Available online on 15.6.2025 at http://ajprd.com

**Asian Journal of Pharmaceutical Research and Development**

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Review Article

# Review on Microemulsion for Nasal Drug Delivery

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## A B S T R A C T

Bacterial meningitis remains a life-threatening central nervous system (CNS) infection with high morbidity and mortality rates, demanding rapid and effective therapeutic intervention. Traditional systemic antibiotic therapies often face challenges such as the blood-brain barrier (BBB) limiting drug penetration, systemic toxicity, and poor patient compliance. Nasal drug delivery emerges as a promising non-invasive alternative route to bypass the BBB and deliver therapeutic agents directly to the brain. Microemulsions, with their nanoscale droplet size, high solubilization capacity, and enhanced permeation properties, offer significant potential for intranasal delivery of antibiotics targeting CNS infections. This review focuses on the formulation strategies, key excipients, and evaluation parameters critical for developing effective microemulsion systems for nasal administration. It also discusses recent advances, in vitro and in vivo studies, pharmacokinetic aspects, and the challenges associated with the clinical translation of such systems. The integration of microemulsion technology with nasal drug delivery holds great promise for improving therapeutic outcomes in bacterial meningitis.

**Keywords**: CNS-targeted microemulsion, Bacterial meningitis, Blood-brain barrier permeability, Amphiphilic surfactants in CNS therapy, Neurotherapeutics

**A R T I C L E I N F O:** Received 11 Jan. 2025; Review Complete 19 March. 2025; Accepted 10 April 2025. ; Available online15 June 2025

**Cite this article as:**

Bhonde A G, Atram SC, Mandwe S. Vrushabh, Bawankar D V, Puri A G, Review on Microemulsion for Nasal Drug Delivery , Asian Journal of Pharmaceutical Research and Development. 2025; 13(3):114-119, DOI: http://dx.doi.org/10.22270/ajprd.v13i3.1564

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## NASAL ROUTE INTRODUCTION

Intranasal administration, traditionally known as Nasya Karma, has long been recognized as a prevalent therapeutic approach within the Ayurvedic system of Indian medicine.[1] In the early 1980s, the nasal route emerged as a promising alternative for systemic drug delivery, offering advantages over conventional administration methods.[2][3] This route is considered easily accessible, user-friendly, and reliable due to the presence of a porous endothelial barrier and a richly vascularized nasal epithelium, which facilitates the rapid absorption of therapeutic agents into the systemic circulation while bypassing hepatic first-pass metabolism. Moreover, intranasal drug delivery allows for dose reduction, faster achievement of therapeutic plasma concentrations, accelerated onset of pharmacological effects, and a lower incidence of adverse effects.[4][5]

The continuous advancement in pharmaceutical research focuses on the design and development of novel drug delivery systems aimed at enhancing the therapeutic efficacy of existing drugs. Among the various delivery platforms explored, the nasal drug delivery system has emerged as a promising approach for targeted drug administration.[6] The initial formulation of microemulsions involved the dispersion of oil in an aqueous solution containing surfactants, with the subsequent addition of an alcohol as a co-surfactant, resulting in a transparent and stable system.[7] The term "microemulsion" was first introduced by Schulman and colleagues in 1959. Since then, the concept has undergone multiple redefinitions. For the purpose of this review, the definition proposed by Danielsson and Lindman in 1981 will be adopted,[8] wherein a microemulsion is characterized as a thermodynamically stable, optically isotropic, single-phase liquid system composed of water, oil, and an amphiphilic component.

In practical applications, the primary distinction between emulsions and microemulsions lies in their thermodynamic stability. Although emulsions may demonstrate considerable kinetic stability, they are inherently thermodynamically unstable and will ultimately undergo phase separation.[9] Additionally, these systems differ in their optical properties: emulsions typically appear cloudy, whereas microemulsions

are generally clear or translucent. Furthermore, the methods required to prepare each system diverge significantly; emulsions necessitate substantial energy input, in contrast to microemulsions, which form spontaneously without the need for intensive energy. This difference has clear implications for the relative cost-effectiveness of their commercial production.[10]

The nasal drug delivery system has conventionally been utilized for the local administration of drugs in the treatment of nasal allergies and infections. In recent years, research has established the nasal route as a safe and acceptable alternative to oral and parenteral drug delivery. This route has proven particularly valuable for targeting therapeutics to the central nervous system (CNS) through various mechanisms [11]. Numerous researchers have reported substantial evidence supporting the nose-to-brain transport of drugs. Consequently, several previously abandoned, yet potent, CNS drug candidates now show potential for successful therapeutic application via intranasal delivery. Recently, nasal formulations such as ergotamine (Novartis), sumatriptan (GlaxoSmithKline), and zolmitriptan (AstraZeneca) have been marketed for the treatment of migraine. Furthermore, scientific efforts have increasingly focused on intranasal drug delivery to the brain, particularly for the treatment of conditions such as bacterial meningitis, epilepsy [12][13], migraine [14][15], emesis, depression [16], angina pectoris [17], and erectile dysfunction [18].

## MICROEMULSION INTRODUCTION

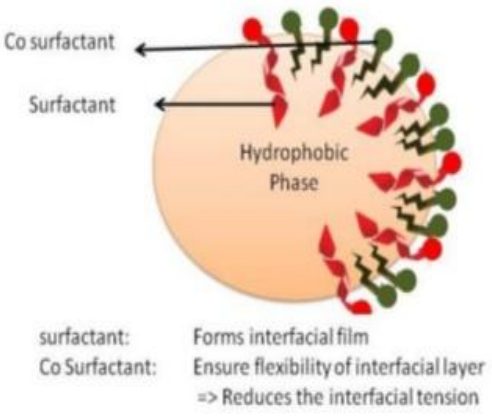
Microemulsions have been extensively explored as a strategy to enhance the bioavailability of poorly water-soluble drugs. These systems present a cost-effective solution for such challenges. Characterized by their ultra-low surface tension and nanometer-sized droplets, microemulsions facilitate superior absorption and permeation. The interest in these multifaceted carriers is continuously growing, with their utility expanding beyond the traditional oral route to various other modes of administration. This growing appeal is largely attributed to their exceptional solubilization capacity and thermodynamic stability, positioning them as innovative platforms for drug delivery. The outcomes reported so far have been notably encouraging.A notable example Is the recent commercialization of a microemulsion-based formulation of a poorly soluble immunosuppressant, presented in the form of a soft gelatin capsule. This capsule comprises a blend of the drug solubilized in oil and surfactant components [19][20]. Upon administration, it spontaneously forms an oil-in-water (o/w) microemulsion in the aqueous environment of the stomach and small intestine. This approach significantly improves the drug's bioavailability and ensures more consistent plasma concentration profiles, which is clinically critical for drugs associated with severe adverse effects. Such advancements represent a substantial progress in the delivery of poorly soluble drugs.Furthermore, microemulsion systems are increasingly being evaluated for other routes of administration, including transdermal [21,22], ocular [23], nasal [24,25], pulmonary [26], vaginal [27,28], rectal [29,30], and intravenous delivery [31].

Microemulsions are inherently dynamic, exhibiting continuous and spontaneous fluctuations at the interfacial layer [32]. Structurally, they are classified into three main types: oil-in-water (o/w), water-in-oil (w/o), and bicontinuous microemulsions. In a w/o microemulsion, discrete water droplets are dispersed in a continuous oil phase, whereas in an o/w microemulsion, oil droplets are distributed within a continuous aqueous phase. When water and oil are present in approximately equal proportions, a bicontinuous microemulsion may form. In all these configurations, the interfacial film is stabilized through a suitable combination of surfactants and/or co-surfactants. The specific combination of oil, water, and surfactant components can lead to the formation of various structural organizations, contingent on the ratios used. The flexibility of the surfactant film plays a crucial role in this structural diversity. A more flexible surfactant interface supports the formation of diverse morphologies, including droplet-like entities, aggregates, and bicontinuous networks, thus broadening the microemulsion's range of existence. In contrast, a rigid surfactant film hinders the formation of bicontinuous structures, thereby limiting the system's adaptability. Beyond microemulsions, structural analyses may reveal the presence of conventional emulsions, anisotropic crystalline phases (hexagonal or cubic), and lamellar formations, depending on component ratios.The internal microstructure of a microemulsion significantly influences phase diffusivity and, consequently, the diffusion behavior of incorporated drugs. Considerable research efforts have been directed toward elucidating the complex phase behavior and the array of microstructures present within microemulsion systems [33].

### Structure of Microemulsion

Microemulsions, also referred to as micellar emulsions, represent dynamic systems characterized by continuously and spontaneously fluctuating interfaces [34]. Based on their structural configuration, microemulsions can be categorized into oil-in-water (o/w), water-in-oil (w/o), and bi-continuous types. In water-in-oil microemulsions, discrete water droplets are dispersed within a continuous oil phase. Conversely, oil-in-water microemulsions consist of oil droplets dispersed in a continuous aqueous phase. When the proportions of oil and water are approximately equal, bi-continuous microemulsions may form, wherein both oil and water phases are interspersed and interconnected throughout the system

[35]. The combination of oil, water, and surfactants can yield a diverse array of structures and phases, contingent upon the specific ratios of the constituent components.




### Components of Microemulsions

Although oils and surfactants are widely available, their application is limited by factors such as potential toxicity,

irritation, and unclear mechanisms of action. Therefore, the components selected for microemulsion formulation must be biocompatible, non-toxic, and acceptable for clinical use. Emphasis is placed on using substances categorized as "generally regarded as safe" [36].

1. Oil phase
2. Aqueous phase
3. Primary surfactant
4. Secondary surfactant (co-surfactant)
5. Co-Solvent

## 1. Oil Phase

The oil phase plays a critical role in microemulsion systems. Beyond serving as a solvent for lipophilic drugs, it facilitates enhanced absorption through the gastrointestinal tract by promoting lymphatic transport, contingent on the triglyceride's molecular structure. Oils impact the curvature of the surfactant monolayer by penetrating and swelling the tail region; shorter-chain oils induce more negative curvature compared to long-chain alkanes due to greater penetration and swelling, thereby lowering the effective hydrophilic-lipophilic balance (HLB). Commonly utilized oils include:

- Saturated fatty acids such as lauric acid, myristic acid, and capric acid
- Unsaturated fatty acids like oleic acid, linoleic acid, and linolenic acid
- Fatty acid esters, including ethyl or methyl esters of lauric, myristic, and oleic acids

Both saturated and unsaturated fatty acids are recognized for their penetration-enhancing properties and have long been studied for this purpose. Fatty acid esters are also effective as oil phases. For optimal formulation, oils are selected based on the drug's solubility, thus minimizing the formulation volume necessary for therapeutic efficacy [37, 38].

## 2. Aqueous Phase

This phase may include hydrophilic active compounds and preservatives. In some formulations, buffer solutions are employed as the aqueous component to maintain stability [39].

## 3. Primary Surfactants

Surfactants primarily function to substantially reduce interfacial tension, facilitating the dispersion process during microemulsion preparation. They also stabilize the interface by forming a deformable, flexible film with suitable lipophilic character. Surfactants utilized in microemulsions may be:

### Non-ionic

- Zwitterionic
- Cationic
- Anionic

The type of surfactant—ionic or non-ionic—affects its interaction with the aqueous phase. Non-ionic surfactants form hydrogen bonds and dipole interactions with water's hydration layer, whereas ionic surfactants gain additional stability via the electrical double layer. Therefore, the salt concentration's influence on emulsion stability is more pronounced in ionic systems. Due to safety concerns, ionic surfactants are generally unsuitable for pharmaceutical applications [40].Non-ionic surfactants, however, are typically regarded as safe for oral administration and are widely used in commercial formulations. Examples include polyoxyl 35 castor oil (Cremophor EL), polyoxyl 40 hydrogenated castor oil (Cremophor RH 40), polysorbates (Tween 20, Tween 80), d-α-tocopherol polyethylene glycol 1000 succinate (TPGS), Solutol HS-15, sorbitan monooleate (Span 80), polyoxyl 40 stearate, and polyglycolyzed glycerides such as Labrafil M-1944CS, Labrafil M-2125CS, Labrasol, and Gellucire 44/14 [38]. For formulation, surfactants with low HLB values (3–6) are suitable for water-in-oil (w/o) microemulsions, while those with high HLB values (8–18) are ideal for oil-in-water (o/w) microemulsions. Surfactants with HLB values exceeding 20 generally require co-surfactants to reduce their effective HLB into a suitable range [41].

## 4. Secondary Surfactant (Co-surfactants)

Single-chain surfactants alone often cannot sufficiently reduce interfacial tension to enable microemulsion formation. Co-surfactants contribute flexibility to the interfacial film, allowing the formation of microemulsions across a broad compositional range. To maintain a single surfactant layer, surfactant molecules should possess short lipophilic chains or incorporate fluidizing groups such as unsaturated bonds. Short- to medium-chain alcohols (C3–C8), including ethanol and butanol, are commonly used as co-surfactants due to their capacity to further reduce interfacial tension and enhance interface fluidity. Additional co-surfactants include glycols (e.g., propylene glycol), medium-chain alcohols, amines, and acids. Their use helps eliminate liquid crystalline or gel structures that might otherwise inhibit microemulsion formation. In most systems, co-surfactant-free microemulsions are feasible only at elevated temperatures.Key functions of co-surfactants include:Enhancing interfacial fluidityDisrupting liquid crystalline or gel phases that impede microemulsion formationModifying HLB and spontaneous curvature by altering surfactant partitioning characteristics

## 5. Co-solvents

Stable microemulsions generally necessitate high concentrations of surfactants (typically >30% w/w). Organic solvents such as ethanol, propylene glycol (PG), and polyethylene glycol (PEG), which are suitable for oral delivery, facilitate the solubilization of hydrophilic surfactants or drugs within the lipid matrix. These solvents can also function as co-surfactants within microemulsion systems [42].

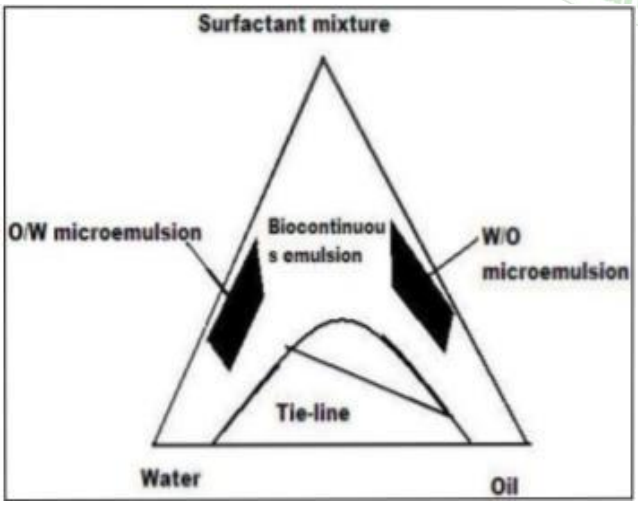
Pseudo-ternary phase diagrams are commonly employed to characterize the microemulsion region. The formation of a microemulsion system fundamentally requires three components: an oil phase, an aqueous phase, and a surfactant. In instances where a cosurfactant is utilized, it is often represented in a fixed ratio with the surfactant and considered collectively as a single "pseudo-component." The relative proportions of these three constituents are typically illustrated using a ternary phase diagram. Gibbs phase diagrams are useful in depicting how variations in the volume fractions of different components affect the system's phase behavior under constant temperature and pressure conditions [43].

### Ternary Phase Diagram

In such diagrams, each of the three constituents occupies a vertex of the triangular diagram, corresponding to 100% volume fraction of that component. Progressing away from a vertex reduces that component's fraction while increasing the fraction of one or both of the other components. Every point within the triangle denotes a specific composition comprising the three components or pseudo-components. According to Gibbs' phase rule, these mixtures may exhibit one, two, or three phases. These compositions form distinct regions within the diagram, demarcated by boundaries that define the phase behavior at equilibrium.

It Is important to note that these phase diagrams are derived from empirical visual observations of system states and may not accurately reflect the actual number of coexisting phases in a given formulation. Some systems that appear to be single-phase under visual inspection may in fact consist of multiple isotropic phases. For example, the seemingly clear heptane/AOT/water microemulsion system comprises multiple phases. Such systems can exist in equilibrium with other phases, and are often sensitive to disruptions in this equilibrium, such as fluctuations in temperature or the addition of agents that modify surface tension. This is especially true for systems containing high volume fractions of two immiscible components, which are particularly prone to destabilization.

Nevertheless, certain microemulsions demonstrate a high degree of stability. For instance, it is hypothesized that the process of neutralizing acid build-ups in automotive engine oils involves water-in-oil (w/o) microemulsions with low aqueous phase volume. From a theoretical standpoint, the transport of acidic aqueous droplets to dispersed calcium carbonate particles within the oil is expected to be most effective when the droplets are sufficiently small to carry a single hydrogen ion. Smaller droplets correspond to a higher droplet count, thereby accelerating the neutralization process. These microemulsions are presumed to maintain stability across a relatively broad temperature range.




**Microemulsions can generally be classified into three types based on their composition:**

- Oil-in-water (O/W) microemulsions, where oil droplets are dispersed within a continuous aqueous phase.
- Water-in-oil (W/O) microemulsions, where water droplets are dispersed in a continuous oil phase.
- Bicontinuous microemulsions, which consist of interpenetrating microdomains of oil and water throughout the system.

In all three cases, the interfacial region is stabilized by a suitable combination of surfactants and/or co-surfactants. A fundamental distinction between emulsions and microemulsions lies in their thermodynamic properties; emulsions, despite potentially exhibiting significant kinetic stability, are inherently thermodynamically unstable and will eventually undergo phase separation [44]. Another key difference pertains to their optical properties: emulsions typically appear cloudy, whereas microemulsions are clear or translucent. Furthermore, the preparation of these systems also varies significantly; emulsions require substantial energy input for their formation, whereas microemulsions form spontaneously without such input. This characteristic has important implications for the comparative cost-efficiency of commercial production of these two systems.

## Method of Preparation

### Phase Titration Method

Microemulsions can be formulated via the spontaneous emulsification technique, commonly referred to as the phase titration method. This approach is effectively illustrated using phase diagrams, which serve as valuable tools for analyzing the intricate interactions among components during formulation. The generation of microemulsions often coincides with the formation of various self-assembled structures, such as emulsions, micelles, lamellar, hexagonal, cubic phases, gels, and oily dispersions. These structural forms are influenced by the specific chemical composition and concentration of the formulation components. A thorough understanding of phase equilibria and precise identification of phase boundaries is critical in such studies. Given the complexity and interpretational challenges of quaternary phase diagrams (involving four components), pseudo-ternary phase diagrams are frequently utilized. In these diagrams, each apex corresponds to a pure component, facilitating the delineation of zones such as the microemulsion region. The classification of microemulsions as water-in-oil (w/o) or oil-in-water (o/w) is based on the relative abundance of oil or water in the system. It is essential to conduct meticulous observations to exclude metastable systems from analysis. The methodology is elaborately discussed by Shafiq-un-Nabi et al. [45].

### Phase Inversion Method

Phase inversion in microemulsion systems can be induced through the addition of excess dispersed phase or by modifying temperature conditions. This inversion is characterized by significant physicochemical transformations, such as changes in droplet size, which may subsequently influence drug release profiles in both in vivo and in vitro environments. This method exploits alterations in the spontaneous curvature of surfactants. For non-ionic surfactants, phase inversion can be triggered thermally, resulting in a shift from an o/w microemulsion at lower temperatures to a w/o microemulsion at elevated temperatures—a phenomenon referred to as transitional phase inversion. Upon cooling, the system transitions through a state of zero spontaneous curvature and minimal interfacial tension, facilitating the formation of finely dispersed oil

droplets. This specific thermal method is known as the phase inversion temperature (PIT) method. Apart from temperature, other physicochemical parameters such as ionic strength (e.g., salt concentration) or pH can also modulate the system. Furthermore, the spontaneous radius of curvature may be adjusted by varying the water volume fraction. The progressive addition of water to an oil phase initially yields dispersed water droplets within a continuous oil medium. As the water fraction increases, the curvature preference of the surfactant shifts, resulting in a transition from a w/o to an o/w microemulsion at the inversion point. Short-chain surfactants facilitate this transition by forming flexible monolayers at the o/w interface, ultimately leading to a bicontinuous microemulsion structure at the inversion locus.

## Characterization of Microemulsion

- **Physical Appearance**

  The physical attributes of a microemulsion, including its homogeneity, fluidity, and optical transparency, can be evaluated visually to assess the overall formulation quality.

- **Drug Solubility**

  To evaluate drug solubility, approximately 1 mL of oil was precisely measured into a 10 mL glass beaker. The drug was incrementally added and stirred using a magnetic stirrer at a moderate speed to facilitate dissolution, followed by sonication to ensure complete solubilization. The drug was continuously added until a supersaturated solution was formed. The total amount of solubilized drug was subsequently quantified using a UV-spectrophotometer. This procedure was similarly employed to assess drug solubility in various surfactants, co-surfactants, and oils [46].

- **pH Determination**

  The apparent pH of all formulated microemulsions was measured by directly immersing the electrode into the formulation using a digital pH meter [47].

- **Viscosity Measurement**

  Microemulsions are characteristically low-viscosity systems. The viscosity of the prepared formulations was determined using a Brookfield viscometer [48].

- **Drug Content**

  To determine the drug content in the microemulsion formulations, an amount equivalent to the drug dose was dissolved in phosphate buffer. After appropriate dilutions, the absorbance was measured using a UV-spectrophotometer, with phosphate buffer serving as the blank. All measurements were conducted in triplicate to ensure accuracy [49].

- **Conductivity Measurements**

  Electrical conductivity measurements serve as a critical method for characterizing microemulsions, offering insights into the system's continuous phase—whether oil or water. Additionally, conductivity can be used to detect percolation and phase inversion phenomena. Percolation typically signifies a transition from isolated droplets to a bicontinuous structure. The structural behavior of microemulsions is influenced by the water-to-oil ratio [50].

- **In Vitro Diffusion Study**

In vitro diffusion was assessed using a modified Franz diffusion cell. A glass cylinder, open at both ends, was used, with sheep nasal mucosa affixed to one end to function as the diffusion membrane. The formulation was introduced into the donor compartment, which was placed into a receptor compartment containing 20 mL of phosphate buffer. Continuous agitation was maintained with a magnetic stirrer, and temperature was controlled. At predetermined intervals, samples were withdrawn from the receptor compartment and replaced with equal volumes to maintain sink conditions. The concentration of the diffused drug was determined spectrophotometrically using a UV-spectrophotometer, referencing a standard calibration curve prepared in phosphate buffer. The cumulative amount of drug released was plotted against time.

## CONCLUSION

Microemulsion-based intranasal drug delivery offers a promising, non-invasive approach for the treatment of bacterial meningitis. This method benefits from improved drug solubility and enhanced brain targeting via the olfactory and trigeminal pathways, potentially circumventing the blood-brain barrier. Numerous studies underscore the advantages of microemulsions in increasing drug permeation, stability, and bioavailability while minimizing systemic adverse effects. Nevertheless, comprehensive in vivo studies, long-term safety assessments, and clinical trials are essential to substantiate their full therapeutic efficacy and potential for clinical translation. Further advancements in formulation strategies and the development of mucoadhesive systems are anticipated to enhance the performance of nasal microemulsions in treating central nervous system infections.

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