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# LIPID NANOCARRIERS FOR NOSE TO BRAIN DELIVERY: RECENT UPDATES

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**Keywords:**

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**ABSTRACT:** In recent years, the nasal route is gaining increasing importance for systemic administration of drugs and targeting to brain. The drug delivery to the brain is limited due to several factors, including presence of blood-brain barrier, enzymatic degradation, and efflux of drug by P-glycoprotein. Nasal route is employed to target the brain using various direct pathways *via* nasal mucosa and to bypass blood-brain barrier. The nasal route has limitations like small surface area, possibility of nasal irritation, and low volumes of administration. Various strategies have been employed in order to enhance nasal absorption and drug uptake in the brain. Nanotechnology-based formulations is one of the most investigated approaches in recent years for effective brain targeting. Lipid-based nanocarriers serve as a promising strategy owing to their ability to facilitate drug permeation through the nasal mucosa and reduce drug efflux by the blood-brain barrier by inhibiting efflux transporters. This review summarizes nose to brain drug transport pathways, mechanism of nasal absorption, various strategies used to improve nasal absorption, and a detailed account on lipid-based carriers employed for a nose to brain delivery.

**INTRODUCTION:** Oral administration is one of the most desirable and convenient methods for drug delivery. However, poor dissolution and permeation, low bioavailability and first-pass metabolism limit the drug delivery by this route for many actives [1]. Out of various alternative routes, the intranasal route has shown promise in the effective delivery of drugs and biopharmaceuticals [2]. Conventionally, nasal route has been extensively used for the treatment of local conditions Such as, Perennial rhinitis, allergic rhinitis and nasal decongestion [3]. However, owing to the advances in drug delivery systems and nanotechnology, the currently nasal route is also being extensively explored for systemic drug delivery. The nasal route is reported to be a potential route for targeting therapeutic substances to the brain by taking the olfactory pathway *via* the nasal mucosa and bypassing the blood-brain barrier [4].

Current research is mostly focused on developing various novel drug delivery systems and carriers for a nose to brain delivery, addressing various categories of drugs like antipsychotics, antidepressants, antiepileptic drugs for the treatment of Parkinson's and Alzheimer's disease, hypnotic and sedatives, and also for delivery of protein and peptides [5, 6].

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This review will focus on the current advances in intranasal delivery systems, emphasizing lipid-based nanocarriers utilized in brain targeting.

**Anatomy and Physiology of Nasal Cavity:** The human nasal cavity is situated above the roof of the mouth and below the skull base. The nasal cavity has a surface area of about 150 $cm^{-2}$ and a volume of about 15 to 20 ml. The nasal cavity is divided into four regions; nasal vestibule, atrium, respiratory region, and olfactory region [6].

**Nasal Vestibule:** Nasal vestibule is the anterior-most part of the nasal cavity with a surface area of about 0.6 $cm^{-2}$. The nasal vestibule is responsible for filtering out the air-borne particles. Absorption of drugs in this area is very difficult [7].

**Atrium:** Atrium is present in between nasal vestibule and respiratory regions. Its anterior section is composed of the stratified squamous epithelium and the posterior section by the pseudostratified columnar cells with microvilli [8].

**Respiratory Region:** Respiratory region is an important and largest part of the nasal cavity. The respiratory region is divided into three parts: superior, middle, and inferior, which causes humidification and temperature regulation of the inhaled air. This region is mainly composed of epithelium, basement membrane, and lamina propria. Respiratory epithelial cells have microvilli. These microvilli are responsible for increase the surface area, making this site a major site for drug absorption and systemic delivery [9].

**Olfactory Region:** The olfactory region is the most important part of the nasal cavity; this region, brain, and cerebrospinal fluid targeting is easily achieved. The olfactory region has a surface area of about 10 $cm^{-}2$. It comprises of thick connective tissue, lamina propria, upon which rests the olfactory epithelium [10].

Lamina propria has axons, Bowen's bundle, and blood vessels, whereas epithelium consists of three different cells, *i.e.*, basal cells, supporting cells and olfactory receptor cells, *etc.* Neurons are interspersed between supporting cells. The olfactory receptor cells are bipolar neurons with a single dendrite extending from the cell body to the free apical surface, where it ends in an olfactory knob carrying nonmotile cilia, extending above the epithelium [11].

**Advantages of Nasal Delivery[12]:**

- ✓ Rapid absorption is achieved
- ✓ Avoidance of liver first-pass effect hence results in higher bioavailability with a lower dose for extensively metabolized drugs
- ✓ Fast onset of therapeutic action
- ✓ Avoidance of metabolism by the gastrointestinal tract
- ✓ Reduction in risk of overdose
- ✓ Non-invasive therefore reduced risk of infection and disease transmission
- ✓ Improved patient compliance

**Self-Administration Is Possible**

- ✓ Limitations[13]
- ✓ Small surface area as compared to GI tract
- ✓ Possibility of nasal irritation
- ✓ Low volumes can be administered, hence limit the dose of the drug

**Barriers for Drug Delivery to Brain:** The effective treatment of CNS disorders is often limited due to the presence of one of the following barriers that restrict the drug delivery to the brain [13].

**Blood-Brain Barrier (BBB):** The BBB separates the brain from the blood and consists of a tight junction of endothelial cells covered with perivascular elements (astrocytes and pericytes). The capillary endothelial cells of the brain are tightly bound to each other with no pores and enveloped by a thick covering of pericytes and astrocytes, together constituting the blood-brain barrier, thus restricting the drug permeation by paracellular transport and allowing drug permeation only by transcellular pathway, carrier-mediated transport and receptor-mediated endocytosis [14]. The endothelial cells in the brain also show the presence of efflux transporters, *e.g.*, P-glycoprotein and multidrug resistance proteins, which are responsible for regulating transcellular transport of molecules across BBB and efflux of

potentially toxic molecules. This makes the BBB a rate-limiting factor in drug permeation into brain [11].

**Blood Cerebrospinal Fluid Barrier (BCB):** It is an important barrier that comprises of choroid plexus and arachnoid membrane. Unlike the capillary endothelium of BBB, in BCB, the capillary endothelium is fenestrated (with small pores). However, the entry of the drug is controlled by the tight junction of choroidal cells. The drug permeation occurs by transcellular transport and carrier-mediated transport [15]. Ion transporters like organic anion transporter (OAT) and organic cationic transporters (OCT) are involved in active transport of drug molecules. The cerebrospinal fluid is involved in the exchange of molecules with the interstitial fluid of brain parenchyma. The drug molecules can enter into the brain from cerebrospinal fluid (CSF) through BCB [16].

**Blood Tumor Barrier:** In the case of a brain tumor, although the capillary endothelium becomes leaky and BBB weakens, the complex nature of tumor cells limits the passage of molecules across this barrier. The reduction in the diffusion of drug molecules is observed, making the brain tumor barrier less permeable [6].

**Mechanism for Nasal Absorption:** The drug absorption through nasal mucosa takes place by various mechanisms, including paracellular pathway and transcellular pathway as the major mechanisms for drug permeation. Paracellular transport includes movement between the cells, and this pathway is taken by polar drugs with molecular weight up to 1000 daltons [17]. Trans cellular pathway involves the transport of drugs through the epithelial cells, limiting lipophilic drugs with low molecular weight. The molecular weight, lipophilicity, and ionization of the drug are the rate-controlling factors for a transcellular pathway. Other mechanisms observed are active transport mechanisms, transcytosis, and transport through intracellular junctions [18].

**Nose To Brain Drug Transport Pathways:** The drug administered intranasally can directly reach the brain bypassing the blood-brain barrier. There are various pathways for the delivery of drugs from nose to brain [17]. The drug may either enter directly in brain via olfactory pathway or drug may reach to CSF and then subsequently enter into the brain. The drug is transported by a single or combination of the pathways that are discussed below [3].

**Olfactory Pathway:** Drug administered through nasal cavity travels from olfactory region to the brain for which it has to transfer through the olfactory epithelium by olfactory nerve pathway. The olfactory nerve pathway is further subdivided into intracellular or intraneuronal and extracellular or extraneuronal pathways. The intracellular pathway across the olfactory epithelium involves uptake of the drug by endocytosis into the olfactory sensory neurons, which follow the axonal transport and reach the olfactory bulb or undergo transcytosis through the sustentacular cells of the lamina propria [7]. In the extraneuronal pathway, the drug crosses the gaps between the neurons (perineural channels) and relies on bulk flow transport.

The drug is subsequently transported to the olfactory bulb, from where it enters other brain regions by diffusion or convection. In spite of expressing tight junctions by olfactory ensheathing cells, the continuous re-growth of the olfactory nerve fibers creates open spaces providing an additional path for the drug to reach the brain. This pathway allows the drug to reach the brain in minutes. Since the average diameter of the olfactory axons is about 100 nm, sufficiently small-sized nanoparticles could potentially be transported *via* axons through the olfactory bulb into the olfactory cortex and from there to the caudal pole of the cerebral hemisphere into the cerebrum and the cerebellum [19].

**Trigeminal Nerve Pathway:** Trigeminal nerve pathway is another important pathway for the nose to brain drug delivery. It supplies the respiratory and olfactory epithelium and enters the brain in the pons. A small branch of the trigeminal nerve also terminates in the olfactory bulb. The ophthalmic and maxillary branches of the trigeminal nerve directly pass through the nasal mucosa and hence, are important for the brain drug delivery through the nose [13]. It has entry points into caudal and rostral brain areas via the lacerated foramen and the cribriform plate following intranasal administration. The trigeminal nerve also involves intra neuronal and extraneuronal pathways.

The intracellular/ intra neuronal pathway results in endocytosis of the drug from the respiratory epithelia into the nearby trigeminal nerve, which further transports the drug to the brainstem [20].

**Cerebrospinal Fluid Pathway:** Cerebrospinal fluid pathway which connects the subarachnoid space containing CSF, perineural space along the olfactory and trigeminal nerves, and nasal lymphatic's provide a gateway for intranasally administered drug to CSF and hence to the brain. Drugs reaching the CSF of the subarachnoid space can get distributed to more distant sites in the brain. The drug may move from the nasal passages to the CSF and from there into the brain interstitial spaces and perivascular spaces for distribution throughout the brain [21]. The drug's entry into the CSF depends on its molecular weight, lipophilicity, and degree of ionization. Also, the drug must be able to diffuse through the CSF from the perineural space. The rapid turnover of the CSF would affect the diffusion of large molecules compared to the smaller, highly diffusible molecule. The drug concentration in the CSF and brain will be non-equivalent due to the presence of CSF- brain barrier [19].

**Perivascular Pathway:** Distribution of the drug from the olfactory bulb and the brainstem to other distant parts of the brain may take place via the intracellular pathway involving transfer and uptake of the drug by the second-order neurons, which synapse with the peripheral olfactory sensory neurons or trigeminal ganglion cells. The extracellular pathway resulting in the distribution of drugs to other brain parts involves convective bulk flow or local diffusion of the drug within the perivascular spaces into the parenchyma.

**Other Possible Pathways:** Although perineural transport along the olfactory and trigeminal nerves is one of the major pathways for the nose to brain delivery of drugs, there is also a probability of drug transport along the facial nerve or Gruenberg ganglion into the brain. Also, the intranasally administered drug after reaching the lamina propria can get absorbed into the nasal blood vessels and enter the systemic circulation from where the drug would have to pass the BBB or the BCB to enter the brain. This is possible, especially if the drug is small and lipophilic. Drugs that are not absorbed into the blood vessels may get absorbed in the nasal lymphatic vessels in the lamina propria and drain into the deep cervical lymph node.

**Barriers for Nasal Absorption:** For effective designing of nasal formulations, it is required to understand various barriers of nasal absorption that limit the drug transport *via* the intranasal route. The major barriers for nasal transport are identified as;

- ✓ Low membrane transport
- ✓ Low bioavailability
- ✓ Enzymatic Degradation
- ✓ Low membrane transport

The noxious substances that are coming to the upper respiratory tract are cleared by cilia towards nasopharynx. This results in ciliary movements that are called mucociliary clearance and are affected by environmental conditions and pathophysiological conditions. The mucociliary clearance depends on the beating frequency of cilia which is normally [20] Hz. The beating frequency is influenced by calcium ion concentration. The reduction in membrane calcium will reduce mucociliary clearance. The mucociliary mechanism is responsible for rapid clearance of the drug, reduction in drug residence at the absorption site, and thus results in lower drug transport. The drug transport can be improved by increasing the viscosity of formulations or the addition of a mucoadhesive polymer to the formulation. The clearance of powder and liquid formulations lacking mucoadhesion is reported to occur only in 15 to 20 min.

**Low Bioavailability:** The lipophilic drugs are well absorbed by the nasal route by transcellular transport, whereas the absorption of polar drugs is limited. The low bioavailability is reported for polar drugs compared to lipophilic drugs that demonstrated high bioavailability, in some cases approaching intravenous injections.

**Enzymatic Degradation:** The bioavailability of the drug via the nasal route may also be affected by the enzymatic degradation. The microsomal enzymes, cytochrome P-450 monooxygenases, and carboxylesterases in nasal epithelial cells are responsible for the metabolism and inactivation of the drug.

The activity of exopeptidases and endopeptidases may affect protein and peptide delivery by nasal route. Drug delivery can be improved by protecting a drug in a nano or microcarrier.

**Strategies for Improving Nasal Absorption:** Various approaches are employed and reported in order to increase the drug transport across nasal mucosa by addressing the problems of mucociliary clearance, low drug solubility and permeability, p-glycoprotein efflux, and enzymatic degradation.

**Permeation Enhancers:** One of the commonly used approaches for improving nasal absorption is penetration enhancers. Penetration enhancers act by various mechanisms; alter the mucus membrane properties, interfere with the tight junctions between epithelial cells, and increase the membrane fluidity by extracting the lipid or proteins from the membrane or interacting with the phosphor lipid bilayers. Penetration enhancers also interfere with the mucociliary clearance and enzymatic activity in the nasal cavity.

The absorption of proteins by nasal route is reported to be improved by using penetration enhancers [11]. The major concern related to penetration enhancers is their toxicity and irritant nature. **Table 1** presents various penetration enhancers that are used for the nasal route. Chelating agents are also utilized as penetration enhancers. Those bind with membrane calcium depleting its concentration resulting in low ciliary movements and mucociliary clearance.

**TABLE 1: TYPES OF PERMEATION ENHANCERS**

| Types ofpermeation enhancers | Example |
|---|---|
| Surfactants | Polyozyethylene-9-lauryl ether (Laureth-9), Saponin |
| Bile salts | Trihydroxy salts (glycol- and taurocholate), Fusidic acid derivatives (STDHF) |
| Chelators | Salicylates, Ethylenediaminetetraacetic acid (EDTA) |
| Fatty acid salt | Oleic acid, Caprylate (C8), Caprate (C10), Laurate (C12) |
| Phospholipid | Lysophosphatidylcholine (lyso-PC), Didecanoyl – PC |
| Cyclodextrins: α, ß and γ | cyclodextrins and their derivatives |

**Pro-drug Approach:** This approach is mainly used for improving the nasal bioavailability of drugs, especially proteins and peptides, by increasing their membrane permeability and imparting enzymatic stability to them [22]. Prodrug is usually referred to as pro-moiety that is used to cover or mask the undesired or unstable functional group with another functional group. The prodrug undergoes enzymatic transformation to release the active moiety when it crosses the enzymatic and membrane barrier. The absorption of peptides like angiotensin II, bradykinin, caulein, carnosine, enkephalin, vasopressin and calcitonin was improved by pro drug approach [4].

**Nasal Enzyme Inhibitors:** Nasal metabolism of drugs can be eliminated by using enzyme inhibitors. The absorption enhancers like salts and fusidic acid derivatives also show enzyme inhibition activity to increase the absorption and bioavailability of the drug. The other enzyme inhibitors commonly used are tripsin, aprotinin, borovaline, amastatin, bestatin, and boroleucin inhibitors [23]. Some absorption enhancers also act as enzyme inhibitors like disodium ethylene diamine tetraacetate prevents the enzymatic degradation of beta-sheet breaker peptide, which is used for treating Alzheimer's disease [24].

**Indirect Enhancers:** The brain uptake of the drugs is reduced by P-glycoprotein, the efflux transporters found in abundant concentration in the brain. The drugs transported from the nasal route to the brain fail to achieve the desired concentration in the brain if it acts as a substrate for P-glycoproteins. The drug uptake can be improved by co-administering it with P-glycoprotein inhibitors [13].

**Structural Modification:** Modification of drug structure without altering pharmacological activity is one of the lucrative ways to improve nasal absorption. The chemical modification of drug molecules has been commonly used to modify the physicochemical properties of a drug, such as molecular size, molecular weight, pKa, and solubility that are favorable to improve the nasal absorption of drug [20].

**Mucoadhesion:** Most nasal solutions and powder formulations have low residence time in the nasal cavity due to high mucociliary clearance.

This reduces the drug contact time and hence absorption of the drug through the nasal mucosa. This problem can be addressed by incorporating a viscosity enhancer to the aqueous formulation or designing a mucoadhesive formulation. Various mucoadhesive polymers like dextran, cellulose derivatives, alginate, and chitosan had been employed to increase the residence time of formulation [23]. The increase in contact time with mucosa also facilitates absorption and increases the drug bioavailability. The polymer-like chitosan is not only a mucoadhesive, but it is also a well-known permeation enhancer that increases the paracellular transport of drugs, thus extensively studied in nasal formulations [25].

**Particulate Drug Delivery:** Particle design has an increasingly important role in absorption enhancement. Microspheres, nanoparticles, and liposomes are the particulate systems that can be used as carriers to encapsulate an active drug [26]. The properties of the carriers can be varied to maximize therapeutic efficacy. Overall, this can increase absorption efficacy, stability and reduced toxicity of the active ingredient. Nanoparticles are effectively utilized for the nose to brain delivery owing to their ability to interfere with the tight junctions of blood capillaries, enhanced retention in the brain, ability to permeate by transcytosis process [26]. The retention of nanoparticles in the nasal cavity can be increased further by designing them as mucoadhesive. Various mucoadhesivena noparticles from polymers dextran, chitosan, and biodegradable starch are reported in literature [27].

The new classes of mucoadhesive carriers include thiolated polymers and lectin conjugated polymers. Thiolated polymers react with mucin through disulfide linkage. This linkage being covalent confers strong mucoadhesion properties to the polymer. Thiolated chitosan is extensively studied for improving the nasal transport of actives. Lectin conjugated nanoparticles are able to bind to certain sugar moieties of the cell membrane, thus increases the cellular uptake of the drug. The lectin conjugation of polylactic acid and poly (lactic-co-glycolic acid) is extensively utilized for drug targeting to the brain via nasal route [28]. The problems associated with polymer nanoparticles include; stability, safety concern, lack of suitable sterilization methods, complex synthetic processes for their production, presence of residual solvents, higher cost. Considering these limitations, lipid-based nanoparticle systems offer a promising strategy for nose to brain targeting. Lipids interfere with membrane lipids and increase membrane fluidity, thus enhance the drug permeation through the membrane. They are also reported to promote drug transport by endocytosis by facilitating interaction with BBB and inhibiting p-glycoprotein [16]. The particles below 200 nm will not be taken up easily by the reticuloendothelial system, thus bypass the removal by liver and spleen [29]. The lipid-based nanoparticle systems extensively studied for nasal route are liposomes, niosomes, solid lipid nanoparticles, and nanostructure lipid carriers which are discussed in following sections.

**Vesicular Systems for Intranasal Applications:** Vesicular systems, such as liposomes and niosomes have been developed for improving nasal permeation and targeting drug to brain. Vesicular carriers have numerous advantages including sustained or controlled release of drug, higher drug entrapment, higher uptake and retention in brain. Phospholipids, a major component of vesicular carriers, are similar to membrane lipids, thus can interact with these membrane lipids and enhance the drug penetration and uptake.

**Liposomes:** Liposome is a vesicular system consisting of one or more concentric phosphor lipid bilayers surrounding the central aqueous core. They have the ability to entrap both hydrophilic and hydrophobic moieties hence are extensively studied. Liposomes constitute of natural and synthetic phospholipids, like phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, or phosphatidylserine [30]. One of the major constituents of liposomes, along with phosphor lipid is cholesterol. Cholesterol is incorporated in order to increase the vesicular membrane fluidity and stability of bilayers. Based on the number of bilayers present and size, liposomes are classified [31]

**Fig. 1.** Liposome formulations should have high entrapment efficiencies, narrow size of distributions, long-term stabilities, and ideal release properties (based on the intended application) [31]. Based on the composition of liposomes and the mechanism involved for the delivery, different types of liposomes are reported, *viz.* conventional liposomes, pH-sensitive liposomes, immune

liposomes and long-circulating liposomes [32]. The pH sensitive liposomes have found application in tumor targeting, whereas cationic liposomes are mainly used in cellular targeting and gene delivery. The liposome surface can be pegylated (covalent attachment of Polyethylene glycol) in order to obtain long-circulating liposomes that increase the retention of liposomes in the body by preventing the opsonization process. Various methods have been employed for the preparation of liposomes. Some of these methods are enlisted in **Fig. 2.** Various studies reported applying liposomes in the nose to brain delivery of actives like quetiapine, rivastigmine, tacrine, *etc*. Some of these studies are summarized in **Table 2.**

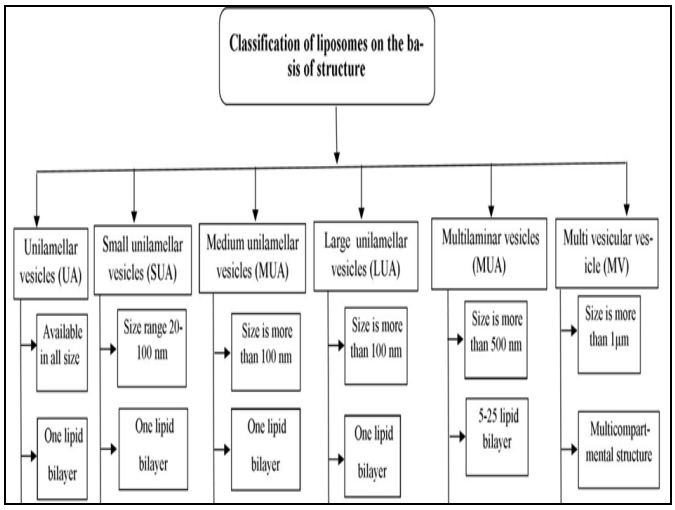


**FIG. 1: CLASSIFICATION OF LIPOSOME ON THE BASIS OF STRUCTURE**

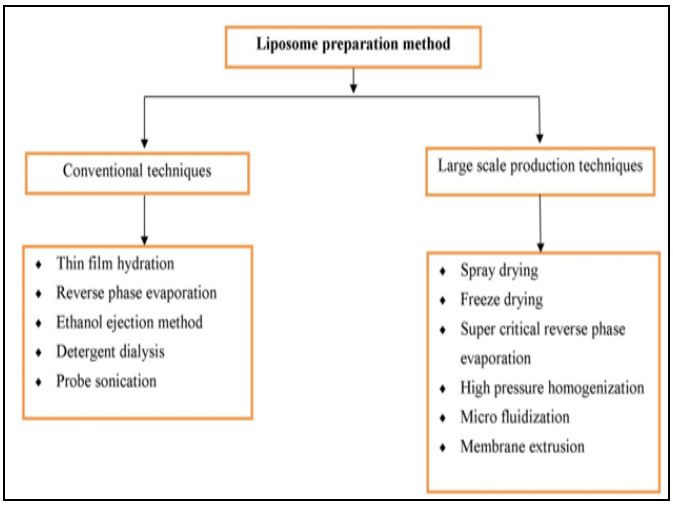


**FIG. 2: METHOD OF PREPARATION OF LIPOSOMES**

**TABLE 2: LIPOSOMAL AND NIOSOME FORMULATIONS FOR NOSE TO BRAIN DELIVERY**

| Drug | Methods | Outcome |
|---|---|---|
| Quetiapine Fumarate33 | Thin-film hydration followed by sonication method was employed in liposome preparation | Liposomes with entrapment efficiency of 75.63±3.77% were obtained and demonstrated 32.33±1.53% of drug permeation through sheep nasal mucosa |
| Imatinib[34] | Imatinib loaded liposomes were prepared by film hydration with size below 150 nm and sustained release | Developed liposomes demonstrated improved brain distribution and retention in rats and did not show cytotoxicity in cell lines |
| Tacrine hydrochloride [22] | Liposome formulations were prepared using the Reverse Phase Evaporation technique followed by membrane filter extrusion. Liposomes were prepared using traditional excipients (cholesterol and phosphatidylcholine), partly enriched with α-tocopherol and/or Omega3 fatty acids. | Liposome formulations showed a mean diameter in the range of 175nm to 219nm with polydispersity index lower than 0.22, a lightly negative zeta potential, and excellent encapsulation efficiency. Liposomes showed good mucoadhesive properties and a marked increase in tacrine permeability. |
| Curcumin [35] | Liposomes with soya lecithin and cholesterol were prepared by solvent dispersion method and coated by xanthan gum | Stable liposomes with sizes below 150 nm were obtained and showed controlled release behavior with higher brain retention as compared to drug solution. |
| Ghrelin (GHRL)[36] | GHRL containing anionic and cationic liposomes were prepared by DHDP or DOTAP by thin-film hydration followed by extrusion and further coated with N-(2- hydroxy)propyl-3-trimethyl ammonium chitosan chloride | Chitosan coating improved mucoadhesion, enhanced permeation through the Calu 3 cells, and provided enzymatic protection against trypsin and carboxylesterase |
| H102 Peptide [37] | The H102 liposomes were prepared using a modified thin-film hydration method. | After intranasal administration, the AUC of H102 liposomes in the hippocampus was 2.92-fold larger than that of the solution group in rats. |
| Donepezil HCl[38] | Liposomes were formulated by reverse-phase evaporation technique using DPPC and cholesterol in 1.6:1 molar ratio and dispersed in thiolated chitosan hydrogel | Liposomes with size 438.7 ± 28.3 nm and entrapment efficiency, 62.5% ± 0.6 with sustained drug release were obtained. Drug distribution was higher as compared to oral formulation. |
| Buspirone | Buspirone hydrochloride niosomes were | The optimized niosomes were of size 181.9±0.36nm and |

| | | |
|---|---|---|
| hydrochloride 40 | prepared by thin-film hydration method and converted into in situ gel | zeta potential, -15.4 mV with sustained drug release and improved permeation through sheep nasal mucosa |
| Melatonon 41 | Melatonin niosomes were prepared by thin-film hydration using cholesterol and span 60 in the organic phase and sodium deoxycholate (SDC) and melatonin in the water phase added to the film during hydration | SDC reduced the size and improved the encapsulation efficiency. *In vivo* studies confirmed the safety of niosomes for nasal mucosa, and intranasal melatonin was bioequivalent to intravenous injection with sleep induction within 15 min |
| Folin acid 42 | Folic acid niosomes were prepared using different nonionic surfactants and cholesterol by using the lipid layer hydration technique. | The prepared niosomes were in the size range of 3.1–5.6 µm, entrapment efficiency of 69.42% and better in vitro drug release of 64.2% at the end of 12 h. |
| Pentamidine | Pentamidine isethionate[43] | Niosomes were prepared by thin film hydration method and coated with chitosan glutamate |

**Niosomes:** Niosomes are vesicular drug carriers that are formed by the self-aggregation of cholesterol and nonionic surfactants in an aqueous medium. In contrast to liposome that contains phospholipids, niosomes vesicles consist of nonionic surfactant and therefore are more stable and less leaky than liposome. Niosomes have long self-life, exhibit high stability and enable the delivery of drugs at target site in a controlled or sustained fashion. The hydrophilic-lipophilic balance (HLB) and critical packing parameter (CPP) of surfactant play a major role in preparation of niosomes. The HLB value of 4-8 is considered to be optimum for vesicle formulation.

This value can be achieved by combining surfactants like polysorbate 80 or polysorbate 20 with cholesterol. The other surfactants used in niosomes are, alkyl ethers, sorbitan fatty acid ester (spans), alkyl amides, fatty alcohols or fatty acids and certain block copolymer like poloxamers. Presence of cholesterol confers significant changes in bilayer fluidity and permeability and imparts stability. Different methods for preparation of niosomes are reported, such as, handshaking, sonication, reverse phase evaporation technique, ether injection and multiple membrane extrusion and spray drying method. Various niosome formulations are reported for delivering CNS acting drugs, anticancer drugs, proteins and peptides, aptamers, antibodies, and antibody fragments. **Table 2** presents the intranasal niosomes preparations employed for brain targeting.

**Colloidal Carriers:** The colloidal carriers that are extensively studied for a nose to brain delivery are solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) [44]. The colloidal lipid carriers are known to increase the drug distribution in tissue, reduce the enzymatic hydrolysis by protecting drug, interacts with the epithelial layer resulting in increased penetration [45].

**Solid Lipid Nanoparticle (SLNS):** Solid lipid nanoparticles are colloidal carriers consisting of lipids and surfactants and lies in a size range of 10 to 400 nm [46]. The drug is either dissolved or dispersed in lipid matrix in a matrix type system, whereas the drug is coated with a lipid shell in a reservoir system [47]. SLNs have numerous advantages; low toxicity, biodegradability, the possibility of large-scale production, controlled or sustained release and drug targeting is achieved. SLNs, due to their small size, increases the contact time with the nasal epithelial layer; this improves membrane permeation resulting in higher drug transport [48]. SLNs are prepared by various techniques, such as solvent emulsification evaporation technique microemulsion method, probe sonication, high-pressure homogenization and super-critical fluid technique [49]. The retention of SLNs in the brain can be enhanced by surface coating with hydrophilic polymers (polyethylene glycol) to prevent the opsonization process [50]. The drug targeting the brain via SLNs can also be improved using ligands like folic acid or transferrin **Table 3.** summarizes various SLN formulations used for the nose to brain delivery.

**Nanostructured Lipid Carrier (NLC):** The major limitation of SLN formulation is limited drug entrapment due to the low solubility of drug in lipid56. NLCs are one of the promising colloidal carriers consisting of solid lipid along with oil. The oil normally is less than 30% of the total lipid content in NLCs [57, 58]. The less ordered arrangement of lipids in NLCs is responsible for high drug entrapment and better stability **Table 4.** Summarizes the studies reported on nose to brain delivery of drug.

**TABLE 3: SOLID LIPID NANOPARTICLE FORMULATION FOR NOSE TO BRAIN DELIVERY**

| Drug | Method of preparation | Outcome |
|---|---|---|
| BACE SRina [51] | SLN were prepared using a modified solvent emulsification evaporation method based on a w/o/w double-emulsion technique | The improved mucoadhesion and also prolonged residence time in the nasal cavity was demonstrated. |
| Carbamazepine[50] | Carbamazepine (CBZ) SLNs were prepared by the homogenization/ultrasonication method | CBZ loaded SLNs showed particle diameter around 160 nm. And almost the 100% of the encapsulated drug. In vivo anticonvulsant activity suggested protection by CBZ-NLC against seizures for at least 2 h. |
| Risperidone (RS)[52] | Risperidone (RSP)-loaded solid lipid nanoparticles (RSLNs) were prepared by solvent emulsification method | RSP loaded SLN the pharmacokinetics and biodistribution studies in mice showed that brain/blood ratio 1 h post-administration of RSLNs (i.n.) was found to be 1.36 ± 0.06 (nearly 10- and 5-fold higher) as compared with 0.17 ± 0.05 for RS (i.v.) and 0.78 ± 0.07 for RSLNs (i.v.), respectively. |
| Rizatriptan benzoate[53] | Rizatriptan loaded solid lipid nanoparticles were prepared by modified solvent diffusion method | SLNs in the size range of 145 to 298 nm were obtained. The maximum in vitro drug release was found to be 91% in 8 h, and maximum entrapment efficiency was 80%. |
| Citral[54] | Citral loaded solid lipid nanoparticles (citral-SLNs) were prepared via a high-pressure homogenization method | The encapsulation of citral in the solid lipid nanoparticle enhanced its stability in acidic surroundings. |
| Haloperidol (HP)[55] | SLNs were prepared by a modified emulsification diffusion technique | Haloperidol release from SLNs was found to be 94.1% after 24 h. The maximum concentration (Cmax) in the brain achieved from intranasal administration of HP-SLNs (329.1±20.8 ng/mL, Tmax 2 h) was significantly higher than that achieved after i.v. (76.9±7.6 ng/mL, Tmax 2h) and i.n. (90.1±6.2 ng/mL, Tmax 2h) administration of HP solution |

**TABLE 4: NANOSTRUCTURED LIPID CARRIER FOR NOSE TO BRAIN DELIVERY**

| Drug | Method of preparation | Outcome |
|---|---|---|
| Rivastigmine (RV)59 | NLCs containing 6.25 % w/w of RV was fabricated by ethanol injection method. | NLCs having particle size of 123.2±2.3 nm, entrapment efficiency of 68.3±3.4% and zeta potential of 32±1.2 mV were obtained. Brain Biodistribution studies indicated enhancement in blood brain barrier (BBB) penetrating potential of RV with IV NLCs (4.6 fold) and intranasal NLCs (5.3 fold) compared to RV given by IV. |
| Curcumin6[0] | NLCs were prepared by hot high pressure homogenization | The CRM loaded NLC developed as a particle with the size of 146.8 nm, a polydispersity index of 0.18, an entrapment efficiency (EE) of 90.8 %, and the zeta potential (ZP) of 21.4 mV. |
| Sumatriptan[61] | Sumatriptan NLC were prepared by solvent diffusion evaporation technique using cholesterol and triolein as solid and liquid lipid respectively | The developed NLC were of size 101 nm with PDI 0.27 and 91% entrapment efficiency. Neuro-pharmacokinetic evaluation revealed higher targeting efficiency and transport percentage of NLC. |
| Ketoconazole (KTZ)[62] | KTZ NLC prepared by high pressure homogenization using Compritol 888 ATO and Miglyol 812 N | NLC showed increased antifungal efficacy and improved brain tissue colonization as demonstrated by the fluorescent dye method |
| Proteins[63] | Chitosan coated nanostructured lipid carriers prepared by microemulsion method. | Formulation displayed a particle size of 114 nm with a positive surface charge of + 28 mV. The in vitro assays demonstrated the biocompatibility of the nanocarrier and its cellular uptake by 16HBE14o- cells. |
| Duloxetine(DLX)[64] | NLC containing DLX was prepared using glyceryl monostearate and capryol by homogenization and ultrasonication method | NLC when evaluated pharmaco-scintigraphically, exhibited higher radioactivity in brain as compared to solution after nasal administration |
| Ondansetron hydrochloride (OND)[65] | NLCs were prepared by high-pressure homogenization [HPH] technique. | Particle size, PDI, Zeta potential was observed in the range of 92.2–135 nm, 0.32–0.46, and −11.5 to −36.2 mV, respectively. |

**Microemulsion:** Microemulsions are thermo-dynamically stable isotropic mixtures of water, oil, surfactant, and co-surfactant. The microemulsion can exist as o/w type, w/o type or bicontinuous, based on the concentration of oil, water and surfactant. The microemulsions are clear and their size lies in the range of 10 to 100 nm. Microemulsions differ from nanoemulsions with respect to their size; the size for the latter is in the range 10 nm to 200 nm [66]. Another major difference in micro and nanoemulsion is their method of preparation67. Microemulsions are prepared without the input of energy by phase titration and phase inversion methods and are therefore thermodynamically stable. Nanoemulsions are prepared with the input of energy wherein size reduction is involved, hence are thermodynamically unstable. Microemulsions (ME) are prepared by the spontaneous emulsification method (phase titration method) and for which the phase diagrams are utilized. During the construction of phase diagram, various changes in the phases (biphasic, monophasic, micelles, lamellar, hexagonal, cubic, and gel structures) are observed when different components are mixed in different concentration68. From these regions, a monophasic microemulsion zone is identified, either o/w type or w/o type, based on whether oil-rich or water-rich [67]. The microemulsions can then be simply prepared by mixing the constituents in the identified proportion. Various Microemulsion formulations are reported for intranasal delivery **Table 5** of CNS-acting drugs, phytoconstituents, anticancer drugs and peptides.

**TABLE 5: MICROEMULSION AND NANOEMULSION FORMULATIONS FOR NOSE TO BRAIN DELIVERY**

| Drug | Method of preparation | Outcome |
|---|---|---|
| Albendazole sulfoxide (ABZ-SO) and Curcumin (CUR)[69] | ME was prepared using Capmul MCM, docosahexaenoic acid (DHA), tween 80 and ethanol | Intranasal docosahexaenoic acid (DHA) ME resulted in high brain concentrations and 10.76 (ABZ-SO) and 3.24 (CUR) fold enhancement in brain area-under-the-curve (AUC) compared to intravenous DHA MEs at the same dose. |
| Rivastigmine[70] | ME were prepared using Capmul MCM, Labrasol: Transcutol P and water and 0.3 % chitosan and cetyl trimethyl ammonium bromide was added to impart mucoadhesion | The average droplet sizeof ME was 53.8 to 55.4 nm. Mucoadhesive ME showed the highest mucoadhesion and no ciliotoxicity. |
| galantamine hydrobromide71 | Fish oil and butter oil-enriched ME of Capmul MCM, tween 80 and transcutol P was prepared by phase titration method | Fish and butter oil increased the droplet size of ME but demonstrated higher permeation to the brain by nasal route as compared to IV |
| Donepezil[72] | Donepezil-loaded ME was prepared using castor oil, Labrasol, Transcutol P, and propylene glycol. | ME system globule size of 58.9±3.2 nm with a polydispersity index of 0.19±0.04 was obtained. A hyperbolic drug release with maximum permeation in the first 4 h was obtained. |
| Huperzine A[73] | ME was prepared using 1,2-propanediol, castor oil and Cremophor RH 40 and converted to thermoresponsive gel using Pluronic F127 and F68 and chitosan | ME with 20 nm globule size and controlled drug release by first-order kinetics was obtained. In vivo pharmacokinetics study demonstrated significant brain uptake of Huperzine A ME. |
| Curcumin[74] | Nanoemulsions were prepared by using Labrafac Lipophile and Labrafac PG , Tween 80, Cremophor RH 40 | Hyaluronic acid-based nanoemulsion formula displayed a particle size of 115.2±0.15nm and a zeta potential of 23.9±1.7mV. |
| Asenapine maleate75 | ME system with Capmul MCM, Tween 80, propylene glycol and water was prepared by phase titration method | ME with droplet size 79.50 nm and PDI 0.356 was obtained. The drug release was by diffusion and the Higuchi matrix model was followed. The developed ME was stable for 6 months with no signs of nasal ciliotoxicity |

**CONCLUSION:** Drug therapy for brain diseases is often challenging due to the unique features of the blood-brain barrier. Several invasive approaches to bypass the blood-brain barrier have been explored but with limited success. Intranasal delivery is a promising approach to deliver the drug directly to the brain in a non-invasive way. Nanotechnology has opened up new avenues for the nose to brain drug targeting. Several particulate drug delivery systems like polymer nanoparticles and lipid-based carriers are gaining the scientific community's interest in targeting drugs to the brain via the nasal route. Lipid-based nanocarriers have shown great promise in this area of brain delivery.

They need to be explored further to investigate their applications in treating CNS disorders that are difficult to treat.

**CONFLICTS OF INTEREST:** None

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