Chapter

Perspective Chapter: Nose-to-Brain Drug Delivery through Liposomes - Recent Applications

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Abstract

Diseases related to the brain are causing a huge problem worldwide. Different drug formulations are available for the management of brain-related disorders, but due to less drug availability for the brain and non-specificity, it becomes difficult to completely cure life-threatening brain disorders. The blood-brain barrier (BBB) restricts the entry of drug molecules/drug-loaded carriers because of the presence of various efflux transporters and drug inactivating enzymes. Researchers have identified an intranasal route for direct delivery to the brain, bypassing BBB. Nanotechnology-enabled lipid-based drug carrier systems have shown potential for the management of brain diseases through nose-to-brain delivery. Liposomes are the most extensively investigated carrier systems because of biocompatibility, controlled release characteristics, easy surface modification, and biodegradability. This chapter highlights the important aspects of nose-to-brain delivery and strategies for enhancing the availability of drugs through liposomes in the management of different brain-related diseases.

Keywords: liposomes, nanotechnology, brain tumor, brain delivery, Parkinson's disease, targeted delivery

1. Introduction

The diseases associated with the central nervous system (CNS) are continuously increasing in the populations worldwide in the last couple of decades. CNS disorders substantially contribute to the loss of health and social challenges across the lifespan of human beings. The CNS diseases causing numerous problems globally include Alzheimer's disease (AD), brain tumor, bipolar disorders, epilepsy, depression, Down's syndrome, Huntington's disease, Parkinson's disease (PD), multiple sclerosis, and schizophrenia [1, 2]. The major problem in the management of the mentioned disorders is the non-accessibility of most of the therapeutic compounds in the desired concentrations. The major hurdle for the entry of active pharmaceutical ingredients into the brain is the presence of blood-brain barrier (BBB), which separates the brain from the blood. The non-permeable nature of BBB is due to the presence of tight endothelial junctions supported by astrocytes and pericytes. Small lipid-soluble drug molecules can enter the brain through BBB and all large molecular weight drugs cannot

enter the brain. Other factors responsible for nonentry of drugs into the brain are the presence of efflux transporters and drug inactivating enzymes onto the surface of BBB. P-glycoprotein is the most abundant efflux transporter, causing the non-availability of drug molecules into brain tissues. It becomes difficult for approximately 98% of drug candidates to enter into the brain tissues [3–6].

Various strategies have been investigated to facilitate the entry of drug molecules/drug-loaded nanocarriers into the brain. It is categorized into invasive and non-invasive approaches [7]. Invasive approaches include intracerebral implants, BBB disruption, and intraventricular infusion, and these techniques are generally used during severe or emergency situations because of technical procedures and hazardous effects. Noninvasive approaches include delivery of drugs through different routes, such as oral, transdermal, and intranasal administration. These routes take advantage of the endogenous system present in the body that transports various nutrients to the brain [8]. Drugs are generally incorporated or attached to a carrier system that transports them through BBB in high concentrations. The intranasal drug delivery route has gained great interest in the last decade because of the direct access of compounds to the brain through olfactory and trigeminal nerves bypassing BBB. This route has other advantages like easy administration, bypassing hepatic metabolism, higher availability of drugs into brain tissues, patient compliance, and reduced adverse effects related to systemic exposure [9, 10]. It has been established now through various studies that this route has more potential in enhancing drug levels in the brain when compared to intravenous administration. The enhanced delivery into the brain has been supported by different preclinical and clinical investigations [11–15].

Pharmaceutical nanotechnology deals with studies related to nanostructures that can be utilized for the delivery of drugs. These nanostructures carry the drugs and can easily move through different biological barriers. The nanostructures can also be tailored to deliver the drugs at specific locations in the body by employing active and passive targeting approaches [16, 17]. Different nanocarriers are liposomes, ethosomes, polymeric nanoparticles, niosomes, solid lipid nanoparticles, micelles, silver nanoparticles nanostructured lipid carriers, carbon nanotubes, nanoemulsions, dendrimers, and gold nanoparticles [18, 19]. Encapsulation/entrapment of drug molecules in the mentioned carrier systems improve solubility, protection from the biological environment, and enhanced accumulation in the brain. In recent times, the intranasal route has been investigated for direct delivery to the brain by incorporating drug molecules in a variety of nanocarriers [20, 21]. Among the mentioned nanostructures, a significant amount of investigation has been centralized on liposomes. Liposomes consist of phospholipids with cholesterol. The components of liposomes make them biocompatible, less toxic, and biodegradable. Liposomes can hold hydrophilic as well as hydrophobic drug candidates into its inner and outer structures, respectively. The surface of liposomes can also be modified by different ligands for active drug targeting. This chapter summarizes the innovative approaches employed for the management of brain disorders through liposome-based nose-to-brain drug delivery [22, 23].

2. Anatomical and physiological aspects of nasal cavity

The primary functions of the nasal cavity are smelling, breathing, filtration of air, and protection. The nasal route, which starts from the nasal vestibule (nasal valve) till the nasopharynx, has a length of approximately 12–14 cm. The space between the

human skull base and the roof of mouth filled by nasal cavity. Mucus layer and ciliary hair structures are found in the nasal cavity and help in trapping foreign particulate matters and pathogenic microorganisms. The total volume of the human nasal cavity is in between 15 and 20 ml with a total surface area of approximately 155 cm^2. The human nasal cavity is divided into the nasal vestibule, olfactory area, and respiratory region [24, 25].

Nasal vestibular part is the dilated area situated just after the nostrils. This part has the smallest surface area as compared to other parts of the nasal cavity. It does not have much significance in drug absorption and transport. The respiratory region of the nasal cavity, which is the largest segment with a large surface area (due to the presence of a large number of microvilli) of nasal cavity helps in the passage of air into the respiratory system. Each nostril's respiratory part consists of four conchae called turbinate bones and is covered by the mucosa of the nasal cavity [26]. Meatuses are present beneath the conchae and have connections till paranasal sinuses. The high vascularity and large surface area makes this section significant for drug absorption and transport. The presence of trigeminal nerves in this area has been investigated as a potential route for the direct entry of drug molecules into brain tissues. The olfactory area is placed in the deeper and upper part of the nasal cavity beneath the cribriform plate (horizontal bone). It helps in the processing of sensory information related to smell. In this area, olfactory neurons connect directly to olfactory bulb area of the brain. This target (olfactory neurons) in conjunction with the trigeminal route help has enhanced the uptake of drug/nanocarriers directly into CNS [27].

The rate of diffusion of drug formulations through the mucus layer and clearance rate from the nasal cavity is influenced by physical and chemical characteristics of polymer/excipient type, solvent system, particle size, shape, and surface charge. In adults, nasal secretions have pH in between 5.5 and 6.5 and contain different types of enzymes. The presence of enzymes deactivates different harmful substances entering from the outside environment. Drugs and polymers/additives can affect the functions of the ciliary structures of the nasal cavity. Rhinitis and nasal polyposis can also hamper the ciliary functioning and nasal absorption of drug molecules [28, 29].

3. Factors affecting drug diffusion from nose-to-brain

The environmental and physiological conditions of the nasal cavity contribute majorly to transportation of drug/carrier systems through nasal mucosa either into the systemic circulation or directly into the brain. The presence of drug-metabolizing enzymes, pH conditions, and tonicity characteristics of nasal secretions may severely affect the fate of drug molecules *in vivo* [30]. The different physicochemical factors related to drug molecule/drug formulation that can affect nasal transport are molecular weight, partition coefficient, degree of ionization, physical state of dosage form, viscosity, formulation pH, formulation osmolarity, and particle size [31]. It is reported that nasal absorption of drug molecules falls sharply if molecular weight exceeds beyond 1000 Da. Nasal absorption is significantly affected by the drug's lipophilicity and molecules with high lipophilic character are considered suitable for nasal delivery. In general, unionized molecules can traverse easily through the nasal barrier due to nonpolar characteristics [32, 33]. Intranasal delivery can be achieved by different states of formulations, such as liquid, powdered, and semisolids, but most of the formulations are developed in a liquid state because of easy administration and uniform distribution over the surface of the nasal cavity. It is desired to incorporate

viscosity-enhancing agents and mucoadhesive materials in the formulation to prolong the residence time of formulation in the nasal cavity [34–36].

Formulation pH also affects significantly with respect to ionization of drug, stability and might cause irritation of nasal mucosa if not adjusted properly. The osmolarity of the formulation can affect ciliary movement that can affect drug permeation and transport through the nasal barrier. The particle size of nanocarrier systems greatly influences the deposition and diffusion characteristics in the nasal cavity. It is generally desirable to have particle size of less than 200 nm for effective permeation and drug release behavior. Administered dose, volume, and administration device also affect the extent of nanocarrier localization and deposition in the nasal cavity [37]. Permeation enhancers can be incorporated into formulations to enhance diffusion through the nasal epithelium. These enhancers must have suitable characteristics such as nonirritating, nonallergic, nontoxic, and not causing any changes in the cells of nasal epithelium. Sodium deoxycholate, sodium taurocholate, sodium taurodihydrofusidate, sodium dodecyl sulfate, and polyoxyethylene-9-lauryl ether are the most commonly investigated permeation enhancers for nasal drug delivery [38].

4. Liposome-based nose-to-brain drug delivery applications

Nanotechnology deals with structures that have size ranges in nanometers. Methods for the preparation of nanocarriers govern the size, shape, encapsulation, and stability characteristics. Nose-to-brain route requires specific size requirements (less than 200 nm) for efficient drug delivery. Liposomes are lipid-based vesicular systems designed for encapsulation of hydrophilic and lipophilic drug molecules. Hydrophilic drug molecules can be incorporated into the inner aqueous compartment of liposomes, while lipophilic drugs in the phospholipid bilayer structure. The availability of biocompatible and biodegradable lipids makes this vesicular system suitable for therapeutic applications [22, 23, 39]. Nose-to-brain approaches have been utilized and reported through liposomes by researchers across the world for the management of different CNS disorders. Passive and active targeting strategies have been adopted to enhance the accumulation of drugs into brain tissues through liposomes. Passive strategy is based on the physiological processes followed by hormones and neurotransmitters of the human body. Active targeting involves the attachment of a ligand onto the liposomal surface, which specifically binds to a specific type of cells in the brain. Stimuli-sensitive liposomal formulations are also developed based on pH change, temperature, and other factors [40, 41].

Recent studies employing liposomal formulations through the intranasal route for the management of brain diseases are briefed herein and summarized in **Table 1** with major outcomes.

4.1 Brain cancer

Cancers are the most difficult disease to treat because variable nature of cancerous cells and high resistance to different drug candidates. Brain cancer is the most challenging aspect of therapeutics due to non-accessibility of drugs. The effectiveness of conventional chemotherapy is limited due to the non-specificity and toxicity of anticancer drugs [55]. In brain tumor situations, formulations first must overcome the BBB. Several researchers have developed liposome-based intranasal formulations

Drug(s) name	Drug category/ disease evaluation	Major outcome	References
Lomustine (LM) and *n*-propyl gallate (NPG)	Brain cancer	Liposomal size of ~127 nm with a sustained release pattern, enhanced nasal permeation, and cell killing activity against *in vitro* cancer cell lines were obtained.	[42]
Curcumin	Anticancer/anti-inflammatory/ antioxidant	The obtained liposomal size was between 100.2 and 150 nm. The optimized formulation exhibited controlled release characteristics with enhanced accumulation of curcumin in the brain via intranasal route when compared to curcumin solution.	[43]
Rivastigmine tartrate	Alzheimer's disease	Liposomal size with ell-penetrating peptide was found to be 178.9 ± 11.7 nm with an entrapment efficiency of ~30%. In vivo intranasal data revealed enhanced accumulation of rivastigmine tartrate in the cortex and hippocampus when compared to intravenous administration.	[44]
Galanthamine hydrobromide	Alzheimer's disease	Flexible liposomes showed size, zeta potential, and entrapment efficiency of 112 ± 8 nm, −49.2 ± 0.7 mV, and 83.6 ± 1.8%, respectively. More anti-acetylcholinesterase activity and higher brain concentration were found with developed intranasal liposomes in comparison to oral administration.	[45]
Donepezil	Alzheimer's disease	Liposomal formulation exhibited size of 102 ± 3.3 nm with an encapsulation efficiency of 84.91% ± 3.31%. A high drug concentration of the drug in the brain was found after intranasal administration through liposomes.	[46]
Hydroxy-α-Sanshool	Alzheimer's disease	The size obtained was 181.77 nm with PDI value of 0.207. The developed liposomal formulation was found to be nontoxic to the nasal mucosa of mouse and significantly improved learning memory deficits of the disease.	[47]
Glial cell line-derived neurotrophic factor (GDNF)	Parkinson's disease	Brain levels improved significantly within 1 h after a single dose (50-μg) of GDNF delivered by liposomal formulation through intranasal administration compared to GDNF delivered by phosphate buffer saline solution.	[48]
Risperidone	Schizophrenia	Vesicular size obtained was between 90 and100 nm with a PDI value of less than 0.5. The amount of risperidone was found to be high in the brain in comparison to plasma through intranasal delivery, depicting preferential transport to the brain.	[49]

Drug(s) name	Drug category/ disease evaluation	Major outcome	References
Quetiapine fumarate	Schizophrenia	The average liposomal size obtained was 152.2 nm with a zeta potential value of 24.7 mV. A higher concentration of drug was observed in the brain of albino mice from liposomal dispersion when compared to simple dispersion of drug.	[50]
Lamotrigine	Epilepsy	Optimized liposomal formulation exhibited a size of 88.90 ± 1.56 nm with an entrapment efficiency of 68.75% ± 0.02%. Significantly high drug permeation was obtained with the liposomal formulation in comparison to simple dispersion.	[51]
Valproic acid	Epilepsy	Liposomal size obtained was in between 90 and 210 nm with entrapment efficiency ranging in between 60% and 85%. Pharmacokinetic studies showed a higher amount of drug in the brain than plasma after intranasal administration.	[52]
Tissue plasminogen activator	Ischemic stroke	Suitable entrapment efficiency with the desired size, sustained release characteristics and proteolytic activity showed the potential of nanoliposomes in the management of cardiovascular conditions.	[53]
Basic fibroblast growth factor (bFGF)	Ischemic stroke	bFGF-loaded liposomes showed the size of 106 ± 9.84 nm, PDI value of <0.2, and zeta potential value of <−15 mV. Liposomal formulation exhibited the highest reduction in infarcted volume when compared to bFGF solution.	[54]

Table 1.
Applications of intranasally delivered drug-loaded liposomes with major outcomes.

for encapsulation of a variety of anticancer drugs. In a very recent study, Katona et al. formulated LM and NPG-loaded liposomes by a novel direct pouring method for targeting glioblastoma multiforme via nose-to-brain route. Phosphatidylcholine and cholesterol were utilized for the preparation of liposomes. The optimized liposomal formulation encapsulated with both drugs exhibited a suitable *Z*-average of ~127 nm, size distribution (PDI value of 0.142 ± 0.009), zeta potential value of -34 ± 1.7 mV, and high encapsulation efficiency of 63.57% ± 1.3% for NPG and 73.45% ± 2.2% of LM, respectively. These results demonstrated the suitability of an optimized formulation for nose-to-brain drug delivery. The dialysis-based release method was adopted and results indicated a sustained release pattern from the optimized liposomal formulation. Nasal permeation studies revealed higher permeation of drugs from the optimized liposomal formulation in comparison to the suspension of drugs. MTT assays of the developed formulation were also performed on murine embryonic fibroblast (NIH/3T3), glioblastoma (U87), and ovarian (A2780) cancer cell lines. The results of *in vitro* cancer cell line indicated a reduction in cancerous cells of all studied types [42].

Phytoconstituents, such as curcumin, a polyphenolic compound obtained from the rhizomes of Curcuma longa and show anti-inflammatory and antioxidant characteristics. Curcumin has potential in the management of brain cancer and other neurodegenerative disorders [56]. Studies have been conducted to enhance the availability of curcumin by incorporation into liposomes through nose-to-brain delivery. In a study, a mucoadhesive liposomal formulation of curcumin was developed and optimized for nasal delivery. The liposomes were formulated by solvent dispersion method employing cholesterol and soya lecithin as lipid bilayer forming material and xanthan gum for mucoadhesion. The vesicular size was found to be between 100.2 and 150 nm. The optimized formulation showed good stability and controlled/sustained release characteristics. The liposomal formulation was also found nontoxic to the nasal mucosa of rats. *In vivo* studies in rats revealed higher curcumin concentration (1240 ng) in the brain when compared to free drug solution (65 ng) when administered intranasally. The authors concluded the potential of curcumin liposomes with xanthan gum coating for enhancement of curcumin concentrations in the brain via the intranasal route [43].

4.2 Alzheimer's disease

AD leads to a decline in thinking, memory, learning, and language capacity. FDA-approved drugs used for AD are donepezil, memantine, galanthamine, and rivastigmine [57]. Yang et al. formulated rivastigmine tartrate-loaded liposomes with ell-penetrating peptide modification. The developed liposomes showed uniform sizes and shapes. A mean diameter of 166.3 ± 17.4 nm was found for simple liposomes and 178.9 ± 11.7 nm with ell-penetrating peptide-modified liposomes with low PDI values. The entrapment efficiency of slightly more than 30% was found for both types of liposomes. The results exhibited that liposomes, especially the ell-penetrating peptide enhanced the permeability through *in vitro* murine brain endothelial cells model. Intranasal administration of rivastigmine in solution and liposomal form demonstrated improvement of rivastigmine distribution and retention in CNS areas, particularly in the cortex and hippocampus, which are the most affected regions in AD when compared to intravenous administration. Developed liposomal formulations exhibited safety potential toward nasal mucosa. The authors concluded the potential of intranasal rivastigmine liposomes with ell-penetrating peptide improved brain delivery with enhancement in pharmacodynamic activity [44]. In another report, galanthamine hydrobromide-loaded flexible liposomes were formulated by the thin film homogenization method with some modification. Liposomal components used were soya phosphatidylcholine and cholesterol. Propylene glycol was used as an edge activator. The average size of drug-loaded flexible liposomes was found to be 112 ± 8 nm with a zeta potential of −49.2 ± 0.7 mV. This negative charge indicated the repulsive power of liposomal vesicles in the liposomal dispersion, which is important for long-term stability. The entrapment efficiency was found to be 83.6% ± 1.8%. The inhibition of acetylcholinesterase was studied by using brain homogenates of rats as an enzyme resource. The microdialysis technique was employed to investigate the pharmacokinetic characteristics of galanthamine hydrobromide in rat brain. It was found that inhibition of acetylcholinesterase was more by intranasal administration when compared to oral administration. The C_{max}, $AUC_{0\rightarrow10}$ from intranasal administration of galanthamine hydrobromide-loaded liposomes were 3.52, 3.36 times more than those through oral administration of galanthamine hydrobromide. The authors

further reported the safety of developed liposomes tested against PC-12 cells [45]. Al Asmari et al. developed liposomes of donepezil using cholesterol, 1,2-distearyl-sn-glycero-3-phosphocholine, and polyethylene glycol by thin film hydration method. The liposomal size was consistent with 102 ± 3.3 nm with proper shape and encapsulation efficiency of 84.91% ± 3.31%. The developed formulation exhibited sustained release behavior. It has found high drug concentration in plasma and brain after intranasal administration. Histopathological examination revealed safety for the developed liposomal formulation of donepezil [46].

In a very recent study, hydroxy-α-sanshool was incorporated into liposomes. This drug helps in cognitive dysfunction. Liposomes were fabricated by a thin film dispersion technique using cholesterol and soya lecithin. Liposomal formulations exhibited a vesicle size of 181.77 nm, PDI value of 0.207, and zeta potential of − 53.8 mV with good stability. Drug release studies revealed slow and consistent release following Higuchi kinetics. Highly drug concentration was found in plasma and brain after intranasal administration. Developed liposomes were not toxic to the mouse nasal mucosa and effectively improved learning memory deficits induced by D-galactose and protected mouse neuronal cells of the hippocampus. The authors concluded that these hydroxy-α-sanshool liposomes might be used for the management of AD [47].

4.3 Parkinson's disease

PD is caused by degenerative effects on dopamine regulating neurons in the area of substantia nigra pars compacta. Levodopa is most commonly a prodrug for the management of PD but its efflux by P-gp and enzymes diminishes its activity. GDNF has shown significant neuroprotective effects on substantia nigra neurons in the 6-hydroxydopamine rat model of PD [58]. GDNF cationic liposomes were prepared by using dioleoylphosphatidylcholine, stearylamine, and cholesterol. Enzyme-linked immunosorbent assay was used to determine brain levels of GDNF and distribution to target areas (striatum and substantia nigra) after intranasal administration at different time intervals. Brain levels enhanced significantly within 1 h after a single dose (50-μg) of GDNF incorporated into the liposomal formulation. In the second study, different doses (10–150 μg) of GDNF in phosphate buffer saline solution were administered. Liposomal formulation delivered 10-fold more amount of GDNF to the brain than phosphate buffer saline. The results suggested the potential of liposomes for enhanced delivery of GDNF in the brain tissues for the management of PD after intranasal administration [48].

4.4 Schizophrenia

Schizophrenia results in psychosis and may affect all aspects of life, including social, educational, personal, family, and occupational functioning. Schizophrenia affects approximately 1 in 300 people worldwide. A variety of drugs are available for the management of this disease but due to non-availability in the right amount in the brain tissue is the major issue in the treatment of this problem [59, 60]. Narayan et al. developed risperidone liposomes employing the method of thin film hydration. Design expert software was used to optimize formulation components. The optimized liposomal surface was modified by stearylamine and MPEG-DSPE coating for the enhancement of brain penetration. The mean vesicular size of liposomes was obtained between 90 and 100 nm with a polydispersity index of less than 0.5 with entrapment efficiency ranging from 50% to 60% and maximum drug entrapment was found with

functionalized liposomes. Transmission electron micrographs revealed smooth and bilayer structures. A prolonged and controlled release behavior was obtained with a developed liposomal formulation. It was further established through *in vivo* studies that risperidone concentration was high in the brain in comparison to plasma from liposomal formulation through intranasal delivery [49]. In another report, quetiapine fumarate was incorporated in liposomal vesicles. Sheep nasal membrane diffusion was compared for simple dispersion and liposomal dispersion of quetiapine fumarate. Simple dispersion was prepared using a colloid mill in SNF pH 6.8. Liposomes of quetiapine fumarate were manufactured by the thin lipid film hydration method. The average particular size from simple dispersion obtained was 139.6 nm with a zeta potential of 32.1 mV. The average vesicular size from liposomal dispersion obtained was 152.2 nm with a zeta potential of 24.7 mV. The drug diffusion from liposomal dispersion was found higher (32.61 ± 1.70) with a high permeability coefficient of 4.1334 ± 0.7321 ($\times 10^{-5}$ cm/s). In vivo studies revealed a higher amount of quetiapine fumarate in the brain from liposomal dispersion in comparison to simple dispersion [50].

4.5 Epilepsy

Epilepsy is characterized by repeated and recurrent seizures involving involuntary movement of the whole body or part. These symptoms are due to electrical discharges in excess from cortical neurons. Management of epilepsy is difficult due to less access to drugs in brain tissues. Nanotechnological developments of already approved drugs have been found to enhance drug concentrations in the brain [61]. Praveen et al. developed nanoliposomes of lamotrigine for the management of seizures. The liposomes were prepared by thin film hydration method employing phospholipid as phospholipon 90G, vesicle stabilizer as cholesterol, and surfactant as tween 80. Plackett-Burman's design was used to optimize the liposomal formulation. Optimized formulation showed the vesicular size of 88.90 ± 1.56 nm with polydispersity index of 0.247 ± 0.04, entrapment efficiency of 68.75% ± 0.02%, and *in vitro* drug release of 79.41% ± 1.15%. These results were in close agreement with predicted responses. The optimized formulation was found to be stable at different storage temperatures. Nasal mucosa (goat) permeation studies showed higher drug permeation from liposomes (72.45% ± 2.15%) in comparison to simple suspension (13.27% ± 1.17%) after 12 h. Confocal laser scanning micrographs revealed higher fluorescence intensity in the deeper layer of the nasal mucosa. The results suggested the high potential of the liposomal system for enhanced delivery of lamotrigine through the intranasal route [51]. In a recent study, valproic acid was incorporated into liposomes utilizing phosphatidylcholine and cholesterol by the method of thin film hydration. The mean vesicular size of optimized liposomes was obtained between 90 and 210 nm with a low polydispersity index of less than 0.5. The entrapment efficiency obtained was between 60% and 85%. Transmission electron microscopy examination revealed the spherical shape of liposomes. Permeation studies involving sheep's nasal mucosa exhibited higher permeation of valproic acid from liposomes in comparison to control samples. Animal studies revealed a higher concentration of drug in the brain than plasma after administration through the intranasal route [52].

4.6 Ischemic stroke

Stroke is the prevalent cause of death globally. Ischemic stroke is caused by blockage or narrowing of a blood vessel supplying blood to the brain. Interruption

of glucose and oxygen supply leads to a reduction in the production of ATP, causing energy failure and irregularities in ion homeostasis. Recombinant tissue plasminogen activator (rt-PA) is approved by the FDA for the management of ischemic stroke. It acts by dissolving the blood clot in cerebral vessels with the restoration of blood flow, which results in the protection of brain tissue. The short half-life (2–6 minutes) causes problem in the management of the disease and requires nanotechnological carrier system interventions [62, 63]. In a recent study, nanoliposomes of tissue plasminogen activators have been reported for improvement of the thrombolytic activity. The results suggested the stability of nanoliposomes with no aggregation when stored at 4°C. A desirable entrapment efficiency, zeta potential, proteolytic activity, and sustained *in vitro* release characteristics were obtained. The authors suggested the use of developed nanoliposomes of tissue plasminogen activators, which could be used in the management of cardiovascular diseases [53]. Another therapeutic basic bFGF has the potential to protect against ischemic stroke. Zhao et al. reported nanoliposomes of bFGF by the technique of water-in-water emulsion followed by freeze-drying. The average vesicular sizes of blank and bFGF-loaded nanoliposomes obtained were 106 ± 9.84, 128 ± 7.65 nm, respectively, with low polydispersity index (<0.2). Negative zeta potential values (<−15 mV) were observed for both types of liposomes. Western blotting was conducted to analyze the bFGF levels in the olfactory bulb, hippocampus, pallium, and striatum after intranasal administration. Intranasal administration of bFGF-loaded nanoliposomes enhanced the concentration of bFGF in pallium and hippocampus. After comparison with intravenous delivery, it was found that intranasal delivery is superior in delivering the bFGF into different brain areas. Further results like recovery of neurological function strengthened the suitability of nanoliposomes of bFGF through intranasal administration. Therapeutic efficacy was determined after ischemia-reperfusion injury followed by the determination of neurological deficit scores. The bFGF-loaded nanoliposomes exhibited higher scores in treated animals than bFGF solution. Liposomal treatment resulted in the highest reduction in the infarcted volume. The authors concluded that intranasal bFGF-loaded liposomal therapy was effective and was able to enhance the recovery effect of bFGF after ischemia-reperfusion injury [54].

5. Conclusions

Pharmaceutical nanocarriers are successfully being evaluated for their potential through intranasal delivery in the improvement of characteristics of already approved molecules and new chemical entities as well as used for brain diseases [64]. Liposomes have attracted researchers globally due to their excellent biocompatible and biodegradable characteristics. A variety of research works have been reported for the delivery of drugs encapsulated in liposomes through the intranasal route [42–44]. Several studies have been reported for intranasal liposomes for the management of brain diseases, such as brain cancer, AD, PD, schizophrenia, epilepsy, and ischemic stroke. Most of the optimization studies included the effect of phospholipid concentration, cholesterol amount, process parameters on the size, encapsulation efficiency, zeta potential, and release characteristics of liposomes. Optimized formulations were investigated for the availability of the drug in the brain and its pharmacological effect after intranasal administration. Research findings revealed favorable physicochemical characteristics of the drug after incorporation into liposomes. Intranasal liposomal formulations exhibited enhanced uptake into the brain with enhanced activity in

the concerned brain disease. Results suggested the potential of intranasal liposomal formulations for the management of brain diseases. A more mechanistic approach is needed for the identification of drug transport to brain areas.

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Conflict of interest

The authors declare no conflict of interest.

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