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*Review*
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# An Update on the Potential of Nanocarriers for Intranasal Delivery

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**Abstract:** Intranasal medicine administration, which includes small and large molecules, peptides and proteins, and genes, is proving to be a dependable and promising method of delivering a diverse range of therapeutic agents to the central nervous system for treating brain disorders. Drug delivery systems are used to create a repeatable high drug concentration. Drug stability, enhanced medication transport, improved physicochemical properties such as water solubility, and greater drug absorption and bioavailability are all benefits of these solutions. Furthermore, characteristics such as the drug's unpleasant taste or odor are concealed. Nasal medication delivery systems are effective both locally and systemically. Several nano-carrier-based approaches, such as nanoparticles, liposomes, and exosomes, have been developed to convey medicinal chemicals to the brain after intranasal delivery. Impediments to brain-targeted medicine delivery include rapid mucociliary clearance in the nasal cavity, enzyme degradation, and the blood-brain barrier (BBB). The current study focuses on nanocarrier surface modification to facilitate nose-to-brain delivery by enhancing penetration ability, lengthening nasal cavity retention time, and encouraging brain targeting. *In vitro*, blood-brain barrier models are also shown, which can aid researchers in conducting more efficient studies on the intranasal transport of drugs into the brain via an indirect nose-to-blood-to-brain pathway.

**Keywords:** intranasal; delivery; nanocarriers; brain; mucosal.

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## 1. Introduction

When systemic effects are desired, oral medication delivery is the preferred method of administration [1]. However, because some chemicals have low oral bioavailability, researchers are looking for more effective ways to deliver them to the body. The mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity, and other mucosal linings, offer specific benefits over peroral administration for systemic drug distribution. These benefits include the ability to skip the first-pass effect, avoidance of pre-systemic clearance of the gastrointestinal tract, and, depending on the drug, bypassing the first-pass effect. Many research groups have looked into the nasal cavity as a potential route for systemic medication administration. However, the potential irritation and irreversible damage to the ciliary action application of nasal dosage forms, as well as the large intra and inter-subject variability in mucus secretion in the nasal mucosa, could significantly affect drug absorption from this site.

Intranasal administration has been employed for various purposes since the last century, including nasal decongestion, rhinitis, and migraine relief. The Red Indians of North America

have employed crushed leaves of Ranunculus acris to treat headaches by nasal inhalation. In China, aloe wood and sandalwood extracts were used to alleviate emesis by inhaling them through the nose. Nasal snuffing has also been used to give tobacco via the nasal route [2]. Because low doses are sufficient to give therapeutic effects with little systemic adverse effects, nasal delivery is appropriate for administering medications to treat local nasal illnesses such as sinusitis and allergic rhinitis. Furthermore, nasal delivery may be appropriate for medications that are efficacious in small dosages but have a low oral bioavailability [3]. The rate of absorption and pharmacokinetic properties of small drug molecules used for systemic therapeutic effects via nasal administration are comparable to those of the parenteral route due to the nature of nasal pathways, which provide a large surface area, rich vascularity, and high drug permeability [4].

Despite having a smaller surface area than the lung, the nose is an effective location for systemic absorption, especially for medicines with low water solubility [5]. Many medications that target the central nervous system (CNS) do not reach the brain after oral or parenteral administration due to the blood-brain barrier (BBB). Because the olfactory area of the nose is not covered by the blood-brain barrier, evasion of the BBB after nasal delivery is possible. This method is effective for drugs that target the brain [6]. Furthermore, because inducing mucosal secretory antibodies at the site of pyrogen entry may give extra immunoprotection, the nose is a desirable location for vaccine administration [7].

## 2. Anatomy of Nose

The nasal channel travels from the nasal vestibule to the nasopharynx and is 12-14 cm long. It is divided into three sections: vestibular, respiratory, and olfactory. The nose is 16-19 $cm^3$ in volume and 180 $cm^2$ in surface area, with two cavities (i.e., nostrils) divided by the nasal septum (Fig. 1).

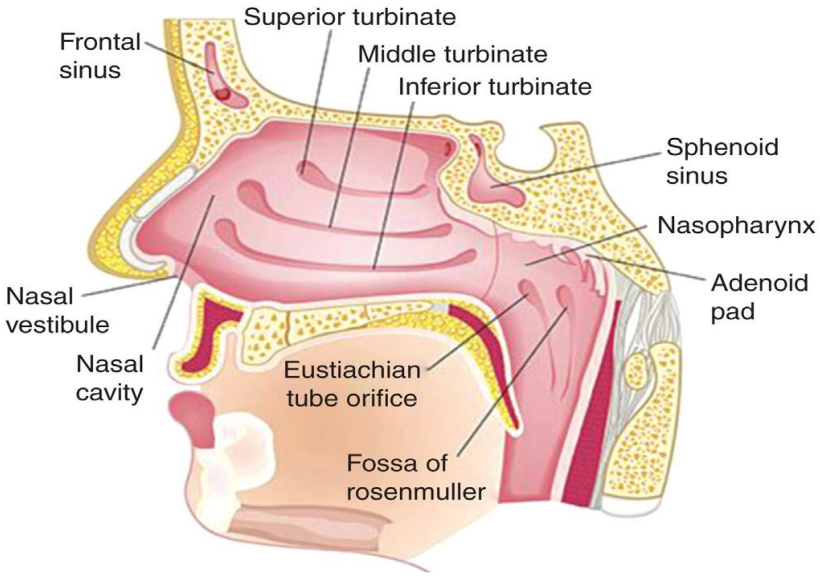


**Figure 1**. Nasal passage for Drug delivery.

The vestibular area, which filters particles from breathed air, is positioned at the front aperture of the nasal passages. However, drug administration and absorption are of the utmost importance in this region. Hair covers this area, filtering inhaled air and preventing airborne particles from entering the respiratory system. The respiratory system has a huge surface area

and strong vascularity (about 130 $cm^2$). The majority of medication absorption takes place in this area. It is lined with pseudostratified columnar epithelium and covered with a thick coating of mucus that flows toward the nasal cavity's posterior openings due to ciliary rhythmic motions [8]. The olfactory region has a surface area of around 15 $cm^2$ and is vital for delivering drugs to the brain and cerebrospinal fluid. It is made up of thick connective tissue and a lamina propria that houses the olfactory epithelium. Nasal mucosa thickness varies between 2 and 4 mm. To capture undesirable particles, epithelial cells border the nasal canal and are covered by a 5 m thick mucus coating. Water makes up 95% of mucous secretion, followed by mucus (2%), salts (1%), proteins (e.g., albumin, immunoglobulin, and lysozyme), lactoferrin, and lipids (1%). IgA, IgE, and IgG antibodies are also found in mucous secretions. The nasal secretion has a pH range of 5 to 6.5. The mucus layer in the nasal cavity is cleared by ciliary activity, and mucus is regenerated 4-6 times per hour. The mucus moves through the nose at a pace of 5-6 mm/min.

## 3. Nasal Drug Delivery

A substance's physico-chemical characteristics have a big influence on how well it gets absorbed by the nose. It will not permeate the mucosa if the drug is too big (more than 1 kDa), too lipophilic (cannot dissolve in the nasal mucous membrane), or has a high degree of ionization (negatively charged particles are repelled by the negatively charged nasal mucosa). The stability and degree of ionization of a drug, as well as the irritation of the nasal mucosa, are all affected by its pH. High hypotonicity formulations may affect ciliary function, leading to decreased absorption. Viscous formulations are more easily penetrated by the nasal mucosa, although they may be less absorbed. Furthermore, the surface, drug concentration, and quantity, and physical state of the dosage all influence the pharmaceutical absorption process.

### *3.1. Local effects.*

Localized disorders are treated with modest effective doses that have fewer systemic negative effects through the nose. Local pathological disorders in the nose are treated with hydrophobic or soluble low molecular-weight drugs. Azelastine, for example, is a fast-acting antihistamine. It is available as a nasal spray and acts as an H1-receptor antagonist as well as a mast cell stabilizer. Beclometasone is an anti-inflammatory corticosteroid that is used to treat inflammation and local nasal allergies [9,10]. Nasal decongestants, such as oxymetazoline, are also used in the nose to treat common colds [11].

Drugs administered directly at the site of action require a smaller medication dose than those administered systemically, and illness symptoms are quickly eased. The topical use of antihistamines has a lesser risk of systemic side effects, such as the characteristic sleepiness associated with antihistamines taken orally [12].

### *3.2. Systemic effects.*

Small lipophilic chemicals travel over the nasal epithelium and into the systemic circulation via the transcellular pathway, which involves passing them through the blood or lymphatic system. The drug must cross the blood-brain barrier (BBB) to reach the human brain, is exposed to the hepatic first-pass mechanism, and has a higher systemic burden on this transport route. By fusing with peripheral trigeminal neurons via endocytosis along the branches of the trigeminal nerves, medicines can be transported directly into the human brain

stem and other brain parts. The olfactory area transports a substantially bigger proportion of the medication to the brain.

Because of their high molecular weight and polarity, most protein and peptide medicines have low bioavailability (1–2%), resulting in poor absorption via the nasal mucosal membranes. Intranasal administration of progesterone and propranolol, for example, may achieve bioavailability levels comparable to parenteral administration [13]. Lower bioavailability can be enhanced by including absorption enhancers in the formulations and utilizing bioadhesive agents to extend the contract duration between the drug and the mucosal membranes. In rats, utilizing 0.1 % N-succinyl chitosan as an absorption enhancer resulted in a considerable increase in the relative bioavailability of isosorbide dinitrate (69.85 %) compared to the 0.5 % chitosan (55.36 %) and control groups (43.32 %) [14]. Steyn and colleagues found that nasal delivery of recombinant human growth hormone boosted bioavailability significantly when combined with N-trimethyl chitosan chloride, an absorption enhancer employed in spheroid technology [15].

The medication can internalize via endocytosis or pinocytosis with the olfactory sensory neurons during transport along the neuronal transport route. Exocytosis releases the drug in the olfactory bulb, which travels to the human brain. This transfer mode is relatively sluggish, taking anywhere from hours to days, whereas the extraneuronal mode takes only a few minutes. Extracellular transport is the quickest mode of transportation. In portions of the olfactory area, the presence of newly produced and mature neurons results in a relatively high permeability. The slow regeneration of neurons in the olfactory tissue and the mass flow of liquor past them contribute to this situation, resulting in an extremely quick transport pathway. The lamina propria, located directly underneath the epithelium in the olfactory area, is responsible for the extracellular transfer of lipophilic substances by active or passive diffusion. It allows this transport pathway by providing a neural source of olfactory axon bundles [16].

*3.3. Vaccines delivery.*

Vaccines and their use in treating respiratory infections via the nose have been extensively studied. Because immune system components are located in the mucosal membrane, the respiratory epithelium is the body's first line of defense against infections [17]. Lymphocytic tissue enriches the nasal mucosa. It boosts systemic levels of particular immunoglobulin G and nasal secretary immunoglobulin A, as well as local immune responses, giving you more protection from invading microorganisms [18]. The nasal mucosa is ideal for immunization due to its permeability, low enzymatic activity, and ability to accommodate nose-associated lymphoid tissue (NALT) [19]. The administration of vaccines by the nose is a handy, needle-free method of infection protection.

For enhanced stability and bioavailability, nasal vaccinations are coupled to nasal administration devices. Nasal delivery methods should not be larger than 100 nm in diameter, as they can cross the nasal mucosa barriers and have a size ratio similar to viruses. The ideal size range is 20 to 80 nm in diameter. The nasal vaccine must interact with the immune system to be effective. The nasopharynx-associated lymphoid tissue, which in the human nose is composed of the Waldeyer's ring, is the nasal system for immune system activation. The delivery of antigen to the nasopharynx-associated lymphoid tissue triggers a significant humoral and cellular immunological response in the body, which occurs on both a mucosal and systemic level [20]. Nasal medication delivery techniques using cationic liposomes are both safe and effective. It studied cationic liposomes in the presence of ovalbumin [21]. Nasal

vaccines are non-invasive, painless, and cost-effective to manufacture. Because preclinical research is typically conducted on rats, there are now only a few products on the market. Implementation, application safety, and efficacy prediction are difficult due to the differences between a rodent and a human nose [22].

*3.4. Nasal drug delivery to CNS.*

The intranasal route (Fig. 2), which uses the olfactory neuroepithelium in the nose to deliver medications to the brain, has been proposed as a method of transferring drugs from the nose to the brain [23]. This method has been considered to treat Alzheimer's disease, brain tumors, epilepsy, pain, and sleep disorders [24]. In rats, nerve growth factor has been delivered to the brain, while clinical research has shown that insulin [25] and proteins [26] may be sent directly to the CNS through the olfactory route of the nose. Malhotra and coworkers used peptide-tagged PEGylated chitosan nanoparticles to deliver siRNA (0.5 mg/kg) to the CNS, with greater brain concentrations than other tissues, to treat neurological diseases [27].

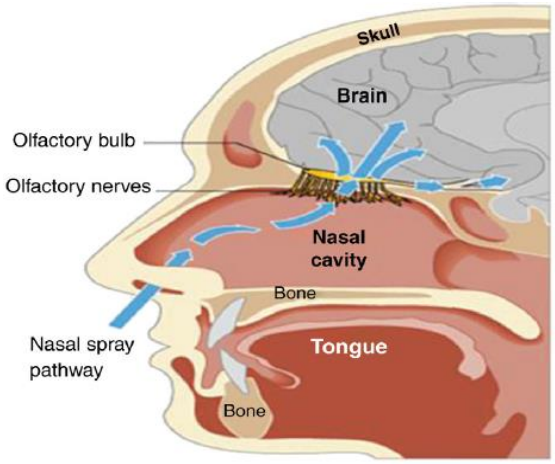


**Figure 2.** Nasal drug delivery to the brain.

The BBB is a tightly closed monolayer network of blood channels compromised by polarised endothelial cells forming the brain and spinal cord capillaries. It is placed centrally in the neurovascular unit. This layer inhibits chemicals from freely flowing between the bloodstream and the brain. Tight junctions and adherent junctions keep epithelial cells in the brain linked. Tight connections regulate the flow of chemicals from the brain to the bloodstream and vice versa [28]. To ensure that neuronal function is not harmed, the BBB regulates the disposal of metabolites, the absorption of vital nutrients into the central nervous system, and the chemical composition of neuronal milieus. The BBB also shields the brain against the passage of blood cells, viruses, transmitters, and neurotoxic plasma components. One option is bypassing the BBB with injections administered intrathecally, intracerebroventricularly, or intraparenchymal. As a result, the medicine directly penetrates the central nervous system's cerebrospinal fluid. They are, however, intrusive procedures that should only be carried out by trained professionals, and they also carry the danger of infection. Administering medications through the nose to the brain (N2B) is a non-invasive technique to get across the BBB and the blood-cerebrospinal fluid barrier [29]. The nose not only has close proximity to the brain, but it also has specific nerves, the olfactory and trigeminal nerves, that have a direct link to the brain that the BBB does not limit.

## 4. Biological Barriers Interfering with Nasal Drug Delivery

*4.1. Nasal blood flow.*

The nasal mucous membrane has a good blood supply, making it suitable for medication absorption. The easier it is for medications to be absorbed and disseminated in the system, the better the blood circulation is. The blood flow inside the nose is also crucial for adjusting the temperature and moisturizing the inhaled air [30].

*4.2. The physical condition of the nose.*

Consistent nasal medication delivery is difficult during the cold season. Nasal drug absorption is influenced by a physiological change in the nasal mucosa caused by disease or allergy. Inflammation or irritation of the mucous membranes induces swelling and alters medication absorption conditions, resulting in decreased drug absorption. Furthermore, the itching and sneezing that occurs, as a result, amplify the effect.

*4.3. Enzymatic activity.*

The stability of nasal medicines can be harmed by various enzymes found in the nasal mucosa. Peptide and protein-based medicines are particularly susceptible. Amino peptidases and proteases are naturally occurring enzymes that may attack and break down peptides and proteins. In addition, the nose contains endopeptidases such as serine and cysteine, which can cleave internal peptide bonds, as well as exopeptidases such as mono- and dipeptidases, which cleave peptides at their N and C termini. Peptides and immunoglobulins, particularly IgS, combine to form massive complexes that cannot permeate the nasal mucosa due to their molecular weight. All of these variables contribute to a decrease in bioavailability [31].

*4.4. Mucociliary clearance.*

The principal defense system for removing foreign materials, germs, and particles from the nose is mucociliary clearance (MCC). Materials are caught in the mucus layer, transferred to the nasopharynx by ciliary movements, and then swallowed to reach the gastrointestinal system. This mechanism reduces drug absorption through the nasal epithelium [32]. It is possible to overcome the MCC and increase the residence time of medications in the nasal cavity by incorporating mucoadhesive substances into the formulation, which may improve nasal absorption. Using conscious sheep, Soane and colleagues demonstrated that the clearance half-life of radiolabeled material in liquid was 15 minutes from the nasal cavity. The half-life of bioadhesive chitosan solutions was 43 minutes, and the half-life of bioadhesive chitosan microspheres was more than 110 minutes. Chitosan may lower MCC, allowing the delivery system to spend more time in contact with the nasal mucosa and boosting medication absorption [33].

*4.5. Low drug bioavailability.*

The low bioavailability of some medications can be attributed to their strong polarity or large molecular size (e.g., peptides and proteins). Low molecular weight hydrophilic medicines have a bioavailability of around 10%, whereas larger molecules such as proteins (e.g., calcitonin) and peptides (e.g., insulin) [34] have a bioavailability of less than 1%. Nasal

administration of therapeutic molecules with molecular weights less than 1000 Da is effective, fast, and safe. Particle size affects absorption via the nasal epithelium for particulate pollutants. It has been observed that intranasal delivery of particles smaller than 1 m can result in fast absorption [35]. Endocytosis transports small amounts of proteins and peptides across the nasal epithelium. Permeation enhancers could boost the bioavailability of polar medicines, peptides, and tiny proteins. Chitosan is a natural mucoadhesive penetration enhancer for water-soluble medicines (such as Atenolol) that loosen the tight connections between cells [36].

*4.6. Enzymatic degradation.*

Enzymatic activity in the nose may degrade some medications, proteins, and peptides. Nasal epithelial cells contain drug-degrading enzymes such as carboxylesterases, aldehyde dehydrogenases, epoxide hydrolases, glutathione S-transferases, and cytochrome P450 isoenzymes. To break down the enzymatic barrier, enzyme inhibitors or enzyme saturators can be used [37,38].

## 5. Dosage Forms for Intranasal Administration

*5.1. Nanogels.*

Intranasal administration has been used as an appealing alternative strategy to treat major depressive disorder, social anxiety disorder, generalized anxiety disorder, and panic disorder. Low medication residence time in the nasal cavity, on the other hand, would reduce the absorption and, as a result, bioavailability, which has long been a problem in clinical practice. The anatomic and physiologic features of nasal mucosa must be considered when creating nasal dosage forms to overcome the rapid mucociliary clearance (MCC) problem. Gel as a nasal mucoadhesive has proven particularly intriguing due to its fluid-like qualities before nasal delivery, and it may be provided via drops to allow for optimal medicine dosing. Furthermore, thermos-sensitive smart polymers that utilize nasal temperature monitoring can be used to create gelation [39]. Compared to the oral route and administration of an equivalent dose, mucoadhesive thermo-reversible in situ nasal gel increased nasal residence time and absorption of venlafaxine hydrochloride across the nasal mucosal barrier to improve drug bioavailability. A thermo-reversible bio-gel method was also reported based on chitosan and glycerophosphate for intranasal administration of doxepin to the brain. Doxepin hydrochloride, an antidepressant, was doped into a combination of chitosan and glycerophosphate with polyethylene glycol. At 37°C, the combination quickly gelled, but when cooled, it reverted to a sol condition. The gels showed promise as a way to deliver drugs to the brain through the nose. Tramadol HCl, intranasal chitosan nanoparticles (NPs)-loaded in situ gel, was also created to treat depression. Ionic gelation was used to make chitosan nanoparticles (NPs), which were then incorporated into a Pluronic and HPMC-based mucoadhesive thermo-reversible gel. Intranasal TRM HCl NP-loaded in situ gels were found to be a promising formulation for treating depression after a depression-inducing forced swim test and various behavioral and physiological measures.

*5.2. In situ gel systems.*

Gels are semi-solid pharmacological forms that are neither solid nor liquid but somewhere in the middle. They’re three-dimensional networks of swelling polymer

compositions that include scattered liquid molecules. In situ gels exist only in their gel form under physiological conditions; before application, they exist as liquid aqueous solutions. They are highly stable, capable of transporting adequate amounts of the active component, and non-toxic. Using in situ gels as medication delivery method has several advantages, including the formulation remaining in the appliance's location and the avoidance of both dropping out of the nose and into the back of the throat. Furthermore, difficulties caused by unpleasant taste or content loss are avoided. The dosage accuracy is extremely accurate, enzymatic breakdown by nasal secretion enzymes is avoided, the application is straightforward, and the extended dwell time in the NC means fewer treatments are required [40].

*5.3. Nanostructured lipid.*

Nanostructured lipid carriers (NLCs), nanostructured particles produced from a two-phased combination of solid and liquid lipids, have sparked a lot of attention in recent years. The NLC is noted for its "imperfections" nanostructure, created by poorly combining geographically different chemicals into a lipid particle-matrix (Fig. 3). Drug loading capacity is increased, and drug loss owing to light, oxidation, and hydrolysis is reduced or eliminated. NLC has been used as a vehicle for delivering therapeutic chemicals to the brain [41]. NLC is created by mixing incompatible liquid-liquid and solid-liquid compositions in which the oil molecules do not contribute to the solid-crystalline liquid's matrix, and the solid-liquid crystal does not dissolve in the liquid-liquid. At temperatures below their melting point, however, this lipid mixture should be homogenous, with no phase separation, i.e., liquid-liquid compartments should exist as nanosized compartments within the solid crystalline matrix.

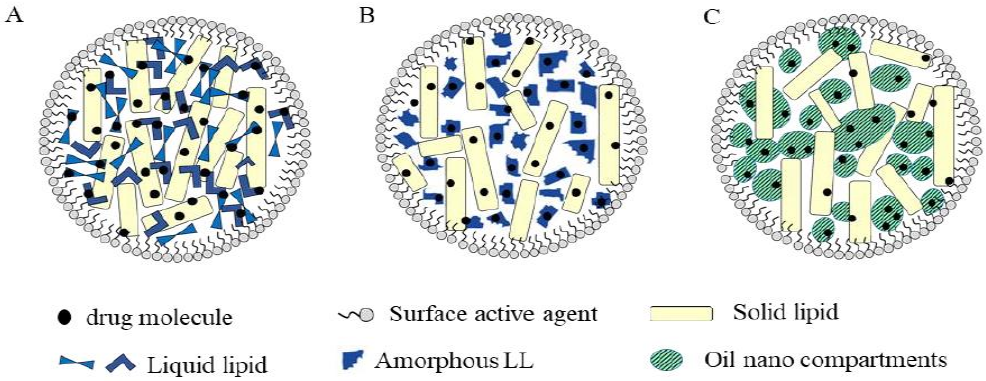


**Figure 3.** Different types of NLCs (a) Imperfect (b) Amorphous (c) Oil-in-fat-in-water.

*5.4. Liposomes.*

Liposomes are spherical vesicles with a hydrophilic core and a cover made up of one (unilamellar) or many (multilamellar) phospholipid bilayers that develop spontaneously. Lipids can be used as carriers for hydrophilic, lipophilic, and amphipathic medicines because of their amphiphilic structure. Hydrophilic active materials are found inside the liposome's aqueous center, amphiphilic substances are found between the two phases, and lipophilic active ingredients are bonded to the phospholipid bilayer, resulting in a significant increase in the lipophilic drug's water solubility. ULVs are unilamellar liposome vesicles with a diameter of 20-250 nm primarily employed to deliver hydrophilic medicines and antigens through a large aqueous core. MLVs are multilamellar liposome vesicles that are made up of two or more concentric phospholipid bilayers and range in size from one to five meters. Encapsulation of

hydrophobic compounds is done with them [42]. Liposomes have a structure similar to that of numerous biological membranes and so can permeate. Bioavailability is improved by enhancing biomembrane penetration through various changes in the lipid surface, particularly concerning N2B drug delivery. Risperidone liposome for schizophrenia nasal treatment is discussed by Narayan *et al*. The surface of the liposome was created using the thin-film approach and filled with stearyl amine and distearyl-phosphatidylethanolamine-m-polyethyleneglycol-2000 to achieve the highest possible concentration of the active ingredient in the brain. Risperidone liposomes reach the maximum drug concentration in the brain four times faster than pure material, according to the researchers. The measured concentration in the brain was twice as high as the pure substance's concentration, and the half-life was similarly doubled [43]. The size of the liposomes is determined by the medicine to be carried and the place of action. Liposomes with a diameter of less than 100 nm are extremely stable; however, they can only transport a small amount of medicinal material. Drug storage capacity is high in liposomes with a diameter of up to 250 nm; however, they are removed twice as quickly as smaller liposomes [44]. The surface of the liposomes is changed to prevent them from being eliminated. Fig. 4 depicts an overview of liposome surface modifications [45].

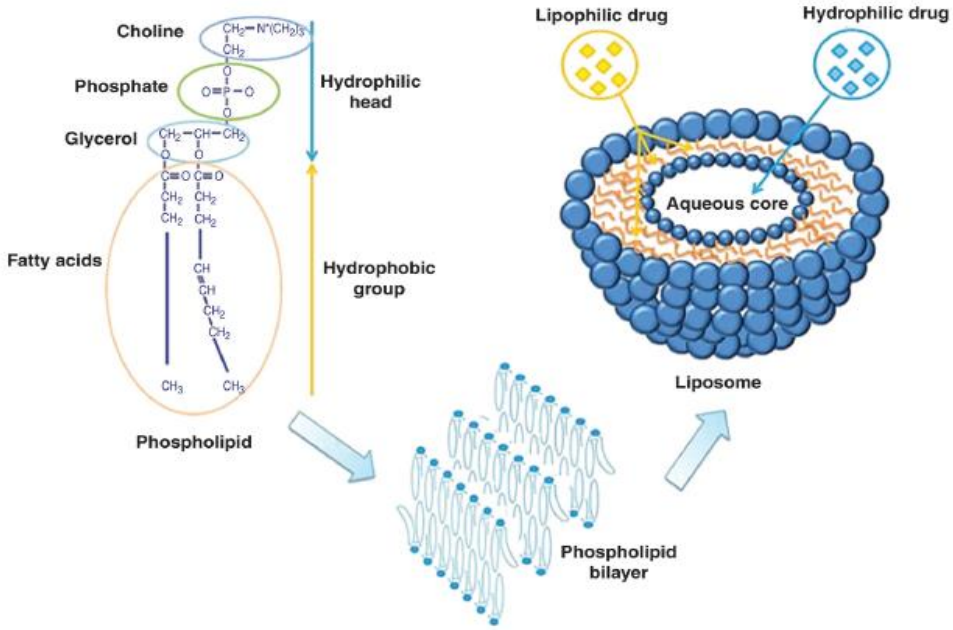


**Figure 4.** Structure of liposomes and the entrapment of lipophilic and hydrophilic drug molecules.

*5.5. Microemulsions.*

Microemulsions (MEs) are dispersal systems with droplet distribution. A ME comprises a hydrophilic phase, a lipophilic phase, a surfactant, and a co-surfactant—individual droplets in the ME range in size from 10 to 200 nanometers in diameter. MEs differ from regular emulsions in that they have turbidity, droplet size, and stability, whereas standard emulsions do not. ME drug delivery systems increase the solubility of poorly soluble medications, resulting in better stability, easier processing, longer shelf life, and improved bioavailability [46]. Rivastigmine is an example of a drug that isn't easily dissolved in water. It's a medication that's used to treat Alzheimer's. Due to its chemical composition, it is poorly water-soluble and has low penetration across cell membranes and an oral half-life of 1.5 hours. Shah *et al*. addressed these disadvantages by combining the medication with a microemulsion drug delivery technique. Adding chitosan to the microemulsion boosted its mucoadhesive

properties and increased absorption even further. Compared to intravenous treatment, nasal delivery of pure medication resulted in a 4.2-fold higher drug concentration in the brain and a 2.4-fold higher drug concentration in the brain. MEs are created by adding lower alcohols such as butanol or hexanol to pre-existing milky emulsions of water in oil (W/O) or water in water (O/W), resulting in nanoscale or colloidal dispersions. Lower alcohols and co-surfactants reduce the interfacial tension between the aqueous and oil phases, allowing a micro-heterogeneous system to emerge almost spontaneously. Depending on the type of ME, the amphiphilic molecules organize themselves in a specific orientation. In an O/W system, the non-polar component of the molecules is in the disperse phase, whereas, in a W/O system, the polar part is in the continuous phase. O/W systems are particularly intriguing in medication delivery since a hydrophobic substance can easily dissolve in the ME's inner oil phase and are transported and absorbed better in the body circulation thanks to the outer aqueous phase [47]. MEs are produced in two ways: during phase titration, the medication is dissolved in an appropriate amount of oil and homogenized, and a specific volume of surfactant and co-surfactant is added. Then, while continually stirring, double-distilled water is added. The size of the ME particles formed is determined by the churning speed. The optimal mixing ratio of oleic acid, tween 80, and propylene glycol was calculated using the phase diagram. On a magnetic stirrer, the mixture was titrated with water for 10 minutes while stirring at 150 RPM. The mixture was titrated with water on a magnetic stirrer for 10 minutes while stirring at 150 RPM continuously. Agomelatine was dissolved in the oil mixture, surfactant and co-surfactant were added, and then the mixture was titrated with water on a magnetic stirrer for 10 minutes while stirring at 150 RPM continuously. Agomelatine has a 5 % oral bioavailability due to its extremely efficient first-pass action. When combined with a microemulsion, it's a powerful combination.

*5.6. Nanoemulsions.*

Nanoemulsions (NEs), in contrast to MEs, are ordinary emulsions with very thin particle dispersion. NEs are colloidal dispersions of two immiscible liquids that are thermodynamically unstable. There are W/O and O/W systems, and the O/W systems, like MEs, are very useful for drug delivery systems. Surfactants and co-surfactants are utilized as stabilizers in the creation of NEs, just as they are in MEs, to ensure stability. Low-temperature emulsification using the phase inversion composition technique, phase inversion temperature method, displacement method, and high-energy emulsification utilizing high-pressure homogenization or ultrasonication are some of the NE manufacturing processes. The oil and water phases are driven through a small hole under high pressure in high-pressure homogenization, resulting in minuscule particles combining. The NE particles will form in smaller sizes as the pressure rises. The micro-fluidization approach also requires the presence of pressure, which is obtained by forcing a regular emulsion to form a NE through pressure and interaction with fine microchannels using a specially constructed apparatus called a microfluidizer. The system is filtered at the end of the manufacturing process to ensure a uniform particle distribution. Small particles are created by rapid cooling and heating in the phase inversion technique based on the inversion temperature approach. Non-ionic surfactants are utilized in this approach. Polyoxyethylene, for example, reacts hydrophilically at low temperatures by drying the polymer chain and lipophilically at higher temperatures by dehydrating the polymer chain. An ultrasonic field and externally applied pressure are used in the ultrasonic method to decrease the particles of a normal emulsion to the point where they

form a NE. For the synthesis of tetrabenazine nanoemulsions, this approach was adopted. With a vortex mixer and high-speed swirling, the active component was dissolved in the oil phase at room temperature ($25^0$ C). Tween 80 and Transcutol P were added after the tetrabenazine had completely dissolved. The appropriate amount of water was added drop by drop until the nanoemulsion was created using continuous sonication and vortexing. They discovered that the nanoemulsion attained a 1.68 times higher drug concentration in the brain than the tetrabenazine suspension. NEs are appropriate for a wide range of active substances due to their varied characteristics. A mucoadhesive polymer was added to several nanoemulsion drug delivery systems to prolong the residence duration at the nasal mucosa and hence boost medication absorption. This was observed in asenapine maleate nanoemulsion tests. To improve the mucoadhesion of the combination, Carbopol 971 was added to the produced nanoemulsion complex. Asenapine maleate is used to treat schizophrenia. It has a low water solubility and a high first-pass effect, resulting in a final bioavailability of less than 2% due to its physicochemical features. Chaturvedi *et al*. were able to demonstrate a 3.5-fold increase in bioavailability in the brain by mixing the active substance with nanoemulsions as drug delivery vehicles, compared to intravenous administration of an asenapine maleate nanoemulsion.

*5.7. Nanoparticles.*

Nanoparticles are compact colloidal systems in which the therapeutic agent is either entrapped within the matrix, conjugated or adsorbs to the particle surface. Nanoparticles are typically made of polymers, lipids, or a combination of the two to achieve sustained, regulated medication release.

*5.6. Residence time increasing nanoparticles.*

The nasal cavity's mucociliary clearance is a substantial obstacle to medicinal delivery to the brain by intranasal treatment. Mucoadhesive and viscosity-raising substances have been utilized to improve drug absorption by increasing drug residence time in the nasal cavity. Mucoadhesive polymers such as chitosan, alginate, gelatin, cellulose, and polyacrylate were frequently employed to make nanoparticles, resulting in longer retention at the absorption site, boosting brain delivery efficiency.

Didanosine, piperine, and quetiapine fumarate [48] have been loaded into chitosan nanoparticles to achieve brain distribution via the nasal route. Following nasal administration, Haque *et al*. discovered that venlafaxine-loaded nanoparticles composed of alginate and chitosan successfully transported the medicine to the brain in a significant amount to treat depression. This could be the result of a combination of factors, including increased absorption time due to decreased nasal mucociliary clearance, increased permeation across nasal mucosa, and modulation of P-GP efflux transporters on the BBB that prevent drugs from entering the brain, and contribution of paracellular transport via tight junction modulation between cells. This method was used to transport not just tiny compounds but also peptides. Gelatin nanoparticles were described by Lu *et al*. as carriers of substance P, a peptide capable of increasing dopamine levels in the brain. The created approach improved functional outcomes and reduced apoptosis in rats with hemiparkinsonism, indicating that it could be used to treat Parkinson's disease.

Furthermore, most mucoadhesive nanoparticles were hydrophilic and prepared gently, making them ideal for gene transfer. For the first time, chitosan nanoparticles were able to

protect siRNA targeting galectin-1, which is overexpressed in glioblastoma, from RNAse degradation. Furthermore, highly concentrated chitosan nanoparticles delivered siRNA into the olfactory bulbus and hindbrain via the nasal mucosa for glioblastoma treatment.

*5.7. Lectin-modified nanoparticles.*

Because they specifically recognize sugar molecules, lectins are sugar-binding proteins that bind glycosylated membrane components. To improve nanoparticles absorption in the brain, creating unique polymeric nanoparticles made of wheat germ agglutinin conjugated to poly (ethylene glycol)-poly (lactic acid) (PEG-PLA). When compared to intranasal delivery of unmodified PEG-PLA nanoparticles, they discovered a two-fold increase in brain concentrations after using the nanoparticles carrier to encapsulate coumarin. They investigated if the nanoparticles carrier could be used to transport peptides to the brain in a later investigation. They used wheat germ agglutinin conjugated PEG-PLA nanoparticles to include a vasoactive intestinal peptide. When compared to vasoactive intestinal peptides delivered intranasally as a solution or in unmodified nanoparticles, the surface-modified nanoparticles produced 5.6- to 7.7-fold higher brain levels when administered intranasally. Using surrogate markers such as tumour necrosis factor-alpha and wheat germ agglutinin-specific antibodies, the novel carrier was tested for toxicity during intranasal use, and it was determined that the nanoparticles were a safe agent for use in intranasal brain therapy.

However, one major difficulty for many lectin members is their severe immunogenicity *in vivo*, exacerbated by their relatively large molecular weight, severely limiting their potential usage in drug delivery systems. Odorranalectin (OL) was discovered in Odorranagrahami skin secretions and was found to be the smallest peptide with lectin-like activity, with substantially lower immunogenicity than wheat germ agglutinin. Odorranalectin can detect L-fucose, which is abundant on the olfactory epithelium of the nasal mucosa, suggesting that it could be a viable ligand for intranasal medication delivery.

*5.8. Lactoferrin modified nanoparticles.*

Lactoferrin is a naturally occurring cationic glycoprotein that binds to iron and is found in mammalian brain cells. It can bind to the lactoferrin receptor at BBB and then convert to a positively charged group that binds to negatively charged BBB under physiological conditions. Age-related neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis have been shown to exhibit lactoferrin receptor overexpression. Additionally, nasal and bronchial epithelial cells showed considerable lactoferrin receptor expression; lactoferrin could be employed as a ligand in nanoparticles to enhance membrane penetration [49].

*5.9. Cell-penetrating peptides modified nanoparticles.*

Cell-penetrating peptides (CPPs), which are made up of short polycationic or amphipathic peptides, have improved the transport of a wide range of molecules, including siRNA, plasmid DNA, antisense ONs, PNA, proteins, and peptides. CPPs promote cargo movement across cell membranes and, in some situations, enable the release of molecules held inside endosomes into the cytoplasm, allowing them to bypass extracellular and intracellular barriers. Some CPPs can successfully enter the negatively charged cell membrane without causing membrane damage due to their partly hydrophobic and cationic properties.

Low-molecular-weight protamine (LMWP) is a cell-penetrating peptide with a number of benefits, such as high cell translocation potency, no peptide toxicity, and the capacity to act as a potent drug carrier. LMWP was functionalized to the surface of PEG-PLA nanoparticles using a maleimide-mediated covalent binding method. The resulting nanoparticles greatly outperformed unmodified NP in terms of cellular accumulation, which was attributable to direct translocation and lipid raft-mediated endocytosis routes that did not result in cytotoxicity. The amount of fluorescent probe identified in the rat cerebrum, cerebellum, olfactory tract, and olfactory bulb after intranasal administration of coumarin-6-loaded LMWP-nanoparticles was substantially higher than that of coumarin-6 carried by unmodified nanoparticles. These findings suggested that modifying CPPs on nanoparticles surfaces could be a safe and effective way to improve nose-to-brain medication delivery in prospective brain illness diagnostic and therapeutic applications.

*5.10. Exosomes.*

Exosomes are naturally occurring membranous nanosized vesicles with a diameter of 50-150 nm. They came from the endosomes of various T-cell types, including immune cells such as dendritic cells, macrophages, B-cells, and T-cells, as well as mesenchymal stem cells, cancer cells, and endothelial cells. Exosomes are a type of bilayered lipid nanosphere that contain various proteins and lipids from the parent cell and have a unique cell tropism. Exosomes can transport proteins with distinct homing specificities that are cell-type-specific and located in the parent T-cell membrane, such as myelin proteins made from oligodendrocytes. The distinctive characteristics of exosomes are the result of their biogenesis. Exosomes are created in three stages: first, endocytic vesicles are formed from the plasma membrane; second, the endosomal vesicle membrane is internally budded to produce multivesicular bodies (MVBs), which are composed of intraluminal vesicles; and third, these MVBs fuse with the plasma membrane to release the vesicular contents known as exosomes [50]. Exosomes perform an important and diversified role in intercellular communication, regulating multicellular organisms' development and function. These extracellular vesicles specialize in long-distance intercellular connections, allowing protein transfer and functioning mRNAs and microRNAs for subsequent protein expression in big T-cells [51]. Exosome secretion is, in fact, a very efficient, smart, and cost-effective method of transmitting information between cells. Exosomes, on their own, have unique biological activities that could be exploited for therapeutic purposes, particularly in terms of immune control and regenerative benefits.

Exosomes generated from mesenchymal stem cells (MSCs) had strong cardioprotective paracrine effects against myocardial ischemia/reperfusion damage. Furthermore, these exosomes inhibited early pulmonary inflammation and vascular remodeling in pulmonary hypertension by suppressing hyperproliferative pathways, such as signal transducer and activator of transcription 3-mediated signaling. Exosomes generated from MSCs have also been found to exhibit neuroprotective properties in stroke patients. Exosomes derived from the same cells may have different functions, largely dependent on the environment. As a result, stroke alters the miRNA profile of exosomes, particularly in miRNAs involved in the recovery process after a stroke. Exosomes produced from MSCs were transmitted to recipient T-cells, changing gene expression and promoting neurite development in primary rat neurons. MSCs have also been used in the therapy of Alzheimer's disease. Exosomes were found to deliver

enzymatically active neprilysin to the brain, which destroys both intracellular and extracellular -amyloid peptide plugs.

Exosomes released by cardio-sphere-derived cells have been shown to have anti-inflammatory, anti-oxidative, anti-apoptotic, anti-fibrotic, and cardiomyogenic properties, owing to their potential to inhibit collagen deposition and exert anti-fibrotic efficiency via paracrine processes. Exosomes generated from endothelial cells have been proposed as a potential treatment for atherosclerosis. In mice fed a high-fat diet, systemic treatment of exosomes produced by human umbilical vein endothelial cells (HUVECs) reduced atherosclerotic plaques. This effect was attributed to the enrichment of miRNA in HUVECs-derived exosomes, specifically miR-143 and miR-145, which regulate the expression of atheroprotective genes. HUVECs-derived exosomes then transported these miRNAs to smooth muscle cells to control gene expression and reduce atherosclerotic lesion formation.

## 6. Future Perspectives

The nasal cavity is a possible delivery pathway for medications to treat various disorders. Drug carriers have been created using various techniques to enhance drug delivery, performance with suitable nasal devices, and drug absorption through the nasal mucosa. An elegant drug delivery system to the nose is made possible by the connection between formulation development and delivery devices, increasing the effectiveness of this route for the distribution of various therapeutic molecules for the treatment of various illnesses.

Current research is mostly focused on medications used to treat central nervous system illnesses. People are living longer, so neurological illnesses are becoming more common. Orally administered medications frequently have a lot of negative effects and need to be given in big dosages to be effective. Oral bioavailability is extremely low for big protein or peptide-based medicines. The dosage can be considerably lowered, and many negative effects can be avoided by employing a nasal drug delivery method. In addition, when a patient is confused, nasal administration is still a choice, whereas oral administration is typically no longer an option. Nasal drug delivery systems offer a more patient-friendly alternative to oral administration, including options such as nasal spray, nasal drops, nasal powder, nasal gels, nasal emulsions, and nasal suspensions.

Additionally, nasal administration might be utilized to mask the taste of an unpleasant active component. The nasal medication delivery techniques are currently limited. The even absorption of medications in the case of an inflamed or swollen nasal mucous membrane, as is the case with allergies or colds, is a considerable challenge. A consistent and uniform absorption of the active ingredient is essential, especially in the case of a chronic condition. In the field of vaccinations, tremendous progress has already been made, and nasal influenza vaccine delivery has been possible for some years. Currently, medications that are particularly effective for the central nervous system are being researched using various delivery systems and are getting excellent results in animal tests, but clinical trials are still needed [52].

The direct nose-to-brain route may be especially appealing for brain administration of medicines with low BBB permeability, particularly if they can be packaged with suitable mucoadhesive and specific targeting ligands on carrier surfaces. Drug absorption into the brain appears to be significantly influenced by nanocarriers. However, because not all nanocarriers have been demonstrated to enhance brain delivery significantly, more research into formulation design and processing is needed. The possible toxicity risks associated with nanocarriers should

also be considered in the future. Additionally, it is challenging to compare pertinent data published by various authors; as a result, standardization of in vitro and in vivo experimental conditions requires extra consideration.

## 7. Conclusions

To make use of this channel for human medication administration, formulation methods alone are insufficient. Novel technologies are being developed to overcome nasal cavity anatomical barriers and target formulation deposition in the olfactory region of the nasal cavity. As a result, intranasal therapeutic delivery will require more complex and automated delivery systems in the coming years to ensure correct and repeatable doses. The discovery of efficient medication for brain disorders such as Alzheimer's, Parkinson's, and stroke has been hampered considerably. This could be due to a lack of knowledge about these diseases' neurological mechanisms and etiology. The development of fresh possible therapy options will be aided by a better understanding of these disorders. The efficient translation of nano carrier-based drug delivery for treating brain disorders from the lab to the clinic could be sped up through closer cooperation and cross-talk between medicine, pharmaceutics, pharmacology, and engineering.

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## Conflicts of Interest

The authors declare no conflict of interest.

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