

Chapter 7: Nanoemulsions and microemulsions for intranasal cns delivery

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Abstract: Central nervous system (CNS) disorders, including Alzheimer's disease, Parkinson's disease, epilepsy, glioblastoma, depression, and multiple sclerosis, are among the leading causes of disability worldwide. Despite substantial advances in neuroscience and pharmaceutical research, the successful treatment of these disorders continues to be limited by the blood-brain barrier (BBB), which severely restricts the transport of most therapeutic molecules into the brain. Conventional oral and parenteral dosage forms often provide inadequate drug concentrations at the target site, while increasing systemic adverse effects. Intranasal drug delivery has emerged as a promising noninvasive strategy for direct brain targeting, utilising the olfactory and trigeminal neural pathways to bypass the BBB. However, physiological barriers such as mucociliary clearance, enzymatic degradation, and limited epithelial permeability reduce drug absorption in the nasal cavity. Lipid-based nanocarriers, particularly nanoemulsions and microemulsions, have attracted considerable interest because of their ability to enhance drug solubility, improve formulation stability, facilitate mucosal permeation, and increase brain bioavailability. Their nanoscale droplet size provides a large surface area for absorption, while the incorporation of mucoadhesive polymers and permeation enhancers further prolongs the nasal residence time and increases neuronal transport. Numerous preclinical investigations have demonstrated improved brain delivery of therapeutic agents, such as rivastigmine, donepezil, rasagiline, quetiapine, curcumin, and selegiline, using intranasal nanoemulsion- and microemulsion-based systems. However, challenges related to formulation stability, large-scale manufacturing, long-term safety, and regulatory approval continue to hinder clinical translation. This chapter summarises the principles of intranasal CNS drug delivery, discusses the formulation and characterisation of nanoemulsions and microemulsions, highlights their therapeutic applications, and outlines the current challenges and future perspectives for the development of clinically successful nose-to-brain drug delivery systems.

Keywords: Nanoemulsions, Microemulsions, Intranasal delivery, Central nervous system, Blood-brain barrier, Brain targeting.

1. Introduction

Neurological disorders represent one of the greatest healthcare challenges of the twenty-first century. Diseases such as Alzheimer's disease, Parkinson's disease, epilepsy, multiple sclerosis, glioblastoma, depression, migraine, and schizophrenia affect hundreds of millions of individuals globally and contribute substantially to mortality, disability, and health care expenditure. Although numerous pharmacologically active molecules have demonstrated promising efficacy in laboratory investigations, only a limited proportion have been successfully translated into clinical practice. One of the primary reasons for this discrepancy is the difficulty in delivering therapeutic drug concentrations to the brain while minimising systemic toxicity [1–4].

The major obstacle to effective CNS drug delivery is the blood-brain barrier (BBB), a highly specialised physiological interface formed by tightly joined endothelial cells, pericytes, astrocytic end-feet, and basement membrane. This dynamic barrier maintains brain homeostasis by regulating molecular transport between the systemic circulation and the neural tissue. While essential for protecting the brain against toxins and pathogens, the BBB also prevents approximately 98% of small-molecule drugs and almost all biological therapeutics, including peptides, proteins, monoclonal antibodies, nucleic acids, and gene-editing systems, from reaching their therapeutic targets in the brain [1,2].

Conventional drug administration routes have several inherent limitations in CNS therapy. Oral formulations often exhibit poor aqueous solubility, incomplete gastrointestinal absorption, extensive hepatic first-pass metabolism, and variable bioavailability. Even after entering the systemic circulation, only a small fraction of the administered dose crosses the BBB. Parenteral administration avoids first-pass metabolism but still fails to achieve efficient brain delivery and often requires repeated injections, reducing patient compliance and increasing healthcare costs. Consequently, high systemic doses are frequently required, leading to dose-dependent adverse effects without producing adequate drug concentrations in the brain [5,6].

These limitations have stimulated the development of alternative brain-targeting strategies that can bypass the BBB. Among the various approaches investigated, intranasal drug delivery has emerged as a promising noninvasive technique. Owing to the unique anatomical connection between the nasal cavity and brain, therapeutic agents can be transported directly through the olfactory and trigeminal neural pathways, thereby reducing systemic exposure while enhancing brain bioavailability. This route also avoids hepatic first-pass metabolism, provides a rapid onset of action, and improves patient acceptability, making it particularly attractive for treating acute and chronic neurological disorders.

Despite these advantages, successful intranasal drug delivery remains challenging because of physiological barriers, such as mucociliary clearance, enzymatic degradation, limited residence time, and poor epithelial permeability. To overcome these limitations, considerable attention has been directed toward lipid-based nanocarrier systems for drug delivery. Among these, nanoemulsions and microemulsions have demonstrated exceptional potential owing to their high drug solubilization capacity, nanoscale droplet size, favourable biocompatibility, and ability to improve nasal permeation and neuronal transport. The incorporation of permeation enhancers, mucoadhesive polymers, and surface-targeting ligands further enhances their therapeutic performance by prolonging the nasal residence time and facilitating direct transport to the brain.

The integration of intranasal administration with advanced nanocarrier technology represents a significant advancement in central nervous system (CNS) drug delivery. Nano- and microemulsions not only improve the physicochemical properties of poorly soluble drugs but also enhance drug absorption, protect labile molecules from enzymatic degradation, and increase therapeutic efficacy. Consequently, lipid-based delivery systems have become an important focus of pharmaceutical research for the treatment of a broad range of neurological disorders. The following sections discuss the anatomical basis of nose-to-brain transport and provide a comprehensive overview of nanoemulsion- and microemulsion-based strategies for targeted CNS drug delivery.

2. Intranasal Drug Delivery for Brain Targeting

2.1 Anatomical Basis of Nose-to-Brain Drug Delivery

The intranasal route has emerged as an attractive noninvasive strategy for delivering therapeutic agents directly to the central nervous system (CNS). Unlike conventional oral and parenteral administration, intranasal delivery exploits the unique anatomical connection between the nasal cavity and the brain, allowing drugs to bypass the blood-brain barrier (BBB) and reach the CNS via neuronal pathways. This approach minimises systemic drug exposure while improving brain bioavailability, making it particularly suitable for treating neurological disorders that require rapid and targeted drug delivery.

The human nasal cavity has an approximate volume of 15–20 mL and a surface area of 150–180 cm² owing to the presence of highly folded nasal turbinates. It is anatomically divided into three functional regions: vestibular, respiratory, and olfactory. The vestibular region primarily serves as a filtration zone containing hair and mucus that trap inhaled particles. The respiratory region constitutes the largest portion of the nasal cavity and is lined with a highly vascularized pseudostratified ciliated epithelium, making it the principal site of systemic drug absorption. In contrast, the olfactory region occupies only 5–10% of the total nasal surface but plays a crucial role in direct brain delivery because it contains olfactory sensory neurons whose axons project through the cribriform plate into the olfactory bulb [5–10].

In addition to the olfactory pathway, the trigeminal nerve provides an important route for drug transport. Branches of this cranial nerve innervate both the respiratory and olfactory mucosa and establish direct connections with various brain regions, including the brainstem and the spinal cord. Consequently, therapeutic agents deposited in the nasal cavity may reach different areas of the CNS via both olfactory and trigeminal neuronal networks.

The nasal mucosa possesses several physiological characteristics that favour drug absorption, including a rich vascular supply, high epithelial permeability for suitable molecules, relatively low enzymatic activity compared with the gastrointestinal tract, and the absence of first-pass hepatic metabolism. These features contribute to rapid drug absorption and a fast onset of pharmacological action, particularly for drugs intended for emergency neurological conditions, such as seizures and migraine attacks [10-12].

2.2 Mechanisms of Nose-to-Brain Transport

Drug transport from the nasal cavity to the brain occurs through multiple complementary pathways, and the relative contribution of each mechanism depends on the physicochemical properties of the drug and its formulation.

2.2.1 Olfactory Pathway

The olfactory pathway is the most direct route for CNS drug delivery. Following deposition in the olfactory region, drug molecules diffuse through the mucus layer and are transported either intracellularly via olfactory neurons or extracellularly through perineural channels surrounding these neurons. Extracellular transport is generally more rapid and contributes significantly to early drug delivery to the olfactory bulb and adjacent brain regions. This pathway enables therapeutic agents to bypass the BBB and directly access the brain tissue [13-16].

2.2.2 Trigeminal Pathway

The trigeminal nerve provides an additional transport route connecting the nasal cavity to deeper brain structures. Drugs absorbed through the trigeminal nerve endings may reach the brainstem, cerebellum, and spinal cord, thereby extending drug distribution beyond the olfactory bulb. This pathway is particularly important for delivering therapeutics intended for widespread central nervous system (CNS) disorders.

2.2.3 Systemic Absorption Followed by BBB Transport

A proportion of the administered dose is absorbed into the systemic circulation through the highly vascularized respiratory mucosa of the nasal cavity. Although this fraction may eventually reach the brain by crossing the BBB, its contribution is generally limited to hydrophilic molecules and large biological therapeutics. However, systemic

absorption may provide additional therapeutic benefits for drugs that can penetrate the BBB [17-20].

2.2.4 Intracellular and Extracellular Transport

Drug molecules may also be transported by intracellular endocytosis, followed by axonal transport or extracellular diffusion along the perineural and perivascular spaces. Extracellular transport generally occurs within minutes, whereas intracellular axonal transport is comparatively slower but contributes to a sustained brain distribution.

2.3 Advantages of Intranasal Drug Delivery

Intranasal administration offers several therapeutic advantages over conventional routes of administration. The most important benefit is the ability to bypass the BBB, thereby increasing the drug concentration within the brain while reducing systemic exposure. This route also avoids gastrointestinal degradation and hepatic first-pass metabolism, improving the bioavailability of many therapeutic agents.

Because the nasal mucosa is richly vascularized, drugs can be absorbed rapidly, resulting in a faster onset of action than oral administration. This characteristic is particularly advantageous for the emergency management of epilepsy, acute migraine, and severe pain. In addition, intranasal administration is painless, noninvasive, and suitable for self-administration, improving patient adherence during long-term treatment of chronic neurological diseases.

The intranasal route is compatible with a wide variety of advanced drug delivery systems, including nanoemulsions, microemulsions, lipid nanoparticles, polymeric nanoparticles, liposomes, dendrimers and in situ gels. These formulations enhance drug solubility, prolong nasal residence time, improve epithelial permeation, and facilitate direct neuronal transport into the brain.

Table 7.1: Advantages of Intranasal Drug Delivery for CNS Targeting

Advantage	Therapeutic significance
Bypasses the blood-brain barrier	Direct brain targeting
Avoids hepatic first-pass metabolism	Improved bioavailability
Rapid onset of action	Suitable for emergency therapy
Non-invasive administration	Improved patient compliance
Reduced systemic exposure	Lower incidence of adverse effects
Direct olfactory and trigeminal transport	Enhanced CNS delivery
Compatible with nanocarriers	Improved drug stability and permeation

2.4 Limitations of Intranasal Drug Delivery

Despite its considerable potential, intranasal drug delivery is associated with several physiological and formulation challenges. Mucociliary clearance rapidly removes foreign materials from the nasal cavity, limiting the residence time of formulations to approximately 15–30 min. Consequently, only a limited absorption window is available across the nasal mucosa.

The nasal mucosa also contains metabolic enzymes, such as esterases, peptidases, and cytochrome P450 isoenzymes, which may degrade susceptible therapeutic molecules before they reach the brain. Furthermore, the relatively small administration volume (typically 100–150 μL per nostril) restricts the dose that can be delivered via this route.

Drug absorption is influenced by several physiological factors, including nasal congestion, inflammation, allergic rhinitis, infection, and interindividual variability in mucus composition and epithelial permeability. Repeated administration of formulations containing high concentrations of surfactants or preservatives may cause local irritation, impair ciliary function, or damage the nasal epithelium if the safety of the formulation is not carefully optimised.

These limitations have driven the development of advanced nanocarrier systems capable of improving drug stability, prolonging nasal residence time, enhancing epithelial permeation, and protecting drugs from enzymatic degradation. Among these, nanoemulsions and microemulsions have shown exceptional promise for efficient nose-to-brain drug delivery.

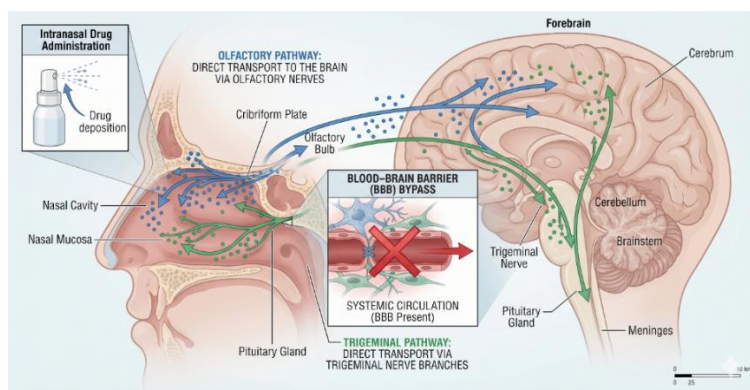


Fig. 7.1: Schematic illustration of direct nose-to-brain drug transport via the olfactory and trigeminal pathways after intranasal administration.

3. Nanoemulsions for Nose-to-Brain Drug Delivery

3.1 Introduction to Nanoemulsions

Nanoemulsions are isotropic colloidal dispersions composed of two immiscible liquids, typically oil and water, stabilised by a suitable combination of surfactants and, when necessary, co-surfactants. The dispersed droplets generally range from 20 to 200 nm in diameter, providing a large interfacial surface area that enhances drug solubilization, dissolution, and absorption. Unlike conventional emulsions, nanoemulsions exhibit excellent kinetic stability and resist creaming, flocculation, and coalescence during storage. Although thermodynamically unstable, their extremely small droplet size enables prolonged physical stability, making them attractive carriers for pharmaceutical applications [21].

Over the past two decades, nanoemulsions have emerged as extensively investigated lipid-based nanocarriers for brain-targeted drug delivery. Their ability to encapsulate poorly water-soluble drugs, improve mucosal permeation, protect drugs from enzymatic degradation, and enhance brain bioavailability makes them particularly suitable for intranasal administration. Lipid droplets readily interact with the nasal epithelium, facilitating drug transport through the olfactory and trigeminal pathways while reducing systemic exposure [22].

Nanoemulsions offer several formulation advantages for CNS-active drugs that exhibit poor aqueous solubility and limited permeability across the blood-brain barrier. The nanoscale droplet size improves drug dissolution, increases contact with the nasal mucosa, and promotes rapid absorption. Furthermore, the incorporation of mucoadhesive polymers and permeation enhancers prolongs the nasal residence time, thereby increasing the opportunity for neuronal transport before mucociliary clearance removes the formulation [23].

Consequently, nanoemulsions have been widely explored for the intranasal delivery of therapeutic agents for Alzheimer's disease, Parkinson's disease, epilepsy, depression, glioblastoma, migraine, and other neurological disorders.

3.2 Composition of Nanoemulsions

The performance of a nanoemulsion depends on the appropriate selection and optimisation of its components. A typical pharmaceutical nanoemulsion consists of an oil phase, surfactant, co-surfactant, aqueous phase, and optional functional excipients, such as mucoadhesive polymers, antioxidants, preservatives, and permeation enhancers. Each component contributes to the stability, drug loading capacity, and therapeutic performance of the final formulation [24].

3.2.1 Oil Phase

The oil phase functions as the primary reservoir for lipophilic drugs and significantly influences drug loading, droplet size, release kinetics, and membrane permeability. Oils with high solubilization capacities improve encapsulation efficiency while minimising drug precipitation during storage.

Medium-chain triglycerides (MCTs), including Miglyol® 812, Captex® 355, and Labrafac®, are among the most commonly used oils because of their low viscosity, excellent solvent capacity, and favourable safety profiles. Long-chain triglycerides, such as soybean, sesame, and olive oils, may also be incorporated to prolong drug release and improve the solubilization of highly lipophilic compounds.

Functional lipids, including oleic acid, Capmul® MCM, and Labrafil®, play a dual role in enhancing drug solubilization and increasing epithelial membrane permeability. Oleic acid, in particular, transiently disrupts the organisation of membrane lipids, facilitating drug transport across the nasal epithelium [25-28].

3.2.2 Surfactants

Surfactants reduce the interfacial tension between the oil and aqueous phases, enabling the formation of nanosized droplets and preventing droplet aggregation. For intranasal applications, non-ionic surfactants are generally preferred because of their superior safety profiles, low toxicity, and excellent mucosal compatibility.

Common pharmaceutical surfactants include Tween® 80, Tween® 20, Cremophor® EL, Solutol® HS15 and Labrasol®.

Among these, Tween® 80 is widely employed owing to its high emulsification efficiency and compatibility with CNS-active drugs. Labrasol® additionally functions as a permeation enhancer by increasing membrane fluidity and improving drug absorption across the nasal mucosa.

The hydrophilic-lipophilic balance (HLB) of surfactants is an important parameter in formulation development. Oil-in-water nanoemulsions intended for intranasal administration generally require surfactants with relatively high HLB values (8–18) to ensure efficient emulsification and long-term stability [29-31].

3.2.3 Co-surfactants

Co-surfactants further decrease the interfacial tension and improve the flexibility of the surfactant film surrounding the dispersed droplets. Their incorporation facilitates spontaneous emulsification, reduces droplet size, and broadens the formulation-design space.

Commonly used co-surfactants include Transcutol® P, Polyethene glycol 400 (PEG 400), Propylene glycol, Ethanol, and Glycerol.

Among these, Transcutol® P has gained widespread acceptance because it acts simultaneously as a co-surfactant, co-solvent, and permeation enhancer, thereby improving drug loading and nasal absorption. The surfactant-to-co-surfactant ratio (Smix) was systematically optimised during formulation development to achieve the smallest droplet size and maximum physical stability.

3.2.4 Aqueous Phase

The aqueous phase forms the continuous external phase of most oil-in-water (O/W) nanoemulsions. Although purified water is commonly employed, pharmaceutical formulations frequently include buffering agents, tonicity modifiers, preservatives, and antioxidants to maintain the physicochemical stability and comfort of the patient.

For intranasal administration, the formulation pH is generally adjusted to 4.5–6.5, which closely corresponds to the physiological pH of the nasal cavity. Maintaining isotonicity minimises mucosal irritation and preserves ciliary function.

Mucoadhesive polymers are often incorporated into the aqueous phase to increase the formulation viscosity and prolong the nasal residence time. Common examples include chitosan, hydroxypropyl methylcellulose (HPMC), hyaluronic acid, carbopol, and sodium alginate (NaAlg). These polymers enhance adhesion to the nasal mucosa, reduce mucociliary clearance, and improve direct nose-to-brain drug transport.

Table 7.2: Major Components of Pharmaceutical Nanoemulsions

Component	Primary Function	Representative Examples
Oil phase	Drug solubilization	Miglyol® 812, Captex® 355, Oleic acid
Surfactant	Reduction of interfacial tension	Tween® 80, Cremophor® EL, Labrasol®
Co-surfactant	Improve emulsification	Transcutol® P, PEG 400, Propylene glycol
Aqueous phase	Continuous phase	Purified water, phosphate buffer
Mucoadhesive polymer	Increase nasal residence time	Chitosan, HPMC, Hyaluronic acid
Preservatives	Microbial protection	Benzalkonium chloride, Phenoxyethanol
Antioxidants	Prevent lipid oxidation	α -Tocopherol, BHT

3.3 Preparation Methods

Nanoemulsions can be prepared using either high-energy or low-energy emulsification techniques. High-energy methods employ external mechanical forces to reduce droplet size, whereas low-energy techniques utilise spontaneous physicochemical processes driven by changes in composition or temperature.

High-pressure homogenization and microfluidization are the most widely used industrial methods because they produce uniform droplets below 200 nm in size with excellent reproducibility. Ultrasonication is frequently employed at the laboratory scale because of its simplicity and rapid processing.

Low-energy techniques, including spontaneous emulsification and phase inversion methods, require a lower energy input and are particularly suitable for thermolabile drugs. The selection of an appropriate preparation method depends on the drug properties, formulation composition, scalability, and manufacturing cost [21,25,27].

3.4 Characterisation of Nanoemulsions

Comprehensive physicochemical characterisation is essential for ensuring formulation quality, stability, and therapeutic performance. The most important quality attributes include droplet size, polydispersity index (PDI), zeta potential, viscosity, pH, drug content, entrapment efficiency, in vitro drug release, ex vivo nasal permeation, and storage stability of the formulation.

Dynamic light scattering is routinely used to determine the droplet size and PDI, whereas electrophoretic light scattering measures the zeta potential. Drug release studies are generally performed using dialysis membrane diffusion techniques, whereas ex vivo permeation is evaluated using excised animal nasal mucosa in Franz diffusion cell studies.

For intranasal applications, an ideal nanoemulsion should exhibit a droplet size below 200 nm, PDI below 0.30, physiological pH, high drug loading, uniform drug distribution, and excellent physical stability without phase separation or precipitation during storage.

Overall, nanoemulsions are versatile lipid-based carriers that can improve the solubility, permeability, and brain bioavailability of CNS-active drugs. Their favourable physicochemical characteristics and compatibility with intranasal administration have established them as one of the most promising platforms for targeted nose-to-brain delivery [21,23,24].

4. Microemulsions for Nose-to-Brain Drug Delivery

4.1 Introduction to Microemulsions

Microemulsions are transparent or translucent isotropic dispersions of oil, water, surfactants, and co-surfactants that form spontaneously when the interfacial tension between the oil and aqueous phases is sufficiently reduced. Unlike nanoemulsions, which are kinetically stable, microemulsions are thermodynamically stable systems and do not require continuous external energy to maintain their structure. Their droplet size typically ranges from 10 to 100 nm, resulting in a large interfacial surface area that promotes efficient drug solubilization and absorption [23, 24].

The spontaneous formation and long-term stability of microemulsions make them attractive carriers for pharmaceutical applications, particularly for poorly water-soluble drugs (pWSDs). In intranasal drug delivery, these systems improve drug permeation across the nasal epithelium, protect drugs from enzymatic degradation, and facilitate direct transport to the brain via the olfactory and trigeminal pathways. Their ability to accommodate lipophilic, hydrophilic, and amphiphilic drugs further broadens their therapeutic applicability in CNS disorders.

Recent studies have demonstrated the enhanced brain delivery of drugs, such as donepezil, rivastigmine, rasagiline, olanzapine, quetiapine, curcumin, and various anticonvulsants, using intranasal microemulsion formulations. These systems have consistently shown increased brain drug concentrations, improved pharmacokinetic profiles, reduced systemic exposure, and enhanced therapeutic efficacy compared to conventional dosage forms [31-34].

4.2 Composition of Microemulsions

The successful formulation of pharmaceutical microemulsions requires careful optimisation of the oil phase, surfactant, co-surfactant, aqueous phase, and optional functional excipients. The interactions among these components determine the droplet size, phase behaviour, drug-loading capacity, thermodynamic stability, and biological performance.

4.2.1 Oil Phase

The oil phase acts as the principal reservoir for lipophilic drugs and strongly influences drug solubilization, release kinetics and membrane permeation. Medium-chain triglycerides (MCTs), including Miglyol® 812, Captex® 355, and Labrafac®, are widely used because of their excellent solvent capacity, low viscosity, and favourable safety profiles. Long-chain triglycerides, such as soybean and sesame oils, may be incorporated when prolonged drug release is desired.

Functional lipids, such as oleic acid, Capmul® MCM, and Labrafil®, also serve as permeation enhancers by increasing membrane fluidity and improving epithelial transport. The selection of the oil phase is generally based on equilibrium solubility studies, compatibility testing, and stability evaluation to maximise drug loading while maintaining formulation stability [35-37].

4.2.2 Surfactants

Surfactants are essential for reducing the interfacial tension and stabilising the oil–water interface. Non-ionic surfactants are preferred for intranasal formulations because of their excellent biocompatibility and low-irritation potential. Commonly used surfactants include Tween® 80, Tween® 20, Cremophor® EL, Solutol® HS15 and Labrasol®.

These surfactants facilitate spontaneous microemulsion formation, improve drug solubilization, and contribute to the formation of flexible interfacial films. Surfactants with high hydrophilic–lipophilic balance (HLB) values are generally selected for oil-in-water microemulsions intended for nasal administration [38].

4.2.3 Co-surfactants

Although surfactants substantially reduce interfacial tension, co-surfactant incorporation is necessary to achieve the ultralow interfacial free energy required for spontaneous microemulsion formation. Co-surfactants are inserted between surfactant molecules, increasing interfacial flexibility and promoting the formation of stable nanosized droplets. Frequently used co-surfactants include Transcutol® P, PEG 400, Propylene glycol, Ethanol, Glycerol, and Isopropyl alcohol.

Among these, Transcutol® P has gained particular importance because it simultaneously functions as a co-solvent, co-surfactant, and permeation enhancer. The surfactant-to-cosurfactant ratio (S_{mix}) was optimised experimentally to obtain the largest microemulsion region with desirable physicochemical characteristics [39, 40].

4.2.4 Aqueous Phase

The aqueous phase serves as a continuous external phase in most pharmaceutical microemulsions. Purified water is commonly employed with buffering agents, tonicity modifiers, preservatives, and antioxidants to improve formulation stability and patient acceptability.

For intranasal administration, the pH is maintained between 4.5 and 6.5, and the osmolarity is adjusted close to physiological conditions to minimise irritation. Mucoadhesive polymers, such as chitosan, carbopol, HPMC, hyaluronic acid, and sodium alginate, are frequently incorporated to increase viscosity, prolong nasal residence time, and enhance direct nose-to-brain drug transport [31,40].

Table 7.3: Principal Components of Pharmaceutical Microemulsions [41,45]

Component	Function	Representative Examples
Oil phase	Drug solubilization	Miglyol® 812, Oleic acid, Capmul® MCM
Surfactant	Reduction of interfacial tension	Tween® 80, Labrasol®, Cremophor® EL
Co-surfactant	Improve spontaneous emulsification	Transcutol® P, PEG 400, Propylene glycol
Aqueous phase	Continuous phase	Purified water, phosphate buffer
Mucoadhesive polymer	Prolong nasal residence	Chitosan, HPMC, Hyaluronic acid
Auxiliary excipients	Stability and preservation	Benzalkonium chloride, EDTA, α -Tocopherol

4.3 Pseudo-Ternary Phase Diagrams

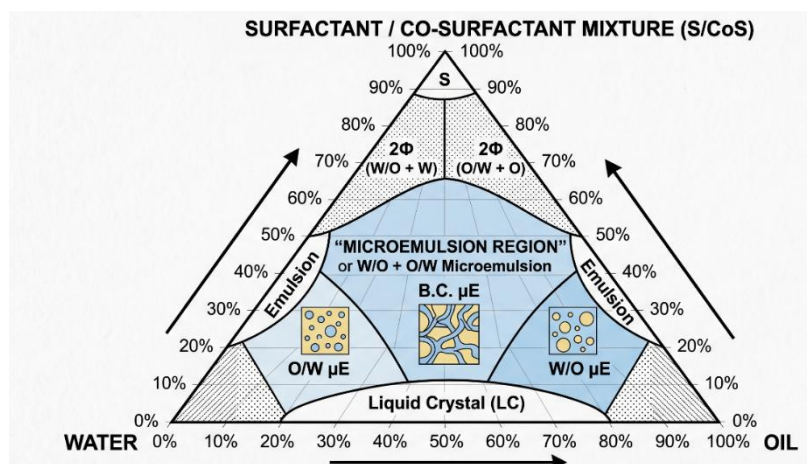


Fig. 7.2: Representative pseudo-ternary phase diagram illustrating the microemulsion region obtained by varying the proportions of oil, water, and surfactant/co-surfactant mixture.

The construction of a pseudo-ternary phase diagram is a critical step in microemulsion development because it identifies the concentration ranges of the oil, water, and surfactant/co-surfactant mixture capable of producing stable microemulsions. The diagram consists of three vertices representing the oil, aqueous, and surfactant/co-surfactant mixture (Smix) phases. By systematically varying the proportions of these components and observing the resulting phase behaviour, researchers identified transparent, isotropic regions corresponding to microemulsion formation.

Different Smix ratios, such as 1:1, 2:1, 3:1, and 4:1, are typically evaluated. The composition that produced the largest microemulsion region while maintaining acceptable droplet size, viscosity, and stability was selected for further optimisation. This systematic approach minimises trial-and-error experimentation and supports quality-by-design (QbD)-based formulation development [31, 32, 39, 40].

4.4 Preparation of Microemulsions

Microemulsions are generally prepared by spontaneous emulsification because their formation is thermodynamically driven. The oil phase was first mixed with the selected surfactant and co-surfactant to obtain a homogeneous mixture. The aqueous phase was then added slowly under continuous magnetic stirring until a clear and transparent system was obtained. Mild stirring is usually sufficient, and high-energy homogenization is not required for this process.

Critical formulation variables, including oil concentration, Smix ratio, temperature, and mixing sequence, were optimised to achieve rapid self-emulsification, minimum droplet size, and long-term thermodynamic stability. Modern pharmaceutical development frequently incorporates Design of Experiments (DoE) and Quality by Design (QbD) approaches to establish robust and reproducible manufacturing processes [39, 40, 45].

4.5 Characterisation of Microemulsions

Comprehensive characterisation is essential to ensure the quality, stability, and therapeutic performance of formulations. The principal evaluation parameters included droplet size, polydispersity index (PDI), zeta potential, pH, viscosity, conductivity, refractive index, drug content, entrapment efficiency, in vitro drug release, ex vivo nasal permeation, and stability.

Droplet size and PDI were measured using dynamic light scattering, whereas zeta potential was determined using electrophoretic light scattering. Conductivity measurements help distinguish oil-in-water and water-in-oil systems, whereas the refractive index and transparency confirm isotropic microemulsion formation [31, 39, 45].

Drug release studies using dialysis membrane techniques and ex vivo permeation studies employing Franz diffusion cells provide valuable information regarding the formulation performance. Stability evaluation includes centrifugation, heating–cooling cycles, freeze–thaw testing, and long-term storage under the recommended conditions. Stable formulations should not exhibit phase separation, precipitation, or significant changes in droplet size during storage.

Table 7.4: Major Characterisation Parameters of Microemulsions

Parameter	Analytical Technique	Significance
Droplet size	Dynamic light scattering	Brain permeation and stability
Polydispersity index	Dynamic light scattering	Droplet size uniformity
Zeta potential	Electrophoretic light scattering	Colloidal stability
pH	Digital pH meter	Nasal compatibility
Viscosity	Brookfield viscometer	Residence time and sprayability
Conductivity	Conductivity meter	Identification of microemulsion type
Drug content	UV spectroscopy/HPLC	Dose uniformity
In vitro release	Dialysis membrane	Drug release behaviour
Ex vivo permeation	Franz diffusion cell	Nasal drug transport
Stability	Accelerated and long-term studies	Shelf-life prediction

5. Therapeutic Applications of Nanoemulsions and Microemulsions in CNS Disorders

Nanoemulsions and microemulsions have emerged as promising lipid-based nanocarriers for the intranasal delivery of therapeutics to the brain. Their ability to bypass the blood–brain barrier (BBB), improve drug solubility, prolong nasal residence time, and enhance drug permeation has resulted in significant improvements in the treatment of various central nervous system (CNS) disorders. Numerous preclinical studies have demonstrated enhanced brain targeting, increased bioavailability, rapid onset of action, and reduced systemic toxicity compared with conventional dosage forms of these drugs.

Among neurodegenerative disorders, Alzheimer's disease has been extensively investigated using intranasal nanofomulations. Drugs such as donepezil, rivastigmine, and curcumin have shown improved brain uptake and prolonged therapeutic activity after being incorporated into nanoemulsions or microemulsions. Enhanced cognitive performance and reduced oxidative stress observed in animal models suggest that these lipid-based systems may improve the clinical management of Alzheimer's disease (AD).

For Parkinson's disease, nanoemulsion- and microemulsion-based formulations of rasagiline, selegiline, and rotigotine have demonstrated improved transport across the nasal mucosa and greater accumulation in the brain tissue. Direct nose-to-brain delivery reduces peripheral drug exposure and improves motor function, making these systems attractive alternatives to conventional oral therapies.

Intranasal nanoemulsions have shown considerable promise in the management of epilepsy. Antiepileptic drugs such as carbamazepine, diazepam, and clonazepam exhibit faster brain delivery and more rapid seizure control following intranasal administration. The rapid onset of action offered by this route is particularly beneficial for emergency seizure management.

Brain tumours, such as glioblastoma, remain difficult to treat because most anticancer drugs exhibit poor penetration across the BBB. Nanoemulsion- and microemulsion-based formulations of temozolomide, curcumin, and paclitaxel have demonstrated enhanced drug accumulation in brain tissue and improved antitumor efficacy in preclinical studies. These systems may also reduce systemic toxicity by limiting drug distribution to non-target tissues.

In addition to neurodegenerative diseases and brain tumours, lipid-based nanocarriers have been explored for the treatment of depression, schizophrenia, migraine, multiple sclerosis, and other neurological disorders. The incorporation of mucoadhesive polymers, permeation enhancers, and targeting ligands further improves nasal residence time and facilitates neuronal transport, thereby enhancing therapeutic performance.

Although most published studies remain at the experimental stage, the available evidence clearly demonstrates that nanoemulsions and microemulsions significantly improve brain drug delivery compared to conventional formulations. Continued advances in formulation design, large-scale manufacturing, and clinical evaluation are expected to accelerate the translation of nanocarrier systems into routine clinical practice [18, 45, 46].

Table 7.5: Therapeutic Applications of Nanoemulsions and Microemulsions for Nose-to-Brain Delivery

CNS Disorder	Representative Drug	Nanocarrier	Major Benefit	Therapeutic
Alzheimer's disease	Donepezil, Rivastigmine, Curcumin	Nanoemulsion/Microemulsion	Improved brain uptake and cognitive function	
Parkinson's disease	Rasagiline, Selegiline, Rotigotine	Nanoemulsion	Enhanced dopaminergic drug delivery	
Epilepsy	Carbamazepine, Diazepam, Clonazepam	Nanoemulsion	Rapid seizure control and higher bioavailability	brain
Glioblastoma	Temozolomide, Paclitaxel, Curcumin	Nanoemulsion/Microemulsion	Increased accumulation and reduced systemic toxicity	brain

Depression	Venlafaxine, Duloxetine	Nanoemulsion	Improved CNS delivery and therapeutic response
Migraine	Sumatriptan	Nanoemulsion	Rapid onset of action and improved pain relief
Schizophrenia	Olanzapine, Quetiapine	Microemulsion	Enhanced brain targeting and reduced peripheral side effects

6. Clinical Translation and Regulatory Considerations

Despite encouraging preclinical findings, the clinical translation of intranasal nanoemulsions and microemulsions remains limited. The successful development of lipid-based nanocarriers requires enhanced therapeutic efficacy, reproducible manufacturing processes, long-term physicochemical stability, regulatory compliance, and comprehensive safety evaluation.

One of the major challenges is maintaining consistent critical quality attributes (CQAs), including droplet size, polydispersity index, zeta potential, drug loading, viscosity, and stability, during large-scale manufacturing. Variations in these parameters may affect drug release, nasal deposition, and brain-targeting efficiency. Therefore, pharmaceutical development increasingly adopts the Quality by Design (QbD) approach, which emphasises the systematic optimisation of formulation variables and manufacturing processes to ensure product quality and batch-to-batch consistency.

Safety assessment is another essential requirement for clinical application. Intranasal formulations should be evaluated for nasal irritation, ciliotoxicity, mucosal compatibility, systemic toxicity, and safety after repeated dosing. The selection of pharmaceutically acceptable excipients, particularly surfactants and preservatives, is critical because excessive concentrations can damage the nasal epithelium or impair mucociliary clearance.

From a regulatory perspective, agencies such as the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) require comprehensive characterisation, stability studies, pharmacokinetic evaluation, and clinical evidence to demonstrate product safety, efficacy, and quality. Compliance with Good Manufacturing Practice (GMP) guidelines and validated manufacturing processes is essential for commercialisation.

Despite several challenges, continuous advances in formulation science, scalable manufacturing technologies, and regulatory frameworks are expected to facilitate the successful clinical translation of intranasal nanoemulsion- and microemulsion-based drug delivery systems.

7. Challenges and Future Perspectives

Intranasal lipid-based nanocarriers offer considerable promise for brain-targeted drug delivery; however, several scientific and technological challenges continue to limit the widespread clinical application of these carriers. Rapid mucociliary clearance, limited nasal dosing volume, inter-patient variability in nasal physiology, enzymatic degradation, and potential irritation associated with prolonged use remain important obstacles to achieving consistent therapeutic outcomes.

In addition, maintaining long-term stability during storage and large-scale manufacturing remains challenging, particularly for formulations containing high concentrations of surfactants and thermolabile drugs. Standardised *in vitro* and *in vivo* evaluation methods are required to establish reliable correlations between preclinical findings and clinical performance.

Future research should focus on developing multifunctional nanocarriers that incorporate mucoadhesive polymers, receptor-targeting ligands, stimuli-responsive materials, and controlled-release technologies to enhance drug retention and site-specific delivery. Advances in artificial intelligence (AI), machine learning (ML), computational modelling, and Quality by Design (QbD) are likely to accelerate formulation optimisation while reducing development time and manufacturing costs.

Furthermore, the combination of nanocarriers with biologics, peptides, nucleic acids, and gene-editing therapeutics may expand the therapeutic potential of intranasal drug delivery for neurodegenerative disorders, brain tumours, and other complex CNS diseases. Continued collaboration between academia, industry, and regulatory agencies is essential to translate these innovative technologies into safe and effective clinical products.

8. Conclusion

Intranasal administration has emerged as a promising noninvasive strategy for delivering therapeutic agents directly to the brain, bypassing the blood–brain barrier. Nano- and microemulsions significantly improve the solubility, stability, nasal permeation, and brain bioavailability of CNS-active drugs, resulting in enhanced therapeutic efficacy and reduced systemic adverse effects. Their versatility has enabled successful preclinical applications in a wide range of neurological disorders, including Alzheimer's disease, Parkinson's disease, epilepsy, glioblastoma, depression, and migraine.

Although challenges related to large-scale manufacturing, long-term safety, and regulatory approval remain, recent advances in nanotechnology, pharmaceutical engineering, and formulation optimisation have improved the clinical prospects of these delivery systems. The future integration of targeted nanocarriers, intelligent formulation

design, and personalised medicine is expected to further enhance the effectiveness of nose-to-brain drug delivery. Overall, nanoemulsions and microemulsions represent highly promising platforms for developing next-generation CNS therapeutics.

9. References

- [1] Pardridge WM. The blood-brain barrier: bottleneck in brain drug development. *NeuroRx*. 2005;2(1):3–14.
- [2] Abbott NJ, Patabendige AAK, Dolman DEM, Yusof SR, Begley DJ. Structure and function of the blood-brain barrier. *Neurobiol Dis*. 2010;37(1):13–25.
- [3] Saraiva C, Praça C, Ferreira R, Santos T, Ferreira L, Bernardino L. Nanoparticle-mediated brain drug delivery: overcoming blood-brain barrier to treat neurodegenerative diseases. *J Control Release*. 2016;235:34–47.
- [4] Banks WA. Characteristics of compounds that cross the blood-brain barrier. *BMC Neurol*. 2009;9(Suppl 1):S3.
- [5] Illum L. Transport of drugs from the nasal cavity to the central nervous system. *Eur J Pharm Sci*. 2000;11(1):1–18.
- [6] Vasave L, Jadhav S, Bachhav R, Mahajan S, Sonawane D. Formulation and evaluation of gastro-retentive in-situ gel of anti-ulcer drug misoprostol. *Prospects Pharm Sci*. 2025;23(4):93-102. doi:10.56782/pps.441.
- [7] Djupesland PG. Nasal drug delivery devices: characteristics and performance from a clinical perspective. *Ther Deliv*. 2013;4(2):261–272.
- [8] Hanson LR, Frey WH II. Intranasal delivery bypasses the blood-brain barrier to target therapeutic agents to the central nervous system. *BMC Neurosci*. 2008;9(Suppl 3):S5.
- [9] Lochhead JJ, Thorne RG. Intranasal delivery of biologics to the central nervous system. *Adv Drug Deliv Rev*. 2012;64(7):614–628.
- [10] Jadhav SP, Dhakad PK, Gupta T, Gilhotra R. Formulation development and evaluation of iloperidone loaded nanosuspension for solubility enhancement. *Indian J Pharm Educ Res*. 2025;59(4):1323-1333. doi:10.5530/ijper.20250282.
- [11] Costantino HR, Illum L, Brandt G, Johnson PH, Quay SC. Intranasal delivery: physicochemical and therapeutic aspects. *Int J Pharm*. 2007;337(1–2):1–24.
- [12] Djupesland PG, Messina JC, Mahmoud RA. The nasal approach to delivering treatment for brain diseases. *Ther Deliv*. 2014;5(6):709–733.
- [13] Pardeshi CV, Belgamwar VS. Direct nose-to-brain drug delivery via integrated nerve pathways bypassing the blood-brain barrier: an excellent platform for brain targeting. *Expert Opin Drug Deliv*. 2013;10(7):957–972.
- [14] Jadhav SP, Patil CG, Gavhane AA, Mahajan SK, Sonawane DD. Formulation and evaluation of a Hibiscus-based herbal gel for the treatment of mouth ulcers. *Res J Pharm Dosage Forms Technol*. 2025;17(3):167-171. doi:10.52711/0975-4377.2025.00023.
- [15] Dhuria SV, Hanson LR, Frey WH II. Intranasal delivery to the central nervous system: mechanisms and experimental considerations. *J Pharm Sci*. 2010;99(4):1654–1673.
- [16] Pawar PS, Ahire SM, Jadhav SP, Patil CD, Mahajan SK. Ginkgo biloba and Gastrodia elata: Bridging Traditional Wisdom and Modern Therapy in Parkinson's Disease. From ancient

- roots to nano routes: targeted delivery of Ginkgo and Gastrodia for Parkinson's disease (PD) treatment. 2025;4:56.
- [17] Gizurarson S. Anatomical and histological factors affecting intranasal drug and vaccine delivery. *Curr Drug Deliv*. 2012;9(6):566–582.
 - [18] Agrawal M, Saraf S, Saraf S, et al. Nose-to-brain drug delivery: an update on clinical challenges and progress towards approval of anti-Alzheimer therapeutics. *J Control Release*. 2018;281:139–177.
 - [19] Behl CR, Pimplaskar HK, Sileno AP, et al. Effects of physicochemical properties and other factors on systemic nasal drug delivery. *Adv Drug Deliv Rev*. 1998;29(1–2):89–116.
 - [20] Thakare AS, Jadhav SP, Bhamare MS, Sonawane SK, Deshmukh SP, Pawar VT, Mahajan SK. Advances in green nanotechnology for sustainable pharmaceutical formulations. *Asian J Pharm Technol*. 2026;16(2):171-176. doi:10.52711/2231-5713.2026.00024
 - [21] Gupta A, Eral HB, Hatton TA, Doyle PS. Nanoemulsions: formation, properties and applications. *Soft Matter*. 2016;12(11):2826–2841.
 - [22] Solans C, Izquierdo P, Nolla J, Azemar N, Garcia-Celma MJ. Nano-emulsions. *Curr Opin Colloid Interface Sci*. 2005;10(3–4):102–110.
 - [23] Chavan MV, Bachhav RL, Sonavane DD, Patil CD, Jadhav SP, Mahajan SK, Bhamare MS, Sharma YP. Development and optimization of Ruellia tuberosa loaded Shatadhaut Ghrita-based herbal antifungal cream. *Res J Pharm Technol*. 2026;19(2):501-511. doi:10.52711/0974-360X.2026.00073.
 - [24] Ahire SM, Pawar PS, Jadhav SP, Shewale VV, Patil CD, Mahajan SK, Vishwas S. Nanotechnology-driven antioxidants and immunomodulators for polycystic ovary syndrome (PCOS) therapy. *Nanotechnology NextGen: From Treatment to Transformation in Polycystic Ovary Syndrome (PCOS)*. 2025 Jul 15:184.
 - [25] Tadros T, Izquierdo P, Esquena J, Solans C. Formation and stability of nano-emulsions. *Adv Colloid Interface Sci*. 2004;108–109:303–318.
 - [26] Shakeel F, Ramadan W, Faisal MS. Nanoemulsions as vehicles for transdermal drug delivery. *Expert Opin Drug Deliv*. 2009;6(9):953–974.
 - [27] Mason TG, Wilking JN, Meleson K, Chang CB, Graves SM. Nanoemulsions: formation, structure and physical properties. *J Phys Condens Matter*. 2006;18:R635–R666.
 - [28] Lovelyn C, Attama AA. Current state of nanoemulsions in drug delivery. *J Biomater Nanobiotechnol*. 2011;2(5):626–639.
 - [29] Ahire SM, Pawar PS, Sonawane VN, Jadhav SP. Personalized medicine and pharmacogenomics: impact of genetic variation on drug response and individualized therapy - a review. *Asian J Pharm Technol*. 2026;16(1):91-98. doi:10.52711/2231-5713.2026.00013.
 - [30] Ganta S, Devalapally H, Shahiwala A, Amiji M. A review of stimuli-responsive nanocarriers for drug and gene delivery. *J Control Release*. 2008;126(3):187–204.
 - [31] Lawrence MJ, Rees GD. Microemulsion-based media as novel drug delivery systems. *Adv Drug Deliv Rev*. 2012;64(Suppl):175–193.
 - [32] Tenjarla S. Microemulsions: an overview and pharmaceutical applications. *Crit Rev Ther Drug Carrier Syst*. 1999;16(5):461–521.
 - [33] Kreilgaard M. Influence of microemulsions on cutaneous drug delivery. *Adv Drug Deliv Rev*. 2002;54(Suppl 1):S77–S98.

- [34] Fanun M, editor. Microemulsions: Properties and Applications. Boca Raton (FL): CRC Press; 2008.
- [35] Schulman JH, Stoeckenius W, Prince LM. Mechanism of formation and structure of microemulsions by electron microscopy. *J Phys Chem.* 1959;63(10):1677–1680.
- [36] Hoar TP, Schulman JH. Transparent water-in-oil dispersions: the oleopathic hydro-micelle. *Nature.* 1943;152:102–103.
- [37] Ahire SM, Jadhav SP, Sonawane VN, Shewale VV, Pawar PS, Chavan DB, Mahaparale SP, Mahajan SK. A Compressive Review on Formulation and Evaluation of Herbal Niosomes containing *Phaseolus vulgaris* and *zingiber officinale* for the Treatment of Diabetes Mellitus. *Int j adv multidisc res stud.* 2024;4(6).
- [38] Constantinides PP. Lipid microemulsions for improving drug dissolution and oral absorption: physical and biopharmaceutical aspects. *Pharm Res.* 1995;12(11):1561–1572.
- [39] Date AA, Nagarsenker MS. Design and evaluation of microemulsions for improved parenteral delivery of propofol. *AAPS PharmSciTech.* 2008;9(1):138–145.
- [40] Talegaonkar S, Azeem A, Ahmad FJ, Khar RK, Pathan SA, Khan ZI. Microemulsions: a novel approach to enhanced drug delivery. *Recent Pat Drug Deliv Formul.* 2008;2(3):238–257.
- [41] Kumar M, Bishnoi RS, Shukla AK, Jain CP. Techniques for formulation of nanoemulsion drug delivery system: a review. *Prev Nutr Food Sci.* 2019;24(3):225–234.
- [42] Jadhav SP, Ahire SM, Pawar PS, Mahajan SK, Sonawane DD. Exploring Natural Oils: Role in Antimicrobial Activity and Preservation. *Asian Journal of Research in Pharmaceutical Sciences.* 2026 Jan 5;16(1):59-64.
- [43] Gadhave D, Waghmare J. A short review on microemulsion and its application in extraction of vegetable oil. *Int J Res Eng Technol.* 2014;3(9):147–158.
- [44] Salvia-Trujillo L, Soliva-Fortuny R, Rojas-Graü MA, McClements DJ, Martín-Belloso O. Edible nanoemulsions as carriers of active ingredients: a review. *Annu Rev Food Sci Technol.* 2017;8:439–466.
- [45] Gupta PK, Pothuraju R, Chagalamarri J, et al. Microemulsion-based drug delivery system: a comprehensive review. *Drug Deliv Transl Res.* 2021;11(5):1818–1848.
- [46] Nighute S, Sahu N, Raut A, Jadhav S. Elucidation of patentability considerations for SGLT-2 and DPP-4 inhibitor anti-diabetic drug products in India vis-à-vis USA. *Int J Pharm Sci Res.* 2026;17(2):550-571. doi:10.13040/IJPSR.0975-8232.17(2).550-71.