

A Detailed Review on Bridging Niosomal Carriers for Nose to Brain Drug Delivery: Principles, Translational Pathways and Attributes

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ABSTRACT

Non-invasive nasal drug delivery systems have emerged as a promising route for drug administration. It facilitates rapid therapeutic effect, bypass first pass metabolism, increase patient compliance and provides nose-to-brain drug delivery. The nasal mucosa possesses high vascularization and large surface area enabling efficient uptake of both systemic and locally administered drugs. Nasal administration is especially beneficial in emergency situations such as migraines, seizures, and severe pain. Nasal dosage forms have been developed to enhance drug retention and improve therapeutic efficacy. Niosomal carriers offer a versatile and clinically promising platform to overcome the anatomical and physiological barriers of nose-to-brain drug delivery, combining enhanced mucosal adhesion, tunable release kinetics, and improved drug stability to facilitate direct transport along olfactory and trigeminal pathways. This review synthesizes fundamental principles of niosome design, surfactant selection, bilayer composition, size and surface charge modulation, and functionalization strategies to illustrate how physicochemical attributes govern mucociliary clearance, epithelial uptake, and neuronal translocation. Critical attributes such as encapsulation efficiency, payload versatility, stability under nasal conditions, and potential for targeted ligand decoration are evaluated alongside strategies to mitigate immunogenicity and off target deposition. The niosomal systems poised to expand therapeutic options for central nervous system disorders via minimally invasive intranasal administration.

Keywords: Blood Brain Barrier, Controlled Release, Nasal Delivery, Niosomes, Nose-to-brain Drug Delivery.

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INTRODUCTION

Several routes of drug administration exist to deliver the active molecule and achieve a therapeutic response. The primary routes of drug delivery include oral, intravenous, intramuscular, transdermal and intranasal administration. Oral drug delivery is the most widely used and convenient method but it often restricted due to first pass metabolism, gastric irritation and degradation of drugs through various enzymes. The gastro intestinal epithelium restricts drug permeability and absorption into the bloodstream through its mucus layer, metabolic enzymes, and tight junctions. Furthermore, fluctuations in pH and the composition of gut micro flora also affect drug stability and release, thereby decreasing overall bioavailability (Lou *et*

al., 2023; Azman *et al.*, 2022). The transdermal route is mainly restricted by the strong barrier function of the stratum corneum, which limits the penetration of large molecules, permitting only substances with a molecular weight below 500 Da to pass through effectively (Das *et al.*, 2017). The intravenous administration poses risks including needle stick injuries, infections, phlebitis, thrombosis, and circulatory overload, making it invasive and less suitable for long-term use (Homayun *et al.*, 2019). Further, the intravenous route requires skilled healthcare professionals, adherence to strict aseptic techniques, and patient cooperation, thereby increasing costs and limiting its applicability for large groups or multiple dosing schedules (Panza *et al.*, 2022). The intramuscular injections are commonly used for vaccine delivery, they have several drawbacks, particularly for biopharmaceuticals like peptides and proteins. It often leads to low bioavailability and decreased immunogenicity, as proteins may form aggregates at the injection site, thereby compromising stability and effectiveness (Liang *et al.*, 2016; Nanaki *et al.*, 2017; Fletcher *et al.*, 2018). To avoid all the drawbacks of various routes and to provide localized action, the current review focused to make a note of intranasal route. It administers drugs into the nasal cavity



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where absorption occurs across the respiratory and olfactory epithelia. The nasal mucosa is highly vascularized and linked to the brain through nerve pathways, forming direct connections for molecules to reach central nervous system targets without full systemic circulation and hepatic first pass loss. This anatomical advantage has driven renewed interest in intranasal strategies for neurotherapeutics, vaccines, and rapid symptomatic treatments (Ghosh *et al.*, 2024).

Niosomes are considered advantageous over traditional drug formulations because they overcome several limitations associated with conventional dosage forms, including low bioavailability, rapid breakdown, and non-targeted drug distribution. Traditional formulations often result in fluctuations in drug levels and necessitate either higher or more frequent dosing, thereby elevating the risk of adverse effects. Composed of non-ionic surfactant bilayers, niosomes encapsulate both hydrophilic and lipophilic drugs, safeguarding them from degradation due to chemicals, enzymes, and metabolism. This encapsulation boosts drug stability and extends circulation time. Their ability to provide controlled and sustained drug release maintains therapeutic drug levels for prolonged periods, thereby reducing dosing frequency and improving patient adherence. The current review focus on the detailed description of nasal route applications in localized delivery through nanocarriers.

Search Strategy

A comprehensive literature search was conducted using databases including PubMed, Science Direct, and Google Scholar to identify relevant studies published between 2013 and 2025. Keywords employed in the search included "Niosomes," "Nose-to-brain delivery," "Intranasal drug delivery," "Blood-brain barrier," and "Nanocarriers." The search prioritized articles focusing on formulation attributes, preparation techniques like thin-film hydration and microfluidics, and *in vivo* efficacy in central nervous system disorders. References were screened to ensure they addressed the transport mechanisms via olfactory and trigeminal pathways.

Nasal drug delivery system

Nasal delivery system has been a well-established practice for several decades, and is a frequently employed method of administration for locally acting treatments for conditions such as allergic rhinitis, sinusitis, and congestion, and it is increasingly being utilized and investigated for systemic delivery, e.g., migraine, Alzheimer's and Parkinson's etc. (Williams *et al.*, 2022). Nasal drug delivery systems enhance drug availability at the site of action by modifying its dissolution properties and permeation profile increasing its retention at the nasal mucosa. The nasal cavity's anatomy and physiology are the most important variables influencing nasal administration, primarily because of mucociliary clearance, and the complex shape of the nasal cavity, which influence the drug delivery (Hafne, 2022).

The nasal cavity is a complex anatomical structure that forms a connection between nostrils and nasopharynx, performing several key functions such as respiration, smelling, and filtering airborne particles. The structure and composition of a nasal drug delivery system are vital to its effectiveness (Pal *et al.*, 2024). The nasal anatomy is described in Figure 1.

The nasal cavity is comprised of two distinct regions extending from the nostrils to the nasopharynx. The nasal cavity can be divided into three distinct areas: the vestibular area, the respiratory area, and the olfactory area. The area of the vestibular region is situated at the entrance of the nostrils, covers approximately 0.6 cm², this region comprises nasal hairs, and few ciliated cells (Crisler *et al.*, 2020). The nasal cavity is predominantly made up of the respiratory area, which accounts for up to 80-90% of its total volume. This section of the respiratory system is distinguished by a pseudostratified columnar epithelium and is the most vascular area. The respiratory epithelium is mainly made up of four different cell types: goblet cells, ciliated, non-ciliated columnar and basal cells. The olfactory region covers 10 cm² (Keller *et al.*, 2022; Chamanza *et al.*, 2015). The nasal cavity's extensive surface area, is largely due to the presence of turbinates and meatuses (Helwany *et al.*, 2021). The rich blood supply to the nasal mucosal lining facilitates the targeted distribution of absorbed molecules. The nasal mucosa vascularized by two different vessels, resistance vessels, are muscular vessels with a small lumen; capacitance vessels are thin-walled and elastic (Ugwoke *et al.*, 2001, De *et al.*, 2022). Administering therapeutic compounds through the nose presents a practical option for delivering treatments both directly to the local area and throughout the body. The nasal mucosa offers a considerable surface area that facilitates rapid onset of effects, enables direct access to the CNS, bypasses hepatic metabolism, and provides non-invasive characteristics; collectively, these features can optimize patient convenience, comfort and adherence. Intranasal treatment does not necessitate sterile preparations, it is non-invasive, painless, and can also be easily and quickly administered by the patient (Bhandwalkar *et al.*, 2020).

The drug absorption rate is influenced by physiological factors, including the rate of nasal secretion, mucociliary movement, and metabolism (Kumar *et al.*, 2016). This route also has certain limitations. Absorption through the nose is not possible for all drugs, and it depends on properties such as molecular weight, solubility, pKa, and lipophilicity. Drugs exhibiting low solubility, large molecular weights, or polar configurations may experience impaired absorption due to expedited clearance, reduced permeability, or enzymatic breakdown in the nasal passage (Aulton *et al.*, 2013). The nasal mucosa is highly sensitive to irritation, and factors such as pH, dosage form type, excipients, and drug concentration have a significant impact on the absorption process. Various physiological barriers such as mucociliary clearance, nasal enzymes, and nasal blood flow,

along with conditions like rhinitis, infections, and allergies, can impede drug absorption. Trapped drugs can also be limited in their ability to reach the epithelium by mucus (Ghori *et al.*, 2015).

Strategies for enhancing nasal drug administration

The following methods were employed to improve the drug's accessibility and permeation through the nasal mucosa (jassim *et al.*, 2018). Various strategies of nose to brain delivery are shown in Figure 2.

Increasing the residence time

Sustaining the drug retention in the cavity enhances the availability of drugs. Polymers like methylcellulose, HPMC, and carbopol enhance viscosity and serve as mucoadhesive agents to prolong clearance. Biodegradable microspheres can extend their stay in the nasal area by swelling in the nasal fluids and thickening the formulation's consistency.

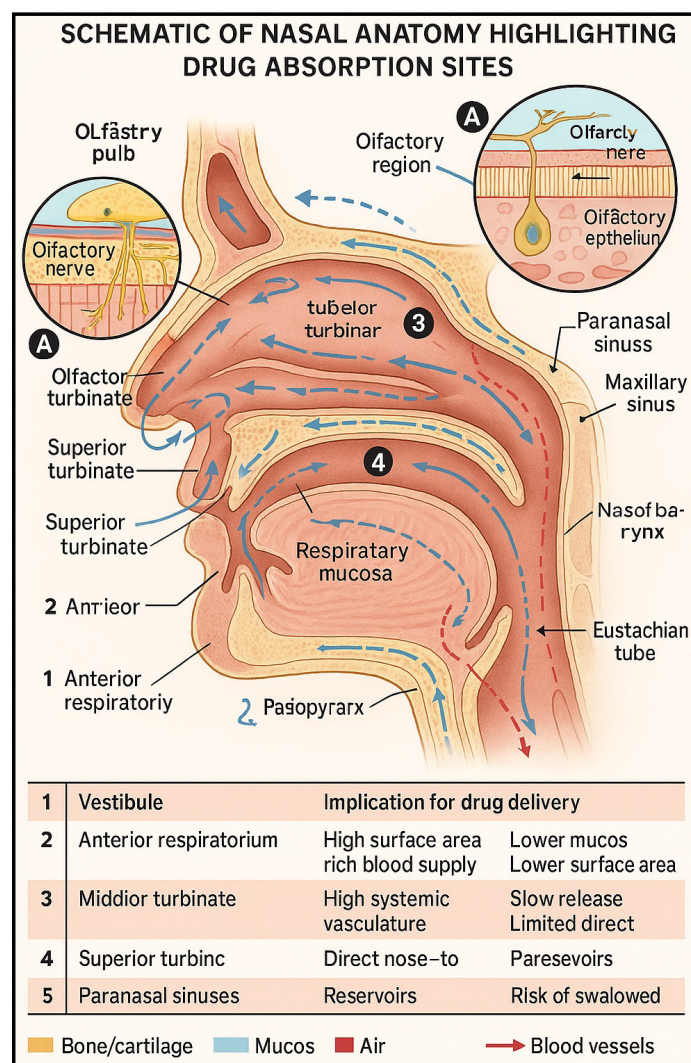


Figure 1: Nasol anatomy highlighting drug absorbtion sites.

Improving Nasal Absorption

Permeation enhancers increase the absorption of drugs across the nasal epithelial layer by modifying membrane permeability. They act by opening tight junctions, reducing mucociliary clearance rates, inhibiting enzymes, or decreasing mucus viscosity. An ideal enhancer should be potent, non-poisonous, non-inflammatory, compatible with medications, and function through safe, well-established processes. Examples of absorption enhancers include surfactants, cyclodextrins, fatty acid slats, phospholipids, bile salts, chelating agents, enzymatic inhibitors, cosolvents, prodrugs.

Targeted drug delivery

Various advanced delivery systems are capable of delivering the drug across the nasal mucosa and facilitate direct access to brain. Liposomes, niosomes, microspheres, nanoparticles, and *in situ* gelling systems can achieve nasal absorption without irritating the nasal mucosa and have good safety profile. Novel dosage forms with neutral or have a slightly negative charge exhibit improved diffuse, whereas positively charged systems frequently bind strongly to mucins and are rapidly cleared. Surface modification, especially through PEGylation, decreases mucus adhesion and improves stability (De *et al.*, 2022).

Improving solubility and stability

Absorption of drug with low solubility and stability can be increased through improving the formulation strategies. Solubility can be improved by adjusting the pH. Stability and solubility of the drug can be enhanced by complex formation using cyclodextrins. Permeation of the drug can be increased by using solvents and cosolvents. Development of prodrugs with muco-penetrative agents, improves the stability of the drug (Keller *et al.*, 2022).

Few reports demonstrated enhanced nasal drug absorption and proved through various reports that niosomal formulations significantly improve nasal drug delivery compared to traditional methods. Intranasal niosomal delivery of nefopam hydrochloride to rats resulted in a 4.77-fold rise in relative bioavailability relative to the oral solution, with notably higher peak plasma concentrations and a longer elimination half-life, suggesting improved permeation and prolonged systemic exposure through the nasal pathway (Abou-Taleb *et al.*, 2018). *In vitro* testing of carvedilol-loaded mucoadhesive niosomes found a maximum of 4.8 times more drug release after 24 hr than the free drug, as well as roughly 1.7 times increase in release compared with uncoated formulations, highlighting improved drug availability at the site of absorption (Azrak *et al.*, 2024). Additional studies indicate that surface-modified niosomes, such as chitosan-coated vesicles, exhibit stronger mucoadhesion and longer nasal residence time than unmodified nanoparticles. These properties enhance nasal epithelial permeation and nose-to-brain transport, demonstrating

superior absorption and targeting efficiency of niosomal systems compared with other nanocarriers (Rinaldi, *et al.*, 2018).

Nose-to-brain drug delivery

Blood brain barrier prevents entry of any pharmaceutical compounds into brain. A non-invasive approach has been designed to deliver drugs directly to the brain by avoiding the blood-brain barrier via intranasal administration through the olfactory nerve pathway (Huanget *al.*, 2023). The nasal cavity's olfactory epithelium serves as a link between the external environment and central nervous system (Shen *et al.*, 2025). This distinctive anatomy of the olfactory epithelium allows the intranasal delivery approach to transport therapeutics across the olfactory epithelium to the olfactory bulb in the brain (Norwood *et al.*, 2019; Spera *et al.*, 2023). The pathways of nose to drug are shown in 3.

Targeted drug delivery from the nasal cavity into the brain takes place along multiple routes, which involve both direct neural pathways via the olfactory and trigeminal nerves and indirect systemic transport through the blood vessels and lymphatic system (Mittal *et al.*, 2014). Delivering drugs to the brain through the direct olfactory and trigeminal nerve pathways offers a rapid and efficient method (Keller *et al.*, 2022). The olfactory pathway involves intra- and extra-neuronal transport as well as paracellular and transcellular mechanisms, enabling drugs to cross the olfactory epithelium and reach the olfactory bulb via the cribriform plate (Bourganis *et al.*, 2018). The intracellular pathway includes axonal transport, endocytosis by sensory cells and exocytosis into the olfactory bulb (Crowe *et al.*, 2018). The extracellular pathway directly delivers the drug through the paracellular space, and perineural space into the subarachnoid space around the brain (Selvaraj *et al.*, 2018).

The trigeminal nerve offers an alternative pathway to both the rostral and caudal brain regions via its ophthalmic and maxillary branches (Lochhead *et al.*, 2020). Transport of substances through the respiratory epithelium to the brain may occur indirectly, but the ability of molecules to pass through the BBB is still the main limiting factor and tends to favor small, lipid-loving molecules (Crowe *et al.*, 2018). The blood–brain barrier restricts the effective distribution of many CNS treatments; nonetheless, the intranasal route facilitates direct drug delivery to the brain by circumventing the BBB. Intranasal delivery offers a more effective route for transporting drugs than intravenous delivery (Gharbavi *et al.*, 2023).

Nose-To-Brain Mechanisms

Following intranasal administration, formulations of drugs within the nasal cavity's olfactory and upper respiratory areas interact with the nasal mucosa and cross the epithelial barrier through transport between tight junctions, diffusion across epithelial cells, or endocytosis, especially in the case of peptides, proteins, and nanoparticulate systems. After penetrating the epithelial layer, drugs reach the nerve pathways of the olfactory and trigeminal systems, where they are primarily transported along nerve sheaths to the olfactory bulb and other brain regions within minutes via extracellular or perineural transport, with lesser contributions from intracellular axonal transport (Lochhead and Thorne, 2012). Simultaneously, transport via the trigeminal nerve enables drug distribution to deeper brain structures including the brainstem and cerebellum (Pardeshi *et al.*, 2013). Following this, drug molecules reach the brain's interstitial and cerebrospinal fluids, resulting in a broad distribution throughout the central nervous system with limited systemic exposure and fewer peripheral side effects.

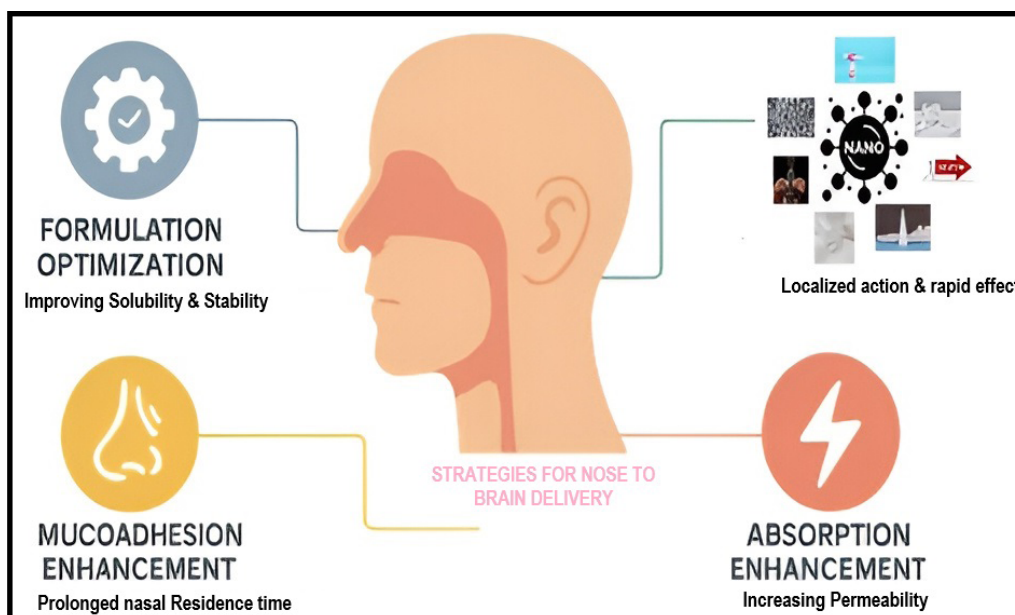


Figure 2: Strategies for nose to brain delivery

PATHWAYS OF NOSE-TO-BRAIN DELIVERY

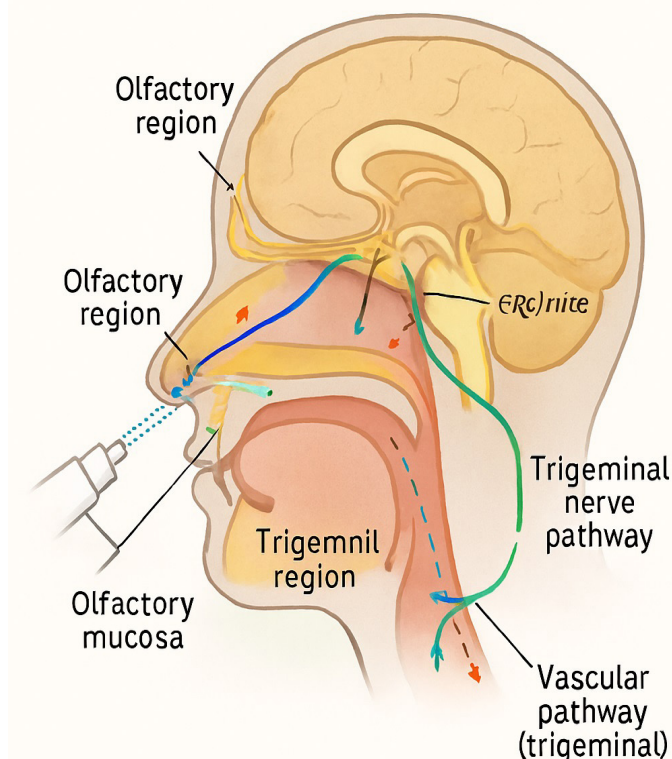


Figure 3: Pathways of Nose to Brain Delivery.

Factors Affecting Nose To Brain Delivery

The process of nasal absorption for delivering drugs directly to the brain is affected by the attributes of the drug, the characteristics of its formulation, and the conditions within the nasal cavity. Drugs with molecular weights under 1000 Da (Pires *et al.*, 2022) and higher lipophilicity tend to pass through the nasal epithelium more easily, although solubility, stability, and pH in comparison to the drug's pKa also impact absorption (Madden *et al.*, 2023). Factors in formulation like particle size, viscosity, osmolarity, and the use of permeation enhancers or mucoadhesive agents influence residence time and mucosal penetration (Shen *et al.*, 2025; Katare *et al.*, 2024). The nasal mucosal integrity, blood flow, temperature, humidity, mucociliary clearance, and mucus production all influence the way drugs are absorbed, which underscores the importance of developing formulations that are tailored to achieve effective delivery of drugs directly to the brain (Cingi *et al.*, 2021; Nguyen *et al.*, 2025; Lee *et al.*, 2021).

Niosomes For Brain Targeting

Intranasal brain targeting may be made more effective through the use of advanced drug delivery systems, which can help to overcome the issue of poor drug bioavailability (Fahmy *et al.*, 2020). Multiple studies have shown that various nanocarriers, such as liposomes, dendrimers, microspheres, nano-emulsions, and carbon-based Nano-formulations, can successfully deliver

drugs to the brain via the nose (Crowe 2018). The ability of niosomes to safeguard drugs in biological fluids and deliver them effectively to targeted cells makes them promising and versatile nasal carriers (Nguyen *et al.*, 2025).

The simplicity and affordability of their manufacturing process, combined with its scalability, help address the challenges linked to liposomes, including high production costs and instability issues. As a result of these advantages, niosomes have garnered significant interest in pharmaceutical uses such as anticancer, antifungal, vaccine, and gene delivery (Thabet *et al.*, 2022; Moammeri *et al.*, 2023). Niosomes provide various benefits for nasal drug delivery, including increased drug stability, better permeation across the nasal mucosa, and protection of encapsulated drugs from enzymatic breakdown. Their mucoadhesive properties allow for increased residence time, thereby overcoming rapid mucociliary clearance to improve absorption and bioavailability.

Niosomes allow for controlled and prolonged release of medications, accommodate both hydrophobic and hydrophilic drugs, and can facilitate direct delivery to the brain via the nose by circumventing the blood-brain barrier. Systemic side effects are reduced, enabling localized delivery and requiring lower doses. In order to overcome the challenges of nasal drug delivery, such as low dosage, degradation, rapid clearance and poor permeability of specific drugs, specialized formulation techniques are necessary.

Attributes Of Niosomes Facilitating Nose-To- Brain Dug Delivery

Niosomes are particularly suitable for Nose-to-Brain (N2B) delivery because of their nanoscale, enabling them to traverse the mucus layer and access the olfactory and respiratory epithelium. Small vesicles (100-250 nm) in size exhibit prolonged residence within the nasal mucosa, which in turn enhances their absorption and transport along the olfactory and trigeminal pathways. The niosome bilayer composition improves drug stability and allows for controlled release, with surfactants functioning as permeation enhancers by temporarily opening tight junctions to facilitate both paracellular and transcellular transport. Positively charged niosomes interact well with the nasal mucosa which is negatively charged, enhancing mucoadhesion and boosting drug bioavailability in the brain. Chitosan-coated nanocarriers below 300 nm have demonstrated efficient transcellular transport to the brain (Nerli *et al.*, 2023).

The hydration of niosomal vesicles facilitates drug penetration by temporarily fluidizing the mucus layer and increasing diffusion. Surfactants like Span, Tween, and Cremophor also function as chemical penetration enhancers, which interact with mucosal lipids and proteins to boost drug permeation through the nasal epithelium without causing damage. Research has shown that intranasal niosomal systems greatly increase brain bioavailability, resulting in a 2-7-fold higher brain delivery compared to

conventional intranasal solutions or gels. Strategies like ensuring pH compatibility, incorporating mucoadhesive agents to extend residence time, and using absorption enhancers or advanced nanocarrier systems are crucial to enhance drug stability, permeability, and overall therapeutic effectiveness (Nguyen *et al.*, 2025).

Broad comparative reviews also highlight that niosomal nanocarriers combine the advantages of both liposomes and polymeric nanoparticles such as the ability to encapsulate hydrophilic and lipophilic drugs with extended stability while being more cost-effective and less complex to manufacture reinforcing their practical superiority over certain lipid-based and polymeric systems in nano-drug delivery applications (Witika *et al.*, 2022). Studies of physiochemical properties show that niosomes retain stability and permeability similar to liposomes, but have enhanced protection against oxidation and hydrolysis due to their non-ionic surfactant structure (Bartelds *et al.*, 2018). Dendrimers offer high drug-loading capacity, but their intricate synthesis and potential for harming cells hinder their use, in contrast to niosomes, which show enhanced compatibility with living tissues and simplified preparation methods (Kazi *et al.*, 2010). Niosomes enable efficient encapsulation of both hydrophilic and lipophilic drugs while avoiding the use of harsh organic solvents commonly required in polymeric nanoparticle preparation. Niosomes maintain their structural integrity and prolong drug release, in contrast to solid lipid nanoparticles which

are limited by restricted drug loading and storage instability (Pardeike *et al.*, 2009). Overall, niosomes offer a well-balanced combination of stability, safety, versatility, and cost-effectiveness among available nanocarrier systems.

COMPONENTS OF NIOSOMES

Non-ionic surfactants

Non-ionic surfactants are crucial for the formation of niosomes due to their amphiphilic nature which includes a polar head group and a non-polar hydrophobic tail. In comparison to anionic, cationic, and amphoteric surfactants, these surfactants exhibit greater stability and lower toxicity. They also function as wetting agents and emulsifiers, increasing solubility, permeability, and the absorption of drugs, while reducing the risk of hemolysis and irritation (Moghtaderi *et al.*, 2022). The surfactants commonly used in niosomes include sorbitan esters, polysorbates and Brij 35. Three key factors, the hydrophilic-lipophilic balance, gel-liquid transition temperature and critical packing parameter, significantly impact entrapment efficiency (Sharma *et al.*, 2015). Surfactants with low HLB values, such as Span 60, are reported to result in the maximization of EE, especially for lipophilic drugs (Wu *et al.*, 2021; Bnyan *et al.*, 2018).

Cholesterol

Cholesterol serves as a widespread component of niosomes, contributing to the stability of the vesicles and the encapsulation of

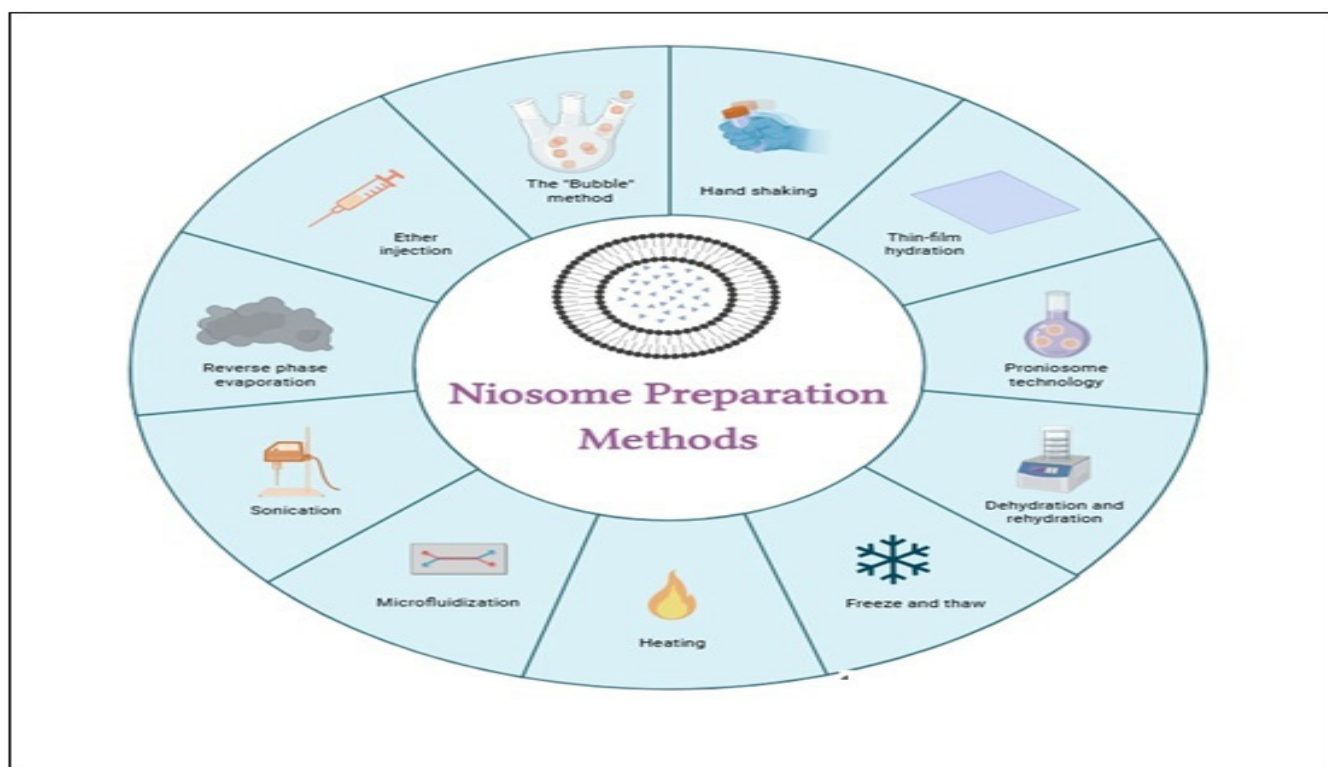


Figure 4: Niosomes preparation Methods.

the drug. It is structurally a cyclopentanoperhydrophenanthrene sterane, composed of four fused rings (Bautista-Solano *et al.*, 2025). The cholesterol enhances membrane cohesion and mechanical strength in niosomes, reduces their bilayer flexibility, controls drug permeability, increases the phase transition temperature, and minimizes drug leakage, thereby increasing encapsulation efficiency and stability. The ratio of surfactant to cholesterol has a significant impact on the structure and viscosity of vesicles. Increasing the cholesterol concentration has been proven to enhance the encapsulation efficiency of hydrophilic markers like carboxy fluorescein in a linear manner, by enhancing the packing of the bilayer and impeding transport across the membrane (Bhardwaj *et al.*, 2020; Chen *et al.*, 2019).

Charge-inducing molecules

Charge-inducing molecules are incorporated into niosomal formulations to give them a positive or negative surface charge, which stabilizes the vesicles through electrostatic repulsion and stops them from aggregation (Lu *et al.*, 2020). The zeta potential reflects its effect, with values $>+30$ mV or <-30 mV represent greater stability, while values between 5-15 mV are in the flocculation region (Umbarkar, 2020). Anionic charge inducers typically used are dicetyl phosphate and phosphatidic acid, while cationic agents comprise stearyl amine, sodium stearyl lactate, and stearyl pyridine chloride (Mohanty *et al.*, 2018). Charge inducers can also enhance encapsulation efficiency and influence vesicle size.

Hydration medium

In niosome preparation, the hydration medium is a crucial element and is usually a buffer chosen based on the solubility and stability of the drug. Buffer pH has a significant impact on vesicle formation, drug loading, and stability (Unal *et al.*, 2023). Selecting a suitable hydration medium, taking into account the physicochemical properties of the drug, is crucial for forming stable niosomes that can efficiently transport drugs (Figure 3).

PREPARATION METHODS

Some of the commonly employed preparation methods for niosomal formulation are mentioned in Figure 4.

Thin film hydration method

The Thin-Film Hydration (TFH) technique, is the most commonly used approach for niosomes preparation (Gharbavi *et al.*, 2023). In this method, cholesterol, non-ionic surfactant, and charge-inducing agents are dissolved in a volatile organic solvent, such as diethyl ether, ethanol or chloroform, inside a round-bottom flask. A thin dry lipid layer is produced on the flask wall by evaporating the solvent using a rotary evaporator. The film is then hydrated with a water-based phase while being gently mixed, leading to the formation of multilamellar niosomes. Drugs that are hydrophilic are incorporated in the aqueous

phase, whereas drugs that are hydrophobic are incorporated in the organic phase prior to film formation. The subsequent step involves hydrating the film by gently mixing it with an adequate aqueous phase, resulting in the swelling and spontaneous self-assembly of surfactant molecules into multilamellar niosomal vesicles.

Reverse phase evaporation

This method is frequently employed to manufacture large unilamellar vesicles. This method involves blending cholesterol and surfactant in various molar ratios in an organic solvent mixture (Alle *et al.*, 2021). A rotary evaporator is employed to evaporate the solvent, resulting in the formation of a thin dry lipid film. The film is subsequently dissolved in appropriate volume of ether, followed by the addition of a specified amount of the drug dissolved in an organic solvent such as acetone combined with buffer (pH 7.4). The mixture is subjected to a bath sonicator for a few minutes, manually agitated, and re-sonicated to achieve uniform dispersion.

Ethanol injection method

An ethanolic lipid solution is readily introduced into an aqueous phase, resulting in the formation of small unilamellar vesicles. Co-solvents such as isopropanol can be added to increase solubility and increase drug entrapment (Machado *et al.*, 2020; Estupinan *et al.*, 2020). The injection temperature and speed can be adjusted to control size and aggregation of vesicles, thus offering flexibility in formulation. This technique is straightforward, cost-effective, and can be easily scaled up without the need for advanced machinery. Niosomes produced using this method is typically smaller than those produced by thin-film hydration and microfluidics.

Microfluidic method

Niosomes are fabricated using microfluidic equipment consisting of central and side passageways, through which the organic and aqueous liquids are propelled at predetermined flow rates into a reaction compartment (Bhardwaj *et al.*, 2020). The rapid mixing process within the microchannels results in the spontaneous formation of small, uniform niosomes, which are then collected from the outlet channel (Machado *et al.*, 2020). This approach enables precise control over particle size and polydispersity by modifying the flow rate ratio and processing conditions. Benefits of this technique comprise minimal solvent use, replicability, expandability, and the capability to manufacture cholesterol-free formulations (Garcia-Manrique *et al.*, 2019; Mawazi *et al.*, 2025). Niosomes produced by microfluidics are typically smaller than those created through thin-film hydration.

Ether injection method

This technique for niosomal preparation dissolving non-ionic surfactants and cholesterol in ether, often combined with a small amount of co-solvent. The resulting solution is then injected

into a buffered solution, under constant stirring and controlled temperature. The temperature difference between the organic and aqueous phases promotes spontaneous formation of niosomal vesicles. This method allows for the gradual and controlled formation of vesicles, with size and characteristics influenced by injection rate, temperature, and stirring conditions (Amreen *et al.*, 2023).

The Bubble Technique

This method eliminates the need for organic solvents and necessitates the use of a three-neck glass flask placed in a water bath to maintain the temperature. The first neck accommodates a thermometer, the second is employed for the inlet of nitrogen gas, and the third is connected to a water-cooled reflux

condenser. Mixture of surfactant, cholesterol, and buffer is then heated sequentially to 70°C to produce a dispersion. Next, the mixture undergoes high-shear homogenization for 15 sec before being subjected to nitrogen bubbling at a temperature of 70°C immediately afterwards. This process yields large unilamellar vesicles (Bhardwaj *et al.*, 2020). Many niosomal formulations are developed in recent years for nose-to-brain drug delivery to treat various CNS related disorders. Few developed niosomal nasal formulations are mentioned in Table 1.

FUTURE DIRECTIONS

Nose-to-brain delivery using niosomal formulations appears promising, but several challenges need to be overcome for clinical application. Future studies on nose-to-brain delivery

Table 1: Niosomal formulations developed for nose-to-brain delivery.

Sl. No.	Drug	Dosage form	Treatment	Outcome	References
1.	Ondansetron HCl	Niosomal gel	Prevent nausea and vomiting caused by chemotherapy	The formulation exhibited a high drug entrapment efficiency of $76.13 \pm 1.2\%$ and achieved sustained drug release rates of 91.76% from the niosomes and 70.6% from the <i>in situ</i> gel over a period of 12 hr, suggesting efficient drug loading and controlled release properties.	(Teaima <i>et al.</i> , 2020)
2.	Lacosamide	Chitosan-coated niosomes (niosomal dispersion)	Epilepsy	The vesicle size is approximately 194 nm, it has an entrapment efficiency of 58.3%, a positive zeta potential of +35.6 mv, and achieves sustained drug release of 81.3% after 8 hr, also enhancing nasal diffusion.	(Tulbahet <i>et al.</i> , 2023)
3.	Bromocriptine mesylate	Niosomes	Parkinson's Disease	Significant increases in brain bioavailability (approximately 10.4-fold) were observed, along with high direct transport (91.06%), an enhanced pharmacodynamic response achievable with a 10-fold reduction in dose, and no notable toxicity.	(Sita <i>et al.</i> , 2020)
4.	Methotrexate	Niosomal thermo-sensitive <i>in situ</i> nasal gel	Brain tumors and CNS malignancies	The <i>in situ</i> gel provided prolonged nasal residence, facilitated controlled release, enhanced brain concentration, decreased systemic exposure, and minimized side effects in comparison to MTX solution.	(Ourani <i>et al.</i> , 2022)
5.	Folic acid	Niosomes	Alzheimer's	Optimized niosomes (Span 60: Cholesterol in a 1:1 ratio) demonstrated good stability at 4°C and 25°C, and they facilitated increased nasal absorption approximately 48% within 6 hr, which suggests enhanced bioavailability relative to conventional formulations.	(Ravouru <i>et al.</i> , 2013)
6.	Buspirone Hydrochloride	Niosomal <i>in situ</i> nasal gel	Treatment of anxiety disorders	The sustained release of drugs ($\sim 83.5\%$ <i>ex vivo</i> in 8 hr) along with stable vesicles and enhanced nasal absorption indicates the potential for effective intranasal delivery compared to conventional gels.	(Mathure <i>et al.</i> , 2018)

Sl. No.	Drug	Dosage form	Treatment	Outcome	References
7.	Clonazepam	Chitosan-coated niosomes	anxiety, seizures	The formulation remained stable for 12 weeks, displayed a sustained release pattern of approximately 50% in 4 hr, enhanced mucoadhesion, experienced a 10-fold increase in nasal permeability, and exhibited a 1.5-fold decrease in toxicity relative to the free drug.	(Sharma <i>et al.</i> , 2015)
8.	Citicoline	Niosomal <i>in situ</i> nasal gel	Management of epilepsy	The enhanced nasal permeation led to the prolonged nasal residence of the incorporated <i>in situ</i> gel, improved brain uptake and demonstrated significant protective effects against seizures at a low dose, compared to the oral drug solution.	(Bekhet <i>et al.</i> , 2022)
9.	Kynurenic Acid	Niosomal <i>in situ</i> nasal gel	Neuroinflammation	The niosomal gel formed a stable structure with effective drug encapsulation, and intranasal delivery greatly increased bioavailability compared to oral administration.	(Chettupalli <i>et al.</i> , 2025)
10.	Risperidone	Niosomal dispersion	Management of schizophrenia	The nanoparticles exhibited good stability and prolonged release properties, resulting in increased nasal absorption and enhanced delivery of the drug to the brain, demonstrated by a 2.32-fold higher nasal permeation rate compared to the suspension.	(Qureshi <i>et al.</i> , 2019)
11.	Olanzapine	Niosomal dispersion	Management of schizophrenia	Higher nasal absorption and prolonged delivery compared to solution formulation; stable over storage; optimised formulation demonstrated a 3-fold increase in brain concentration, indicating enhanced bioavailability.	(Khallaf <i>et al.</i> , 2020)
12.	Pentamidine	Glutamate-coated niosomal dispersion	Potential treatment of CNS infections	Coated niosomes exhibited stability with mucoadhesive characteristics; the entrapment and retention within the nasal cavity indicate a possibility for effective nose-to-brain delivery and enhanced bioavailability.	(Rinaldi <i>et al.</i> , 2018)
13.	Amisulpride	Niosomal <i>in situ</i> nasal gel	Management of schizophrenia	The nasal gel ensured stable encapsulation of the drug, controlled its release, and facilitated enhanced delivery of the drug to the brain, thereby improving bioavailability.	(Patil <i>et al.</i> , 2023)
14.	Flibanserin	Niosomal <i>in situ</i> nasal gel	Treatment of hypoactive sexual desire disorder	The intranasal niosomal <i>in situ</i> gel exhibited stability and a well-structured form, displayed efficient drug encapsulation, promoted enhanced nasal permeation, and significantly increased brain and systemic availability, thereby demonstrating effective nose-to-brain delivery compared to conventional oral administration.	(Moammeri <i>et al.</i> , 2023)

Sl. No.	Drug	Dosage form	Treatment	Outcome	References
15.	Valproic Acid	Niosomal thermo-sensitive <i>in situ</i> nasal gel	Treatment of epilepsy and seizures	The niosomal <i>in situ</i> nasal gel demonstrated effective drug encapsulation, controlled drug release, and acceptable mucoadhesive and gelation properties. The formulation proved safe to nasal tissue, increased drug accessibility, and showed potential for effective nose-to-brain delivery at reduced dosages and with enhanced patient convenience.	(Chaudhari <i>et al.</i> , 2013)

of niosomal formulations should concentrate on improving targeting efficiency, safety, and clinical applicability. Niosomes modified to interact with the surface may greatly enhance targeted transport through the olfactory and trigeminal pathways while reducing systemic exposure. Ensuring reproducibility and scalability for industrial production necessitates optimizing niosomal composition, vesicle size, and manufacturing processes. Additionally, thorough assessment of long-term safety, neurotoxicity, and immunogenicity post repeated intranasal administration is also essential. Future research should focus on the development of the standard regulatory guidelines for intranasal carriers.

CONCLUSION

The nasal route functions as an alternative method of administration for conventional and parenteral methods. It provides a rapid onset of action and bypass hepatic first-pass metabolism. This also enables brain delivery through the trigeminal and olfactory pathways. Various formulation approaches have been investigated to improve drug solubility, absorption, and residence time within the nasal cavity. Niosomal systems have evolved as an advanced delivery platform, offering improved drug stability, controlled release, and increased permeation through the nasal mucosa. Their capacity to enclose both hydrophilic and lipophilic drugs enhances bioavailability and makes it possible for targeted and site-specific delivery, including potential transport across biological barriers such as the nasal mucosa and the blood–brain barrier. Niosomes can prolong nasal residence time, improve drug stability and also facilitate direct drug delivery to brain through olfactory and trigeminal pathways improving the bioavailability and reducing the side effects.

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ABBREVIATIONS

BBB: Blood-Brain Barrier; **CNS:** Central Nervous System; **EE:** Entrapment Efficiency; **HLB:** Hydrophilic-Lipophilic Balance; **HPMC:** Hydroxypropyl Methylcellulose; **MTX:** Methotrexate; **N2B:** Nose-to-Brain; **TFH:** Thin Film Hydration.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTIONS

All authors contributed equally.

REFERENCES

- Abou-Taleb, H. A., Khallaf, R. A., & Abdel-Aleem, J. A. (2018). Intranasal niosomes of nefopam with improved bioavailability: Preparation, optimization, and *in vivo* evaluation. *Drug Design, Development and Therapy*, 12, 3501–3516. <https://doi.org/10.2147/DDDT.S177746>.
- Alle, M., Samed, N., & Kim, J. C. (2022). Niosomes: A Smart Drug Carrier Synthesis, Properties and Applications. In *Smart Nanomaterials in Biomedical Applications* (449–486). Cham: Springer International Publishing.
- Amreen, A., & KV, R. (2023). Formulation and evaluation of tramadol hydrochloride-loaded niosomal gel by ether injection method. *Asian Journal of Pharmaceutical and Clinical Research*, 16, 170–173.
- Aulton, M. E., & Taylor, K. (Eds.). (2013). *Aulton pharmaceuticals: The design and manufacture of medicines* (4th ed.). Elsevier Health Sciences.
- Azman, M., Sabri, A. H., Anjani, Q. K., Mustaffa, M. F., & Hamid, K. A. (2022). Intestinal absorption study: Challenges and absorption enhancement strategies in improving oral drug delivery. *Pharmaceutics*, 15(8), 975. <https://doi.org/10.3390/ph15080975>.
- Azrak, Z. A. T., Taha, M. S., Jagal, J., Elsherbeny, A., Bayraktutan, H., *et al.* (2024). Optimized mucoadhesive niosomal carriers for intranasal delivery of carvedilol: A quality by design approach. *International Journal of Pharmaceutics*, 654, 123935. <https://doi.org/10.1016/j.ijpharm.2024.123935>.
- Bartelds, R., Nematollahi, M. H., Pols, T., Stuart, M. C. A., Pardakhty, A., *et al.* (2018). Niosomes, an alternative for liposomal drug delivery. *Biochimica et Biophysica Acta (BBA) – Biomembranes*, 1860(11), 2494–2506.
- Bautista-Solano, A. A., Dávila-Ortiz, G., Perea-Flores, M. D. J., & Martínez-Ayala, A. L. (2025). A comprehensive review of niosomes: composition, structure, formation, characterization, and applications in bioactive molecule delivery systems. *Molecules*, 30(17), 3467. <https://doi.org/10.3390/molecules30173467>.
- Bekhet, M. A., Ali, A. A., Kharshoum, R. M., El-Ela, F. I. A., & Salem, H. F. (2022). Intranasal niosomal *in situ* gel as a novel strategy for improving citicoline efficacy and brain delivery in treatment of epilepsy: *In vitro* and *ex vivo* characterization and *in vivo* pharmacodynamics investigation. *Journal of Pharmaceutical Sciences*, 111(8), 2258–2269. <https://doi.org/10.1016/j.xphs.2022.02.012>.
- Bhandwalkar, M. J., Inamdar, I. K., Kalbhare, S. B., Changan, A. D., & Mandrupkar, S. N. (2020). A review on *in situ* Nasal Gels for Nasal drug delivery system. *Journal of Pharmaceutical Advanced Research*, 3(12), 1062–1073.
- Bhardwaj, P., Tripathi, P., Gupta, R., & Pandey, S. (2020). Niosomes: A review on niosomal research in the last decade. *Journal of Drug Delivery Science and Technology*, 56, 101581. <https://doi.org/10.1016/j.jddst.2020.101581>.

- Bryan, R., Khan, I., Ehtezazi, T., Saleem, I., Gordon, S., *et al.* (2018). Surfactant effects on lipid-based vesicles properties. *Journal of Pharmaceutical Sciences*, 107(5), 1237-1246. <https://doi.org/10.1016/j.xphs.2018.01.005>.
- Bourganis, V., Kammona, O., Alexopoulos, A., & Kiparissides, C. (2018). Recent advances in carrier mediated nose-to-brain delivery of pharmaceuticals. *European journal of pharmaceuticals and biopharmaceutics*, 128, 337-362. <https://doi.org/10.1016/j.ejpb.2018.05.009>.
- Chamanza, R., & Wright, J. A. (2015). A review of the comparative anatomy, histology, physiology and pathology of the nasal cavity of rats, mice, dogs and non-human primates. Relevance to inhalation toxicology and human health risk assessment. *Journal of Comparative Pathology*, 153(4), 287-314. <https://doi.org/10.1016/j.jcpa.2015.08.009>.
- Chaudhari, S. P., & Chatur, V. M. (2013). Development of valproic acid niosomal *in situ* nasal gel formulation for epilepsy. *Indian Journal of Pharmaceutical Education and Research*, 16, 31-41.
- Chen, S., Hanning, S., Falconer, J., Locke, M., & Wen, J. (2019). Recent advances in non-ionic surfactant vesicles (niosomes): Fabrication, characterization, pharmaceutical and cosmetic applications. *European journal of pharmaceuticals and biopharmaceutics*, 144, 18-39. <https://doi.org/10.1016/j.ejpb.2019.08.015>.
- Chettupalli, A. K., Bukke, S. P. N., Abdul Rahaman, S., Bodige, M., Kanakaraju, V. K., *et al.* (2025). Design, optimization of Niosomal gel capability for solubility and bioavailability enhancement of Kynurenic acid after intranasal administration: *in vitro* and *in vivo* Evaluation. *BMC biotechnology*, 25(1), 134.
- Cingi, C., Bayar Muluk, N., Mitsias, D. I., Papadopoulos, N. G., Klimek, L., *et al.* (2021). The nose as a route for therapy: part 1. Pharmacotherapy. *Frontiers in allergy*, 2, 638136. <https://doi.org/10.3389/falgy.2021.638136>.
- Crisler, R., Johnston, N. A., Sivula, C., & Budelsky, C. L. (2020). Functional anatomy and physiology. In *The Laboratory Rat* (pp. 91-132). Academic Press.
- Crowe, T. P., Greenlee, M. H. W., Kanthasamy, A. G., & Hsu, W. H. (2018). Mechanism of intranasal drug delivery directly to the brain. *Life Sciences*, 195, 44-52. <https://doi.org/10.1016/j.lfs.2017.12.025>.
- Das Kurmi, B., Tekchandani, P., Paliwal, R., & Rai Paliwal, S. (2017). Transdermal drug delivery: opportunities and challenges for controlled delivery of therapeutic agents using nanocarriers. *Current drug metabolism*, 18(5), 481-495.
- De Barros, C., Portugal, I., Batain, F., Portella, D., Severino, P., *et al.* (2022). Formulation, design and strategies for efficient nanotechnology-based nasal delivery systems. *RPS Pharmacy and Pharmacology Reports*, 1(1), rqac003. <https://doi.org/10.1093/rpsppr/rqac003>.
- Estupiñan, O. R., García-Manrique, P., Blanco-Lopez, M. D. C., Matos, M., & Gutiérrez, G. (2020). Vitamin D3 loaded niosomes and transfersomes produced by ethanol injection method: identification of the critical preparation step for size control. *Foods*, 9(10), 1367. <https://doi.org/10.3390/foods9101367>.
- Fahmy, U. A., Badr-Eldin, S. M., Ahmed, O. A., Aldawsari, H. M., Tima, S., *et al.* (2020). RETRACTED: Intranasal Niosomal *in situ* Gel as a Promising Approach for Enhancing Filibanserlin Bioavailability and Brain Delivery: *In vitro* Optimization and *Ex vivo/In vivo* Evaluation. *Pharmaceutics*, 12(6), 485. <https://doi.org/10.3390/pharmaceutics12060485>.
- Fletcher, N. A., & Krebs, M. D. (2018). Sustained delivery of anti-VEGF from injectable hydrogel systems provides a prolonged decrease of endothelial cell proliferation and angiogenesis *in vitro*. *RSC advances*, 8(16), 8999-9005. <https://doi.org/10.1039/C7RA13014G>.
- García-Manrique, P., Gutierrez, G., Matos, M., Cristaldi, A., Mosayyebi, A., Carugo, D., *et al.* (2019). Continuous flow production of size-controllable niosomes using a thermostatic microreactor. *Colloids and Surfaces B: Biointerfaces*, 182, 110378. <https://doi.org/10.1016/j.colsurfb.2019.110378>.
- Gharbavi, M., Parvanian, S., Leilan, M. P., Tavangar, S., Parchianlou, M., & Sharafi, A. (2023). Niosomes-based drug delivery in targeting the brain tumors via nasal delivery. *Nasal Drug Delivery: Formulations, Developments, Challenges, and Solutions*, 279-324.
- Ghori, M. U., Mahdi, M. H., Smith, A. M., & Conway, B. R. (2015). Nasal drug delivery systems: An overview. *American Journal of Pharmaceutical Sciences*, 3(5), 110-119.
- Ghosh, A., Majie, A., Karmakar, V., Chatterjee, K., Chakraborty, S., *et al.* (2024). In-depth mechanism, challenges, and opportunities of delivering therapeutics in brain using intranasal route. *AAPS PharmSciTech*, 25(5), 96.
- Hafner, A. (2022). Advances in development, characterisation and application of nasal drug delivery systems. *Pharmaceutics*, 14(8), 1562. <https://doi.org/10.3390/pharmaceutics14081562>.
- Helwany, M., & Bordon, B. (2021). Neuroanatomy, cranial nerve I (olfactory). In *StatPearls*. StatPearls Publishing.
- Homayun, B., Lin, X., & Choi, H. J. (2019). Challenges and recent progress in oral drug delivery systems for biopharmaceuticals. *Pharmaceutics*, 11(3), 129. <https://doi.org/10.3390/pharmaceutics11030129>.
- Huang, Q., Chen, X., Yu, S., Gong, G., & Shu, H. (2024). Research progress in brain-targeted nasal drug delivery. *Frontiers in aging neuroscience*, 15, 1341295. <https://doi.org/10.3389/fnagi.2023.1341295>.
- Jassim, Z. E., & Al-Akkam, E. J. (2018). A review on strategies for improving nasal drug delivery systems. *Drug invention today*, 10, 2857.
- Jeong, S. H., Jang, J. H., & Lee, Y. B. (2023). Drug delivery to the brain via the nasal route of administration: exploration of key targets and major consideration factors. *Journal of pharmaceutical investigation*, 53(1), 119-152.
- Pardeike, J., Hommoss, A., & Müller, R. H. (2009). Lipid nanoparticles (SLN, NLC) in cosmetic and pharmaceutical dermal products. *International Journal of Pharmaceutics*, 366(1-2), 170-184.
- Katara, P., Pawar Medhe, T., Nadkarni, A., Deshpande, M., Tekade, R. K., *et al.* (2024). Nasal drug delivery system and devices: An overview on health effects. *ACS Chemical Health & Safety*, 31(2), 127-143. <https://doi.org/10.1021/acs.chas.3c00069>.
- Kazi, K. M., Mandal, A. S., Biswas, N., Guha, A., Chatterjee, S., *et al.* (2010). Niosome: A future of targeted drug delivery systems. *Journal of Advanced Pharmaceutical Technology & Research*, 1(4), 374-380.
- Keller, L. A., Merkel, O., & Popp, A. (2022). Intranasal drug delivery: opportunities and toxicologic challenges during drug development. *Drug delivery and translational research*, 12(4), 735-757.
- Khallaf, R. A., Aboud, H. M., & Sayed, O. M. (2020). Surface modified niosomes of olanzapine for brain targeting via nasal route; preparation, optimization, and *in vivo* evaluation. *Journal of liposome research*, 30(2), 163-173. <https://doi.org/10.1080/08982104.2019.1610435>.
- Kumar, A., Pandey, A. N., & Jain, S. K. (2016). Nasal-nanotechnology: revolution for efficient therapeutics delivery. *Drug delivery*, 23(3), 671-683. <https://doi.org/10.3109/10717544.2014.920431>.
- Lee, D., & Minko, T. (2021). Nanotherapeutics for nose-to-brain drug delivery: an approach to bypass the blood brain barrier. *Pharmaceutics*, 13(12), 2049. <https://doi.org/10.3390/pharmaceutics13122049>.
- Liang, F., & Loré, K. (2016). Local innate immune responses in the vaccine adjuvant-injected muscle. *Clinical & translational immunology*, 5(4), e74. <https://doi.org/10.1038/cti.2016.19>.
- Lochhead, J. J., Yang, J., Ronaldson, P. T., & Davis, T. P. (2020). Structure, function, and regulation of the blood-brain barrier tight junction in central nervous system disorders. *Frontiers in physiology*, 11, 914. <https://doi.org/10.3389/fphys.2020.00914>.
- Lochhead, J. J., & Thorne, R. G. (2012). Intranasal delivery of biologics to the central nervous system. *Advanced Drug Delivery Reviews*, 64(7), 614-628.
- Lou, J., Duan, H., Qin, Q., Teng, Z., Gan, F., *et al.* (2023). Advances in oral drug delivery systems: challenges and opportunities. *Pharmaceutics*, 15(2), 484. <https://doi.org/10.3390/pharmaceutics15020484>.
- Lu, X., Fang, M., Yang, Y., Dai, Y., Xu, J., *et al.* (2020). PEG-conjugated triacontanol micelles as docetaxel delivery systems for enhanced anti-cancer efficacy. *Drug Delivery and Translational Research*, 10(1), 122-135.
- Machado, N. D., García-Manrique, P., Fernández, M. A., Blanco-López, M. C., Matos, M., *et al.* (2020). Cholesterol free niosome production by microfluidics: Comparative with other conventional methods. *Chemical Engineering Research and Design*, 162, 162-171. <https://doi.org/10.1016/j.cherd.2020.08.002>.
- Madden, S., Carrazana, E., & Rabinowicz, A. L. (2023). Optimizing absorption for intranasal delivery of drugs targeting the central nervous system using alkylsaccharide permeation enhancers. *Pharmaceutics*, 15(8), 2119. <https://doi.org/10.3390/pharmaceutics15082119>.
- Mathure, D., R Madan, J., N. Gujar, K., Tupsamundre, A., A. Ranpise, H., *et al.* (2018). Formulation and evaluation of niosomal *in situ* nasal gel of a serotonin receptor agonist, buspirone hydrochloride for the brain delivery via intranasal route. *Pharmaceutical nanotechnology*, 6(1), 69-78. <https://doi.org/10.2174/221173850666180130105919>.
- Mawazi, S. M., Ge, Y., & Widodo, R. T. (2025). Niosome preparation techniques and structure—An illustrated review. *Pharmaceutics*, 17(1), 67. <https://doi.org/10.3390/pharmaceutics17010067>.
- Mittal, D., Ali, A., Md, S., Baboota, S., Sahni, J. K., *et al.* (2014). Insights into direct nose to brain delivery: current status and future perspective. *Drug delivery*, 21(2), 75-86. <https://doi.org/10.3109/10717544.2013.838713>.
- Moammeri, A., Chegeni, M. M., Sahravi, H., Ghaflehbash, R., Memarzadeh, F., *et al.* (2023). Current advances in niosomes applications for drug delivery and cancer treatment. *Materials Today Bio*, 23, 100837. <https://doi.org/10.1016/j.mtbio.2023.100837>.
- Moghtaderi, M., Sedaghatnia, K., Bourbour, M., Fatemizadeh, M., Salehi Moghaddam, Z., *et al.* (2022). RETRACTED ARTICLE: Niosomes: a novel targeted drug delivery system for cancer. *Medical Oncology*, 39(12), 240.
- Mohanty, D., Jhansi, M., Bakshi, V., Haque, A., Swapna, S., *et al.* (2018). Niosomes: A Novel Trend in Drug Delivery. *Research Journal of Pharmacy and Technology*, 11(11), 5205-5211.
- Nanaki, S., Tseklima, M., Terzopoulou, Z., Nerantzaki, M., Giliopoulos, D. J., *et al.* (2017). Use of mesoporous cellular foam (MCF) in preparation of polymeric microspheres for long acting injectable release formulations of paliperidone antipsychotic drug. *European Journal of Pharmaceutics and Biopharmaceutics*, 117, 77-90. <https://doi.org/10.1016/j.ejpb.2017.03.016>.
- Nerli, G., Robla, S., Bartalesi, M., Luceri, C., D'Ambrosio, M., *et al.* (2023). Chitosan coated niosomes for nose-to-brain delivery of clonazepam: formulation, stability and permeability studies. *Carbohydrate Polymer Technologies and Applications*, 6, 100332. <https://doi.org/10.1016/j.carpta.2023.100332>.
- Nguyen, T. T. L., & Duong, V. A. (2025). Advancements in nanocarrier systems for nose-to-brain drug delivery. *Pharmaceutics*, 18(5), 615. <https://doi.org/10.3390/ph18050615>.

- Norwood, J. N., Zhang, Q., Card, D., Craine, A., Ryan, T. M., *et al.* (2019). Anatomical basis and physiological role of cerebrospinal fluid transport through the murine cribriform plate. *elife*, 8, e44278. <https://doi.org/10.7554/eLife.44278>.
- Ourani-Pourdashti, S., Mirzaei, E., Heidari, R., Ashrafi, H., & Azadi, A. (2022). Preparation and evaluation of niosomal chitosan-based *in situ* gel formulation for direct nose-to-brain methotrexate delivery. *International Journal of Biological Macromolecules*, 213, 1115-1126. <https://doi.org/10.1016/j.ijbiomac.2022.06.031>.
- Pal, R., Pandey, P., Koli, M., Srivastava, K., Tiwari, V., *et al.* (2024). The comprehensive review: Exploring future potential of nasoliposomal drug delivery systems for nasal route drug administration. *Journal of Drug Delivery and Therapeutics*, 14(3), 126-136. <https://doi.org/10.22270/jddt.v14i3.6444>.
- Panza, G. A., Steere, L., & Steinberg, A. C. (2022). A new force-activated separation device for the prevention of peripheral intravenous restarts. *Journal of Infusion Nursing*, 45(2), 74-80. <https://doi.org/10.1097/NAN.0000000000000455>.
- Patil, V. S., Sutar, K. P., Pockle, R. D., Usulkar, S., & Jadhav, V. A. (2023). Formulation, optimization and evaluation of amisulpride-loaded niosomal intranasal gel for brain targeting. *Therapeutic Delivery*, 14(10), 635-647. <https://doi.org/10.4155/tde-2023-0059>.
- Pardeshi, C. V., Belgamwar, V. S., & Tekade, A. R. (2013). Nose to brain drug delivery: Influence of formulation parameters. *Journal of Pharmaceutical Investigation*, 43(1), 1-14.
- Pires, P. C., Rodrigues, M., Alves, G., & Santos, A. O. (2022). Strategies to improve drug strength in nasal preparations for brain delivery of low aqueous solubility drugs. *Pharmaceutics*, 14(3), 588. <https://doi.org/10.3390/pharmaceutics14030588>.
- Qureshi, M., Aqil, M., Imam, S. S., Ahad, A., & Sultana, Y. (2019). Formulation and evaluation of neuroactive drug loaded chitosan nanoparticle for nose to brain delivery: *in vitro* characterization and *in vivo* behavior study. *Current Drug Delivery*, 16(2), 123-135. <https://doi.org/10.2174/1567201815666181011121750>.
- Ravouur, N., Kondreddy, P., & Korakanchi, D. (2013). Formulation and evaluation of niosomal nasal drug delivery system of folic acid for brain targeting. *Current drug discovery technologies*, 10(4), 270-282.
- Rinaldi, F., Hanieh, P. N., Chan, L. K. N., Angeloni, L., Passeri, D., *et al.* (2018). Chitosan glutamate-coated niosomes: A proposal for nose-to-brain delivery. *Pharmaceutics*, 10(2), 38. <https://doi.org/10.3390/pharmaceutics10020038>.
- Selvaraj, K., Gowthamarajan, K., & Karri, V. V. S. R. (2018). Nose to brain transport pathways an overview: Potential of nanostructured lipid carriers in nose to brain targeting. *Artificial cells, nanomedicine, and biotechnology*, 46(8), 2088-2095. <http://doi.org/10.1080/21691401.2017.1420073>.
- Sharma, V., Anandhakumar, S., & Sasidharan, M. (2015). Self-degrading niosomes for encapsulation of hydrophilic and hydrophobic drugs: an efficient carrier for cancer multi-drug delivery. *Materials Science and Engineering: C*, 56, 393-400. <https://doi.org/10.1016/j.msec.2015.06.049>.
- Shen, H., Aggarwal, N., Cui, B., Foo, G. W., He, Y., *et al.* (2025). Engineered commensals for targeted nose-to-brain drug delivery. *Cell*, 188(6), 1545-1562.
- Sita, V. G., Jadhav, D., & Vavia, P. (2020). Niosomes for nose-to-brain delivery of bromocriptine: Formulation development, efficacy evaluation and toxicity profiling. *Journal of drug delivery science and technology*, 58, 101791. <https://doi.org/10.1016/j.jddst.2020.101791>.
- Spera, I., Cousin, N., Ries, M., Kedracka, A., Castillo, A., *et al.* (2023). Open pathways for cerebrospinal fluid outflow at the cribriform plate along the olfactory nerves. *EBioMedicine*, 91.
- Teaima, M. H., El Mohamady, A. M., El-Nabarawi, M. A., & Mohamed, A. I. (2020). Formulation and evaluation of niosomal vesicles containing ondansetron HCL for trans-mucosal nasal drug delivery. *Drug development and industrial pharmacy*, 46(5), 751-761. <https://doi.org/10.1080/03639045.2020.1753061>.
- Thabet, Y., Elsabahy, M., & Eissa, N. G. (2022). Methods for preparation of niosomes: A focus on thin-film hydration method. *Methods*, 199, 9-15. <https://doi.org/10.1016/j.jymeth.2021.05.004>.
- Tulbah, A. S., Elkomy, M. H., Zaki, R. M., Eid, H. M., Eissa, E. M., *et al.* (2023). Novel nasal niosomes loaded with lacosamide and coated with chitosan: A possible pathway to target the brain to control partial-onset seizures. *International journal of pharmaceutics*, 53(1), 100206. <https://doi.org/10.1016/j.ijphx.2023.100206>.
- Ugwoke, M. I., Verbeke, N., & Kinget, R. (2001). The biopharmaceutical aspects of nasal mucoadhesive drug delivery. *Journal of pharmacy and pharmacology*, 53(1), 3-22. <https://doi.org/10.1211/0022357011775145>.
- Umbarkar, M. G. (2021). Niosome as a Novel Pharmaceutical Drug Delivery: A Brief Review Highlighting Formulation, Types, Composition and Application. *Indian Journal of Pharmaceutical Education & Research*, 55. <https://doi.org/10.5530/ijper.55.1s.34>.
- Unal, D. N., Sadak, S., Erkmen, C., Selcuk, Ö., & Uslu, B. (2023). Review of Surfactants, Structural Properties and Their Role in Electrochemistry. <https://doi.org/10.1039/BK9781837671182-00001>.
- Williams, G., & Suman, J. D. (2022). *In vitro* anatomical models for nasal drug delivery. *Pharmaceutics*, 14(7), 1353. <https://doi.org/10.3390/pharmaceutics14071353>.
- Witika, B. A., Basse, K. E., Demana, P. H., Siwe-Noundou, X., & Poka, M. S. (2022). Current advances in specialised niosomal drug delivery: Manufacture, characterization and drug delivery applications. *International Journal of Molecular Sciences*, 23(17), 9668. <https://doi.org/10.3390/ijms23179668>.
- Wu, K. W., Sweeney, C., Dudhipala, N., Lakhani, P., Chaurasiya, N. D., *et al.* (2021). Primaquine loaded Solid Lipid Nanoparticles (SLN), nanostructured lipid carriers (NLC), and nanoemulsion (NE): effect of lipid matrix and surfactant on drug entrapment, *in vitro* release, and *ex vivo* hemolysis. *AAPS pharmsci tech*, 22(7), 240.

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