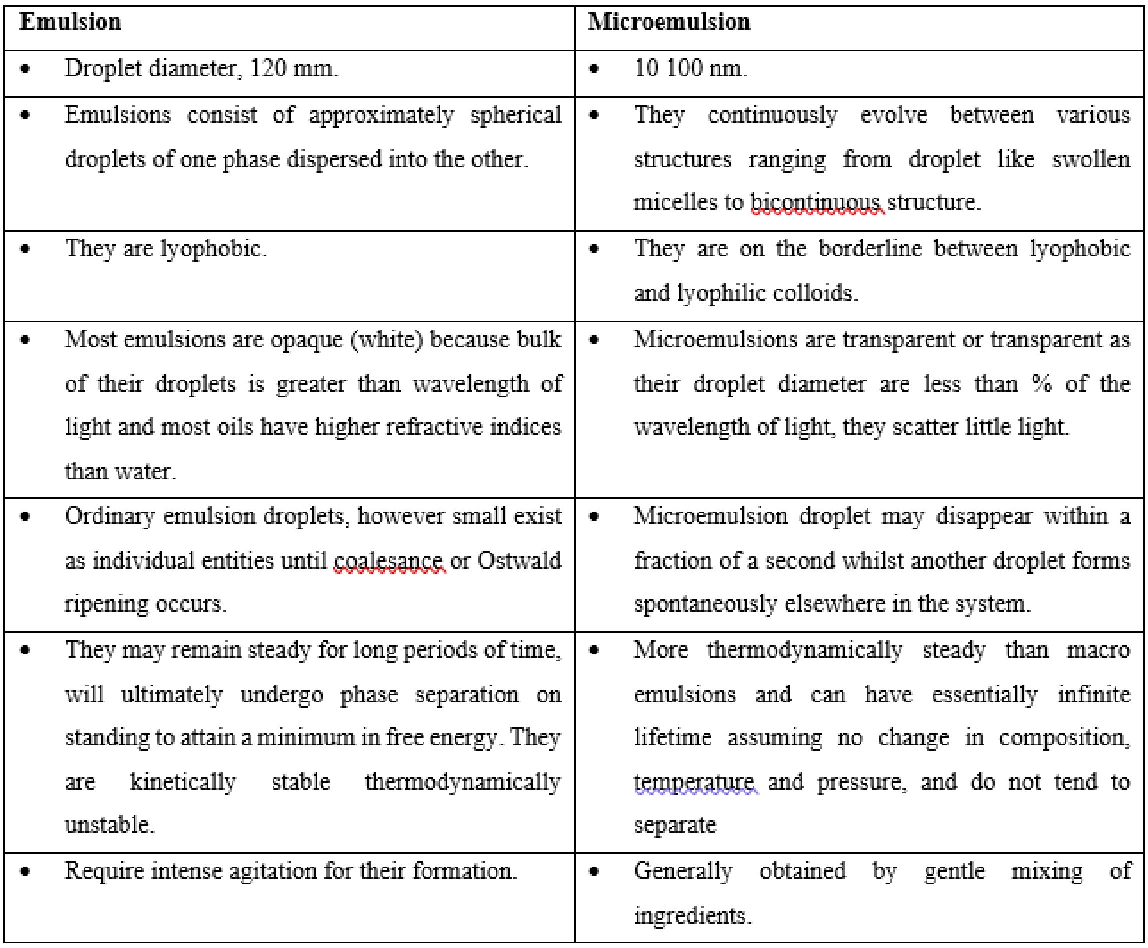
Disadvantages

Microemulsions, while offering significant advantages as drug delivery systems, also present notable disadvantages. Firstly, they may exhibit a limited solubilizing capacity for high melting point substances, potentially restricting their utility for certain drugs. Secondly, ensuring the surfactants used are nontoxic for pharmaceutical applications adds complexity to formulation selection. Additionally, stabilizing microemulsion droplets often requires a large quantity of surfactants, increasing formulation complexity and cost. Moreover, microemulsion stability is susceptible to environmental parameters like temperature and pH, which can impact their performance and shelf life. Furthermore, keeping surfactant concentrations low for toxicological reasons may compromise the efficacy or stability of the formulation. Finally, the toxic or irritant properties of microemulsion components may limit their potential for topical applications. These disadvantages underscore the importance of careful consideration and optimization when utilizing microemulsions as drug delivery systems [4].

Comparison between emulsion and microemulsion

In comparing emulsions to microemulsions, distinct differences emerge in their structural characteristics and practical applications. Emulsions, characterized by larger droplet sizes ranging from tens to hundreds of micrometers, often require continual agitation or emulsifying agents to maintain stability, owing to their thermodynamic instability. Consequently, emulsions typically exhibit a milky or creamy appearance due to light scattering and opacity. Conversely, microemulsions feature much smaller droplets, typically ranging from 10 to 100 nanometers, and demonstrate thermodynamic stability, forming spontaneously without external energy input. This structural disparity imparts microemulsions with a transparent or translucent appearance, attributed to minimal light scattering and high optical clarity. Moreover, while emulsions are limited in their solubilization capacity and are primarily utilized for lipophilic or oil-based formulations, microemulsions boast enhanced solubilization capabilities owing to their smaller droplet sizes and larger interfacial area. This superior solubilization capacity enables microemulsions to efficiently accommodate both hydrophilic and lipophilic drugs, positioning them as favored vehicles for pharmaceutical drug delivery applications. Consequently, while emulsions find diverse applications across industries such as food and cosmetics, microemulsions are particularly prized in the pharmaceutical sector for their stability, enhanced solubilization potential, and capacity for controlled drug release [5].

Table 1: Comparison between emulsion and microemulsion



Emulsion	**Microemulsion**
• Droplet diameter, 120 mm.	• 10 100 nm.
• Emulsions consist of approximately spherical droplets of one phase dispersed into the other.	• They continuously evolve between various structures ranging from droplet like swollen micelles to bicontinuous structure.
• They are lyophobic.	• They are on the borderline between lyophobic and lyophilic colloids.
• Most emulsions are opaque (white) because bulk of their droplets is greater than wavelength of light and most oils have higher refractive indices than water.	• Microemulsions are transparent or transparent as their droplet diameter are less than % of the wavelength of light, they scatter little light.
• Ordinary emulsion droplets, however small exist as individual entities until coalesance or Ostwald ripening occurs.	• Microemulsion droplet may disappear within a fraction of a second whilst another droplet forms spontaneously elsewhere in the system.
• They may remain steady for long periods of time, will ultimately undergo phase separation on standing to attain a minimum in free energy. They are kinetically stable thermodynamically unstable.	• More thermodynamically steady than macro emulsions and can have essentially infinite lifetime assuming no change in composition, temperature and pressure, and do not tend to separate
• Require intense agitation for their formation.	• Generally obtained by gentle mixing of ingredients.

Components of microemulsion

Oils

Oils serve as a crucial component in microemulsion systems, primarily due to their ability to solubilize lipophilic drugs, thereby facilitating effective drug delivery. They play a pivotal role in enhancing the absorption of lipophilic drugs through the intestinal lymphatic system. Oils are characterized as low-polarity liquids with minimal miscibility in water. Common examples include saturated fatty acids such as lauric acid, myristic acid, and capric acid, along with fatty acid esters like ethyl or methyl esters of lauric, myristic, and oleic acids [7].

Surfactants

Surfactants, or surface-active agents, are indispensable in microemulsions for their ability to reduce surface or interfacial tension between immiscible phases. They possess both hydrophilic and lipophilic properties, making them compatible with polar and non-polar solvents. Commonly used surfactants include polysorbates (Tween 20, 40, 60, 80), sorbitan esters (Span), lecithins (soybean, egg, lysolecithin), and anionic surfactants such as sodium dodecyl sulfate (SDS) and dioctyl sodium sulfosuccinate (Aerosol OT).

Co-surfactants

Co-surfactants are often required to complement surfactants in reducing the oil-water interfacial tension sufficiently to form a stable microemulsion. These typically include short-chain alcohols like ethanol, propanol, isopropanol, and butanol, as well as glycols such as propylene glycol and 1,2-butanediol. Other examples include polyoxyl 40 hydrogenated castor oil (Cremophor RH40) and polyglyceryl–6–dioleate (Plurololeique), which enhance the flexibility and stability of the interfacial film.

3. Classification of Microemulsion

Microemulsions are thermodynamically stable, but are only found under carefully defined conditions. According to Winsor, there are four types of microemulsion.

The categorization of microemulsions into oil-in-water (o/w), water-in-oil (w/o), bio continuous, and single-phase homogeneous systems delineates their structural configurations and equilibrium states. In oil-in-water microemulsions, the lower phase consists of two phases, with the o/w microemulsion phase in equilibrium with an excess of oil in the upper phase. Conversely, water-in-oil microemulsions exhibit two phases, with the w/o microemulsion phase in the upper layer, in equilibrium with an excess of water in the lower phase. Bio continuous microemulsions, featuring three phases, showcase a middle phase comprising a bi-continuous mixture of o/w and w/o microemulsion phases. This middle phase is in equilibrium with an upper layer of excess oil and a lower layer of excess water. Lastly, single-phase homogeneous microemulsions manifest as a singular phase wherein oil, water, and surfactant are homogenously mixed. These structural distinctions elucidate the diverse compositions and equilibrium states of microemulsions, thereby influencing their stability, solubilization capacity, and suitability for various applications in drug delivery and related fields [8].

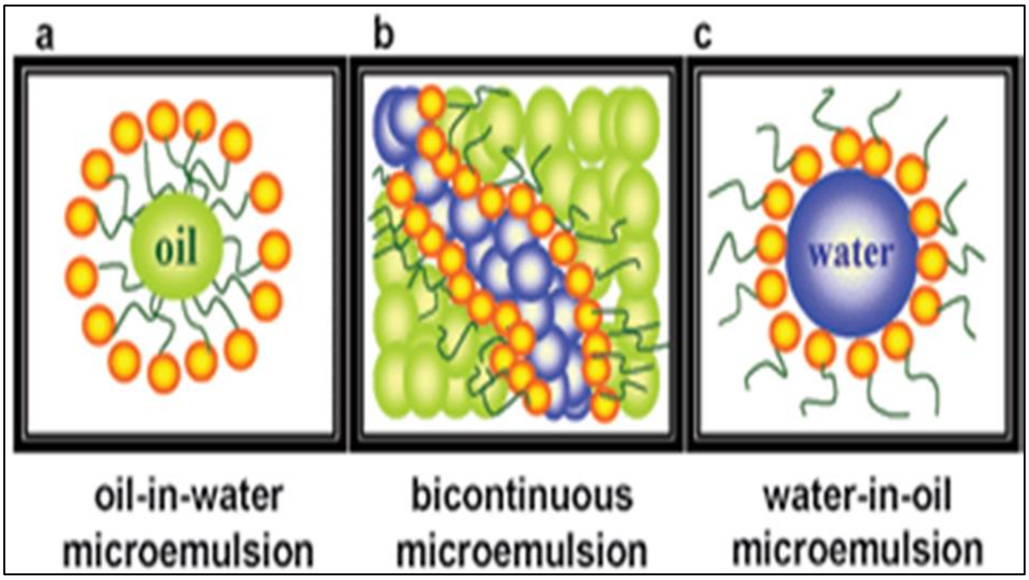


Fig. 2: Types of microemulsion

4. Theories of Microemulsion Formation

Historically, three approaches have been used to explain microemulsion development and stability. They are as follows: Interfacial or mixed film theories; Solubilization theories.; Thermodynamic treatments. The free energy of microemulsion formation can be considered to depend on the level to which surfactant lowers the surface tension of the oil water interface and change in entropy of the system such that,

$$Gf = \gamma a - T S……………(1)$$

Where, Gf = free energy of formation A = change in interfacial area of microemulsion S = change in entropy of the system T = temperature γ = surface tension of oil water interphase. When microemulsion is formed the change in A is very large due to the large number of very small droplets formed. For a microemulsion to be formed(transient) negative value was required, it is predictable that while value of A is always positive, it is very small and it is offset by the entropic constituent. The dominant favorable entropic involvement is very large dispersion entropy arising from the mixing of one phase in the other in the form of large number of small droplets. However, there are also predictable to be favorable entropic contributions arising from other dynamic processes such as surfactant diffusion in the interfacial layer and monomer-micelle surfactant exchange. Thus, a negative free energy of formation is achieved when large reductions in surface tension are accompanied by significant favorable entropic change. In such cases, microemulsion is impulsive and the resulting dispersion is thermodynamically stable [9].

5. Preparation of Microemulsions

5.1 Phase titration method

Microemulsions are prepared by the phase titration method. These is also called as spontaneous emulsification method. Microemulsions can be characterized by the phase diagram. As four compartment system is difficult to intercept and time-consuming process. So, in the preparation of microemulsions we are using the pseudo ternary phase diagram. These are having the different zones and microemulsion zones. These showing the 100% of the components. In this phase titration method, we are using the oils, water, surfactants & mixture of co-surfactants in fixed weight ratios. This phase diagram is responsible for the mixing of ingredients. All these mixtures will be stirred at room temperature, then the monophasic/biphasic system will be confirmed by the visual inspection. In phase separation turbidity may appears, the samples should be considered as biphasic because the monophasic is visualized as clear and transparent mixtures after continuous stirring. The obtained points should be marked in phase diagram [10].

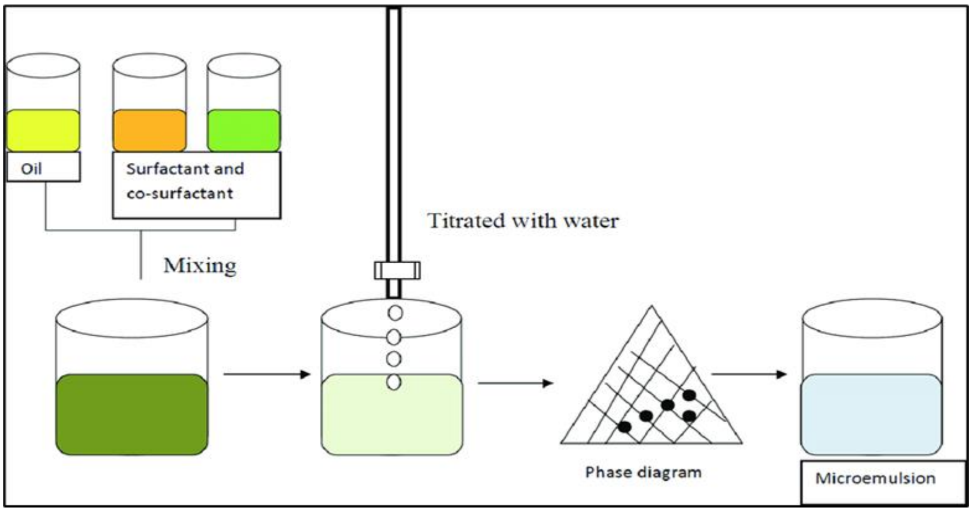


Fig. 3: Phase titration method

5.2 Phase inversion method

Phase inversion of microemulsion is carried out upon addition of excess of the dispersed phase or in response to temperature. In the process of phase inversion method, physical changes can occur, also changes in particle size, these can be ultimately affected drug release in in-vitro and in-vivo. For non-ionic surfactants can be accomplish by the changing the temperature of the system, in these processes an o/w microemulsion at low temperature changes to w/o microemulsion. This is also called as transitional phase inversion method. During the cooling, the system crosses the zero-point spontaneous shape and maintaining the surface tension, and increasing the formation of oil droplet dispersion. Apart from temperature salt concentration and pH value may also considered. In this phase inversion method, transition in the radius can be occur by changing in the water volume fraction. Initially water droplets are formed in a continuous oil phase by addition of water in to oil. Water volume fraction can be increased, surfactants from stabilizing a w/o microemulsion to an o/w microemulsion using temperature [11].

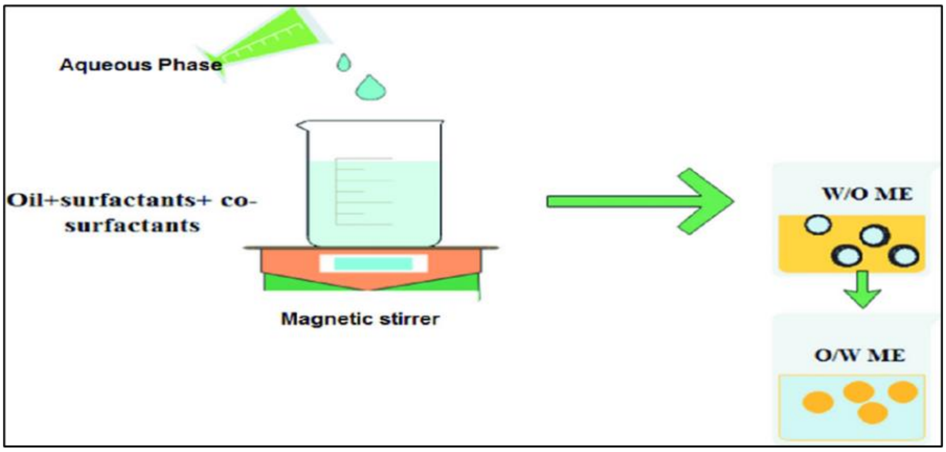


Fig. 4: Phase inversion method

6. Application of Microemulsion system

Microemulsions are versatile drug delivery systems that have found applications across various routes of administration due to their ability to improve solubility, stability, and bioavailability of poorly soluble drugs. Below are the key applications:

6.1 Parenteral Administration

Microemulsions offer a solution to the challenges of delivering drugs with limited solubility via the parenteral route, particularly intravenously. These systems enhance drug solubilization, enabling a higher drug payload to reach the target site, thereby improving therapeutic efficacy.

6.2 Oral Administration

Oral delivery of drugs formulated in microemulsions addresses challenges like poor solubility and stability in gastrointestinal fluids. These formulations enhance drug absorption, improve clinical efficacy, and reduce toxicity compared to conventional oral dosage forms.

6.3 Topical Administration

Topical delivery through microemulsions provides targeted drug delivery directly to the affected site, bypassing hepatic first-pass metabolism and reducing systemic side effects. This approach is especially useful for treating skin and ocular conditions.

6.4 Ocular and Pulmonary Administration

Microemulsions have been explored for ocular and pulmonary drug delivery to improve the solubility of poorly soluble drugs and achieve sustained release. They provide a promising alternative for treating eye disorders and pulmonary conditions.

6.5 Ophthalmic Delivery

For ophthalmic applications, microemulsions provide a stable medium for both water-soluble and insoluble drugs. They offer advantages over traditional forms like aqueous solutions or suspensions by enhancing drug solubility and retention time.

6.6 Nasal Delivery

Nasal administration using microemulsions improves drug uptake through the nasal mucosa. The inclusion of mucoadhesive polymers further enhances the residence time of the formulation, facilitating better absorption and prolonged therapeutic effects.

6.7 Tumor Targeting

Microemulsions modified with folate or other ligands have shown promise in targeting tumors. Studies demonstrate that folate-linked microemulsions with PEG chains effectively deliver drugs to tumor cells, enhancing therapeutic potential.

6.8 Brain Targeting

Microemulsions with mucoadhesive properties have been found to significantly increase drug distribution to the brain compared to intravenous administration. This approach is beneficial for delivering therapeutic agents across the blood-brain barrier.

6.9 Cosmetic Applications

Microemulsions are gaining popularity in the cosmetic industry for personal care products. They offer enhanced stability, improved efficiency, and superior product features, making them an attractive option for skincare and beauty formulations.

7. Marketed products of Microemulsion

Several marketed products utilize microemulsion technology for drug delivery. One notable example is Sandimmune Neoral®, a microemulsion formulation of cyclosporine used to prevent organ rejection in transplant patients. By encapsulating cyclosporine in a microemulsion, Sandimmune Neoral® enhances drug solubility and bioavailability, leading to improved therapeutic outcomes. Another example is Restasis®, an ophthalmic emulsion containing cyclosporine for the treatment of chronic dry eye disease. Restasis® utilizes microemulsion technology to deliver cyclosporine directly to the ocular surface, providing sustained relief from dry eye symptoms. These marketed products demonstrate the successful translation of microemulsion technology into clinically effective therapies, highlighting the potential of this drug delivery approach in improving patient care.

8. Recent patents on Microemulsion

Recent patents on microemulsion technology showcase advancements in various fields, including pharmaceuticals, oil recovery, and environmental applications. For instance, a composition patent (ES-2881766-T3) introduces a nano- or micro-emulsion formulation containing oil, nonionic and anionic surfactants, ceramide compounds, and water, potentially offering enhanced drug delivery capabilities. Another patent (US-10731071-B2) proposes an enhanced oil recovery method utilizing stable invert emulsions of acrylamide polymers in oil and gas wells. Additionally, patents such as US-10421707-B2 and AU-2013239828-B2 focus on oil and gas industry applications, detailing methods incorporating alkyl polyglycoside surfactants and microemulsion flowback aids. These patents underscore the versatility of microemulsion technology across diverse sectors and highlight ongoing innovations aimed at addressing various industrial and environmental challenges (Table 2).

Table 2: Recent Patents on Microemulsion

Application no	**API**	**Tittle**	**Inventors**	**Year of publication and grant**
ES-2881766-T3	The present invention relates to a composition in the form of a nano- or micro-emulsion, comprising: (a) at least one oil; (b) at least one nonionic surfactant with an HLB value of from 8.0 to 14.0, preferably from 9.0 to 13.5, and more preferably from 10.0 to 13.0; (c) at least one ceramide compound; (d) at least one anionic surfactant; and (e) water.	Composition in the form of nano- or microemulsion	Maki Koide, Anne-Laure Bernard	2021
US-10731071-B2	Enhanced oil recovery method consisting in continuously dissolving, in the injection water, a stable invert emulsion of acrylamide (co)polymer containing at least one inverting agent, and a water soluble polymer	Methods and compositions for use in oil and/or gas wells comprising microemulsions with terpene, silicone solvent, and surfactant	Hasnain Saboowala, Randal M. Hill, Angus Fursdon-Welsh	2020
US-10421707-B2	In some embodiments, the emulsion or the microemulsion comprises an aqueous phase, a solvent, a surfactant comprising alkyl polyglycoside, an alcohol, and, optionally, one or more additives.	Methods and compositions incorporating alkyl	Siwar Trabelsi, Randal M. Hill	2019

		polyglycoside surfactant for use in oil and/or gas wells		
AU-2013239828-B2	he microemulsion flowback aid composition includes: (i) an oil-like phase comprising at least one nonionic surfactant having a hydrophilic-lipophilic balance (HLB) of less than about 9; (ii) a coupling agent capable of stabilizing the microemulsion flowback aid composition; (iii) at least one water-soluble or dispersible nonionic surfactant that is different from the at least one nonionic surfactant in the oil-like phase; (iv) at least one additional surfactant selected from anionic, cationic, amphoteric, and combinations thereof; and (v) water.	Microemulsion flowback aid composition and method of using same	Duy Nguyen	2016

9. Conclusion

In conclusion, microemulsions represent a commercially simple and convenient vehicle for the delivery of medicaments, offering enhanced drug absorption while minimizing systemic side effects. These optically isotropic and thermodynamically stable liquid solutions of oil, water, and amphiphile exhibit numerous advantages, including spontaneous formation, ease of manufacturing and scale-up, improved drug solubilization and bioavailability, and extended shelf life. Notably, microemulsions allow for optimized drug targeting without a concurrent increase in systemic absorption, making them valuable tools in pharmaceutical formulations. However, careful selection of excipients, particularly cosurfactants, and thorough safety evaluations are essential in microemulsion formulation to ensure efficacy and safety. Furthermore, ongoing research efforts aim to develop safer and more compatible microemulsion constituents, further enhancing the utility of these novel drug delivery vehicles. With their potential for delivering multiple medicaments simultaneously, microemulsions continue to garner attention as promising candidates for modern drug delivery systems. Thus, in today's world, microemulsions stand poised as a potent force in advancing pharmaceutical technology and improving patient care.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authorship contribution statement

Akshata Bhonge: Supervision, Validation, Methodology, Investigation, Writing – original draft, Dr. **B. V Patil:** Conceptualization, Administration, Funding, Data Curation.

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