ejpmr, 2022, 9(6), 105-116

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

A BRIEF REVIEW ON NOSE-TO-BRAIN DELIVERY OF LIPID BASED NANOSYSTEMS FOR EPILEPSY

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Article Received on 03/04/2022 **Article Revised on 23/04/2022** **Article Accepted on 13/05/2022**

ABSTRACT

Epileptic seizures or Convulsion crisis are severe conditions that require fast and effective treatment, targeting the brain. Current emergency anti-epileptics and anticonvulsants have limited brain bioavailability, following oral, intravenous or rectal administration. This relates with the limited extent at which these drugs bypass the blood brain barrier (BBB). Thereby, the development of strategies that significantly improve the brain bioavailability of these drugs, along with a simple and safe administration by patients, attenuating and/or preventing epileptic seizures or convulsant crisis, are still a major need. In this respect, the nasal/intranasal route has been suggested as a promising strategy for drug targeting to the brain, thus avoiding the BBB. Besides, the use of lipid-based nano-systems, such as solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC), liposomes, nano-emulsions and microemulsions, have been demonstrating high efficiency for nose-to-brain transport. This review highlights the potential of using lipid-based nano-systems in the management of epilepsy or convulsion, by means of the nasal/intranasal route. So far, the reported studies have shown promising results, being required more in vivo experiments to further advance for clinical trials.

KEYWORDS: Antiepileptics; convulsion; Anticonvulsant; Epilepsy; Lipid-based nano-systems; Nasal/intranasal route.

INTRODUCTION

A seizure or convulsion emergency condition includes prolonged seizures or frequently visible seizures that require immediate medical attention. Seizures extending for more than five minutes are treated analogously to extremely severe and fatal seizures called status epilepticus. IV benzodiazepines including lorazepam, midazolam and diazepam remain as first-line therapeutic agents for the immediate treatment of status epilepticus once the patient reaches the hospital, while second line-therapy includes IV phenytoin sodium or fosphenytoin. The availability of benzodiazepines suitable for administration by alternative routes (other than IV and IM) such as rectal, buccal and intranasal offers additional advantages, facilitating their use immediately and outside of the hospital. In fact, these benzodiazepines are short acting, with an elimination half-life of 1.5 h; thus, a second dose is mostly needed after 5 min or second-line Anti-Epileptic Drugs (AED) have to be started immediately. When using benzodiazepines, there is an increased risk of fatal respiratory failure or arrest, which increases with frequent repeated doses.[1-3]

Advantages of intranasal drug delivery

- ✓ Rapid drug absorption via highly vascularized mucosa.
- ✓ Ease of administration, non-invasive.
- ✓ Improved bioavailability.
- ✓ Improved convenience and compliance.
- ✓ Self-administration.
- ✓ Large nasal mucosal surface area for dose absorption.
- ✓ Avoidance of the gastrointestinal tract and first-pass metabolism.
- ✓ Rapid onset of action.
- ✓ Lower side effects.
- ✓ Drugs which cannot be absorbed orally may be delivered to the Systemic circulation through nasal drug delivery system.
- ✓ Convenient route when compared with parenteral route for long term therapy.
- ✓ Bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.

Disadvantages of intranasal drug delivery

- ✓ Some drugs may cause irritation to the nasal mucosa.
- ✓ Nasal congestion due to cold or allergies may interfere with absorption of drug.
- ✓ Drug delivery is expected to decrease with increasing molecular weight.
- ✓ Frequent use of this route leads to mucosal damage.

- ✓ The amount of drug reaches to different regions of the brain and spinal cord varies with each agent.

Limitations of intranasal drug delivery

- ✓ The absorption enhancers used to improve nasal drug delivery system may have histological toxicity which is not yet clearly established.
- ✓ Absorption surface area is less when compared to GIT.
- ✓ Once the drug administered cannot be removed.

Nasal cavity

To understand the different mechanisms of drug absorption through the nasal cavity to the brain, it is essential to know the anatomical and cellular structure of the nasal cavity.

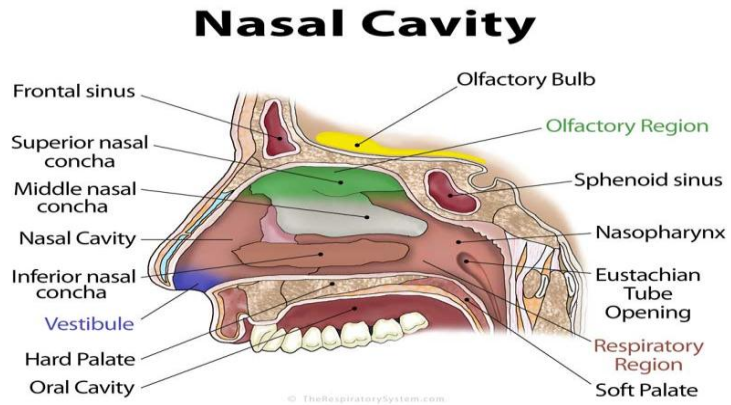

Fig. No. 1: Nasal cavity.

Anatomy of the nasal cavity

The nasal cavity extends around 12–14 cm in length, 5cm in height, has a total volume of 15–20mL, and a surface area of between 150 to 200 cm^2.[4-6] There are three kinds of turbinate: the superior, the middle, and the inferior turbinate, and they are responsible for humidifying, filtering, and warming the inspired air through nostrils.[7,8] The nasal cavity can be divided into three sections: the nasal vestibule, the respiratory section, and the olfactory section (Figure-1). The nasal vestibule is located in the most anterior part of the nasal cavity, and it consists of hairs, sebaceous, and sweat glands.[8,9] The respiratory section is mainly dominated by the middle and the inferior turbinate, and it serves as a passage for air to the lungs. The olfactory area is located on the superior turbinate, covering about 10 cm^2, and contains olfactory receptors, which are responsible for the sense of smell.[8,10,11] In terms of drug absorption through intranasal delivery, respiratory and olfactory mucosa are the main sites of interest.

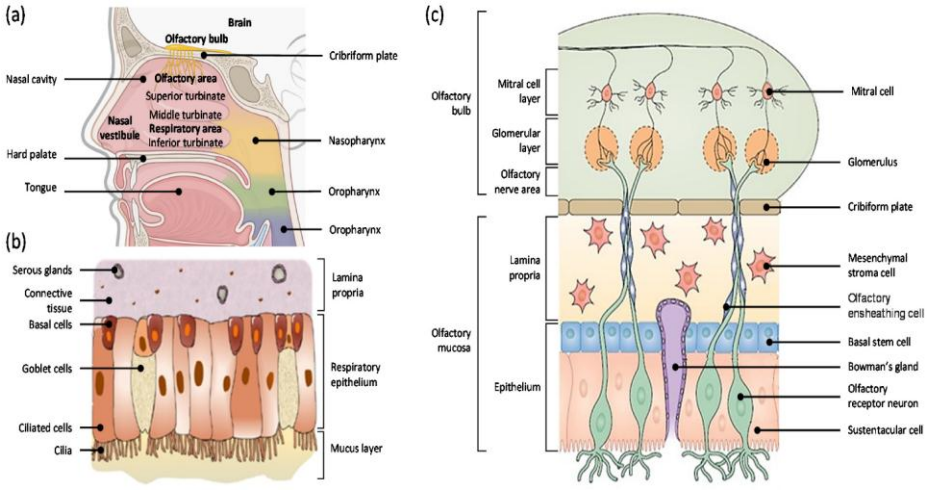

Fig. no. 2: Anatomy of human nasal cavity.

(a) Squamous mucosa is located at the nasal vestibules. Respiratory mucosa is consisted of inferior, middle, and superior turbinate forming respiratory area. The olfactory mucosa is located underneath the cribriform plate in the olfactory area.

(b) The respiratory mucosa. It is comprised of the lamina propria, respiratory epithelium, and a mucus layer. Within the respiratory epithelium, there are basal, goblet, and ciliated cells.

(c) The olfactory system consists of the olfactory mucosa, which is in the nasal cavity, and the

olfactory bulbs, which are in the brain. The mucosa is composed of a pseudostratified epithelium containing olfactory receptor neurons (OSNs), Bowman's glands, sustentacular cells, basal cells, and the lamina propria. OSNs have receptors that can entrap molecules and transmit information to glomeruli in the olfactory bulb. These neurons are unsheathed by glia, known as olfactory unsheathing cells (OECs). After damage or during normal cell turnover, newly formed OSNs are guided back by OECs into the olfactory bulb, where they re-synapse with glomeruli.[12]

Respiratory mucosa

Respiratory mucosa consists of 80–90% of the total surface area in the human nasal cavity, and it is highly vascularized, making it a significant site for systemic drug absorption.[5] Respiratory mucosa consists of various cell types and glands, such as basal cells, goblet cells, ciliated epithelial cells, and serous glands (Figure-2, B).[7,8] Basal cells are progenitor cells that can differentiate into other cell types found within the epithelium and also help to attach ciliated and goblet cells to the basal lamina.[13] Goblet cells secrete mucus composed of mucin (high molecular weight glycoproteins), water, salts, a small group of proteins, and lipids.[14] Mucus forms a layer in the respiratory epithelium and serves as a first-line defense by entrapping any inhaled materials or irritants.[15,16] Ciliated cells help to remove this mucus towards the nasopharynx, which results in muco-ciliary clearance (MCC).[5,17] Serous glands secrete watery fluid and other antimicrobial proteins, which serve as part of innate immunity.[18]

Olfactory mucosa

The olfactory mucosa is located on the top of the nasal cavity and takes up about 5~10% of the total surface area of the human nasal cavity.[5] The olfactory mucosa (Figure-2, C) consists of olfactory receptor neurons, so-called olfactory sensory neurons (OSN), the olfactory epithelium, and the lamina propria.[7,12] The olfactory nerve is the first cranial nerve that transmits sensory information related to smell.[19] OSNs are non-myelinated neurons and located in the nasal epithelium. OSNs have direct contact with airborne substances through odorant chemoreceptors located in the apical surface of the olfactory mucosa, and each OSN expresses only one receptor.[20] Humans have approximately 400 olfactory receptors, whereas rodents have approximately 1000 olfactory receptors.[21] Each OSN forms thick axon bundles in the lamina propria, and these bundles become olfactory nerves. They innervate the cribriform plate and create synaptic connections with glomeruli of mitral and tufted cells in the olfactory bulb.[20,22,23] OSNs have direct contact with the environment, airborne irritants, and microbial agents, so these exogenous compounds may cause injury or cell death of OSN. To maintain its function, neurogenesis of OSNs occurs in the nasal epithelium to regenerate the neurons. A few studies have suggested that the life span of OSNs is between 30–60 days, and the systemic apoptosis of OSNs occurs to protect the brain from infections.[8,20,24] During the neuronal regeneration, there is a delay of tight junction formation, which causes some gap and allows some substance penetration.[25]

Olfactory epithelium, just like respiratory epithelium, consists of ciliated columnar cells covered by a mucus layer. However, cilia in the olfactory epithelium are non-motile and longer than those in the respiratory epithelium.[23] In the olfactory epithelium, two types of basal cells account for neuronal regeneration: globose basal cells and horizontal basal cells. Globose basal cells are progenitor cells for OSNs, and they account for the homeostasis of normal tissue in olfactory mucosa.[26,27] Horizontal basal cells are multipotent progenitor cells in the olfactory epithelium for normal turnover and help its regeneration from acute injury.[28] Not only basal cells but also supporting cells are present in the olfactory epithelium. Sustentacular cells (SUS) are supporting cells that enclose the OSNs in the olfactory epithelium region. Their primary function is to stabilize the structural and ionic integrity of OSNs.[29]

Lamina propria of olfactory mucosa consists of numerous cell types and structures such as Bowman's glands (BG) and olfactory unsheathing cells (OEC).[30] BGs innervate the olfactory epithelium and secrete a mucus layer in the olfactory system.[31] The exact composition of the olfactory mucus is still unknown, but a histological study showed that these glands are positive for periodic acid-Schiff staining, indicating the presence of neutral glycoproteins.[8,32] OECs are glial cells that enwrap non-myelinated bundles of OSN and help to promote the regeneration of OSNs.[33]

Pathways for nose-to-brain delivery

Drug transport through the olfactory mucosa has been studied to deliver therapeutic substances to the brain to treat CNS diseases. As described earlier, it has the significant advantage of bypassing BBB and reducing systemic exposure. The pathways for N2B delivery have not been fully understood, but many recent studies have suggested some major possible pathways. One way is the direct transport of drugs to the brain through neuronal pathways such as olfactory or trigeminal nerves. The other way is the indirect transport of drugs through the vasculature and lymphatic system, leading to the brain crossing BBB.[34] Drug absorption from nose to brain may not be limited by one single mechanism, but may involve several pathways.

Olfactory pathway

Major routes of drug transport from the olfactory pathway can be subdivided into four different categories: intra-and extra-neuronal pathways and paracellular and transcellular pathways.[7,22]

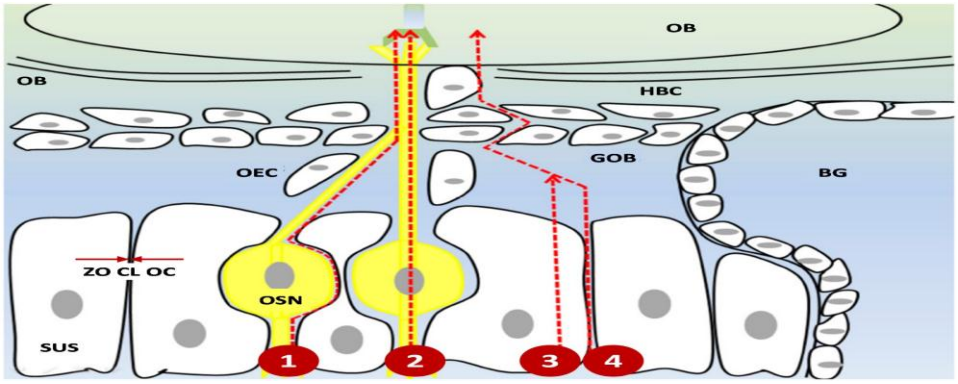

Fig. no. 3: Four different routes of nose-to-brain drug delivery through olfactory mucosa.

(1) Extra-neuronal pathway
(2) Intra-neuronal pathway
(3) Transcellular pathway
(4) Paracellular pathway

The drug has to pass tight junctions (marked with red arrows) such as ZO, CL, and OC to travel through the intercellular space. N2B delivery is a mixture of these different pathways. Abbreviations: ZO: zonula occludent; CL: claudin; OC occluding; SUS: sustentacular cells; OSN: olfactory sensory neuron; OEC: olfactory unsheathing cell; GOB: globose basal cells; HBC: horizontal basal cells; BG: Bowman's gland; CP: cribriform plate; OB: olfactory bulb. Modified from.[8]

Olfactory neurons play a major role in the N2B delivery system. Therapeutic moieties can undergo endocytosis by OSN and form vesicles, leading to the intracellular axonal transport along the neurons, cross the cribriform plate, and to the olfactory bulb. Once they reach the brain, they will undergo exocytosis and will be distributed in the CNS.[35] The diameter of the human olfactory axon is between 0.1–0.7 µm, which makes it one of the smallest axons in the CNS.[36] This small diameter suggests that only small molecules within this range can be transferred through this intracellular axonal transport. Another limitation of intracellular axonal transport is the delayed-release. The mean speed of axonal transport is 25mm per day, which means that it may take hours and days for active moieties to be delivered to the brain.[37] Since many studies showed a rapid delivery of molecules through intranasal administration, it suggests that this pathway may not be the predominant one.[25,38]

An extra-neuronal pathway of molecules occurs by crossing the gap between the OSN and the SUS in the epithelial layer. Then they reach the lamina propria, and are incorporated in the cleft between the axons and the OECs.[5] The active substances need to cross a tight epithelial junction to reach the cleft, but there is some gap due to the neuronal turnover in the olfactory epithelium, which allows the drug transport to occur, even for larger moieties.[20,25]

A paracellular pathway occurs by crossing the olfactory epithelium through the gap along the SUS and crossing the basement membrane. Instead of incorporating in the cleft, the therapeutic molecules can reach the subarachnoid space and get delivered to the brain by crossing the blood-CSF barrier. This route does not require drugs to bind to receptors, and it is particularly suitable for hydrophilic and small molecules.[39] A transcellular pathway occurs by receptor-mediated endocytosis or passive diffusion of inhaled molecules through the membrane of the SUS.[40] This pathway is suitable for hydrophobic molecules.

Trigeminal pathway

A trigeminal nerve is the fifth cranial nerve and is the largest cranial nerve which innervates both the olfactory and the respiratory mucosa. It has three different branches, consisting of the ophthalmic, maxillary, and mandibular nerves, and is responsible for delivering sensory and motor information of these areas to the spinal cord, the medulla, and the pons.[38,41] Among those branches, the ophthalmic and maxillary branches are involved for N2B delivery. Ophthalmic branches pass through the dorsal nasal mucosa and anterior part of the nose, and maxillary branches through the lateral wall of nasal mucosa.[10] Similar to the olfactory nerve pathway, drug transport via the trigeminal nerve occurs by multiple pathways. Once drug moieties reach the branches of the trigeminal nerve, they will merge at the trigeminal ganglion and enter the brain near the pons. Also, some portions of the trigeminal nerve are present near olfactory bulbs, so drug molecules can cross the cribriform plate and reach both the caudal and rostral areas of the brain.[42]

Systemic pathway

Drug transport of inhaled substances to the brain can occur indirectly through the respiratory epithelium via systemic circulation and the lymphatic system. Since the respiratory epithelium is highly vascularized with a combination of a continuous and fenestrated endothelium, it gives access to blood circulation. However, these substances need to cross the BBB to reach the CNS, which is the rate-limiting step. The systemic pathway mainly occurs for the small and

lipophilic substances so that they can cross the BBB transcellularly.[43]

Potential role of nanotechnology for nose-to-brain delivery

Pharmaceutical nanotechnology has been widely used to deliver therapeutic molecules to the targeted area. The size of the particles is in the nano range (1–1000 nm), and these particles typically form a colloidal dispersion.[44,45] The use of nanotechnology in N2B delivery is very promising. It can increase the residence time of the drug at the site of absorption, promote its mucosal permeation and cellular internalization, increase drug solubility, control the release of the encapsulated drug, and reduce systemic side effects by decreasing the drug distribution to the non-targeted area. All these characteristics favor the use of nanoparticles (NPs) for N2B delivery.[46]

Although nanotechnology has been widely used in drug delivery for its favorable characteristics, the effect and accumulation in the human body should not be neglected. Once nanocarriers enter the biological system, proteins, lipids, and other biological molecules in the body will be adsorbed on the surface of nanocarriers and form the so-called "bio corona".[47] The bio corona can alter physicochemical properties such as size, shape, and hydrophilicity of original nanocarriers through nanoparticle-biomolecule interactions.[48] Also, the pharmacokinetic profile, such as cellular uptake, half-life, and distribution can be modified.[49,50] The bio corona can be recognized by complement receptors on macrophages and undergo increased cellular uptake and accumulated in the liver and spleen.[51] Some studies showed that metal-based nanoparticles may cause negative effects on the cardiovascular system and the nervous system. Increased inflammatory cytokines, arrhythmia, as well as increased oxidative stress and neurotoxicity could occur after the administration of titanium dioxide and silica nanoparticles, which are a commonly used nano-formulation in the industry.[52,53] Since peptides and lipids are present in the nasal mucus, there is a high chance that the inhaled nanoparticles will form the bio corona and may alter their physicochemical properties and cellular uptake. Therefore, the characteristics of the bio corona need thorough evaluations to effectively translate preclinical data to a safer and more efficient nano-system for clinical application.

Many different types of NPs have been used for N2B delivery, but the two most used types of nanoparticle carriers will be discussed in this review: lipid-based NPs and polymer-based NPs.[54] These nanoparticle carriers help to increase drug accumulation in the brain by increasing stability, solubility, and mucoadherence.

Lipid-Based nanoparticles

Lipid-based nanoparticles have been widely investigated for drug delivery systems. These NPs are amphiphilic, being able to transfer both hydrophilic and hydrophobic materials in one particle.[55] Lipid-based carriers are made from biocompatible, biodegradable lipids similar to those consisting of the cell membrane. These features allow them to penetrate the cells efficiently and limit their toxicity. Most commonly used lipid-based NP formulations are liposomes, nano emulsions formed with micelles, solid lipid nanoparticles (SLN), and nanostructured lipid carriers (NLC).[56,57] These lipid-based NPs are often modified with polymers such as polyethylene glycol (PEG) or poloxamers. PEG is a hydrophilic polymer that is biocompatible and stabilizes NPs.[58] Furthermore, it acts as a mucus penetration enhancer by decreasing interaction with mucin.[59] Poloxamers, similar to PEG, are water-soluble, non-ionic surfactants and consist of a triblock copolymer of hydrophobic polypropylene glycol and two hydrophilic blocks of PEG. They have low toxicity, good drug release, and are compatible with many different chemicals, making them useful tools for drug delivery.[59] Poloxamer 407 (Pluronic F127) and 188 (Pluronic F-68) both have high contents of PEG (70% and 80%, respectively) and can help decrease mucus viscosity and increase penetration by interacting with lipid membranes and tight junctions.[60,61]

It is important that lipid-based NPs can cross the epithelial and respiratory epithelium transcellularly and penetrate to the brain, which makes them an attractive option for N2B delivery. Moreover, lipid-based NPs can be indirectly absorbed into the systemic circulation, and have a good chance of crossing the BBB because of their lipophilic nature.[62] Lastly, medications that target the brain are relatively hydrophobic, which makes lipid-based NP attractive delivery vehicles that can increase drug solubility and bioavailability in the brain.[63]

Liposomes

Liposomes are one of the most widely used lipid-based NPs for drug delivery systems. Typically, a liposome has a single or several phospholipid bilayers, often with other lipids such as cholesterol or phosphatidylcholine. Using various types of lipids, the physical characteristics of liposome membranes may vary in terms of size and surface charge. For instance, neutral or slightly negatively charged liposomes can incorporate both hydrophilic (inside their aqueous core) or hydrophobic (inside the lipid membrane) active ingredients. In contrast, the positively charged liposomes can form multiplexes with negatively charged nucleic acid.[64-68]

Many studies of N2B delivery have used a liposome as a nanocarrier to treat different types of CNS disorders.[69-74] Al Asmara et al. formulated a donepezil-loaded liposome using 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and PEG to evaluate the brain and plasma pharmacokinetics after intranasal administration.[69] Donepezil is a cholinesterase inhibitor, and it is a commonly used medication to treat Alzheimer's disease. In their study,

the size of nanoparticles was 102 ± 3.3 nm, the surface charge was −28.31 ± 0.85 mV, the polydispersity index (PDI) was 0.28 ± 0.03, and drug encapsulation efficiency (EE) was 84.91 ± 3.31%. The drug release from the liposomes had biphasic characteristics: an initial rapid release phase for 2 h followed by a sustained release up to 8 h. The AUC of donepezil liposome through intranasal (IN) delivery was higher than the AUC of oral (PO) and IN of free donepezil. The bioavailability of donepezil delivered by liposomes via the IN route in the brain was two times higher than that of free IN donepezil ($p < 0.05$) but showed no significant difference in terms of half-life. The histopathological study showed no evident signs of injury in major organs such as the liver, lung, heart, spleen, kidney, brain, and olfactory bulb after nasal administration of the liposomal formulation of donepezil in rats. This study showed the promising role of liposome as a carrier for improving the bioavailability of donepezil to the brain with N2B delivery systems.[69] Hoekman and et al. developed a fentanyl-loaded liposome with an arginine-glycine-aspartate (RGD) peptide and underwent aerosolization for intranasal delivery.[75] Rats treated with RGD-liposome IN had a higher analgesic effect than those with free fentanyl IN (AUC 1387.1 vs. 760.1%) and 20% reduced plasma drug exposure ($AUC_{0–120}$ 208.2 vs. 284.8 ng·min/mL). The RGD peptide liposomes bind to integrin proteins on the nasal epithelium and eventually increase the retention of fentanyl in the nasal and olfactory epithelium.[76] In addition, the liposomes worked as a drug reservoir, as there was a significant increase in the overall analgesic effect without affecting the onset of action, but lasted six times longer than the free fentanyl solution. Intranasal liposomal delivery potentially showed increased drug concentration in the brain as well as a decreased systemic exposure.[77]

Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) are the newer generation of lipid-based nanocarriers, which are lipid emulsions where a solid lipid has replaced the liquid lipid. They are usually 100–300 nm in diameter and form a solid lipid matrix. They are often comprised of physiological lipids in water or aqueous surfactants.[78] SLNs have several advantages for drug delivery: they can be produced without using organic solvents, have high physical stability, and enhanced, controlled release of loaded drugs. The major drawbacks of SLNs include limited drug loading efficiency (especially for hydrophilic molecules) due to inflexibility of their shape, and undesired particle growth by agglomeration, which may lead to the burst release of the drug.[70-73]

Patel et al. formulated SLNs that incorporates risperidone, an atypical antipsychotic agent, to increase its bioavailability and biodistribution.[74] Compritol 888 ATO was used for the lipid and Pluronic F-127 for the surfactant components of SLNs. The concentration of the radiolabeled risperidone was about three times higher in the risperidone SLNs delivered via IN group than the risperidone IV group and marginally higher than the risperidone SLN IV group. The concentration of the risperidone in the blood from SLN IN was twice as low as that from IV SLN, which can potentially enhance drug specific activity and lower systematic side effects.[75]

Nanostructured lipid carriers

Nanostructured lipid carriers (NLCs) represent a relatively recent generation of lipid-based NPs that are developed to overcome the disadvantages of SLNs. NLCs have a mixture of solid and liquid lipids, leading to higher drug loading and the prevention of the drug's burst release.[76] NLCs are typically formulated by the double emulsion technique (*w/o/w*) and high-pressure homogenization.[77] Hydrophobic molecules have a higher solubility in liquid lipid than solid lipid, so higher encapsulation efficiency can be achieved.[78] Some limitations of NLC include decreased encapsulation efficiency for a combination of two or more therapeutic agents and relatively low drug loading capacity for hydrophilic drugs.[79] Madane et al. formulated curcumin-loaded NLC to increase brain bioavailability for brain cancer treatment. The study used precirol as a solid lipid, capmul MCM as a liquid lipid, Tween 80 as a surfactant, and soya lecithin as a stabilizer. NLCs were prepared using a high-pressure homogenization technique. The average particle size was 146.8 nm, with zeta potential (ZP) of −21.4 ± 1.87 mV, PDI of 0.18, and good entrapment efficiency (90.86%). The curcumin-NLC had a biphasic release pattern, with burst release at the initial stage followed by sustained release. C max of curcumin-NLCs after the IN administration was about 1.5 times higher than that of curcumin suspension IN. The relative bioavailability of curcumin-NLC IN was 439 ± 9.86% when compared with curcumin suspension IN. This study showed that the NLC could be potentially used for N2B delivery to treat CNS disorders.[80]

Nano emulsions

Nano emulsions are nano-sized colloidal systems comprised of micelles containing an oily phase, emulsifier, and aqueous phase. There are three types of nano emulsions: oil in water, water in oil (so-called "reversed" micelles), and bi-continuous nano emulsion (inter dispersed water and oil domain).[81,82] Nano emulsions can improve the bioavailability and stability of the drug, especially lipophilic drugs, and provide higher drug absorption with a greater surface area from nano-sized droplets.[83] However, it is thermodynamically unstable and can lead to poor stability and the release of the encapsulated molecules during storage.[84] Iqbal et al. used a nano emulsion (NE) to encapsulate letrozole (LZ), an aromatase inhibitor.[85] LZ is clinically indicated for breast cancer, but letrozole has been recently studied to reduce epilepsy. The NE was prepared using Triacetin for the oil phase, Tween 80 for surfactant, and PEG 400 for co-surfactant. The LZ-NE had a mean diameter of 95.59 ± 2.34 nm, a PDI of 0.162 ± 0.012, and a ZP of −7.12 ± 0.12 mV. LZ-NE IN significantly increased the latency to seizure, decreased the number of seizures and

a percent of seizure occurrence in kainic acid-induced status epilepticus mice compared to letrozole solution administered intraperitoneally. Although the study used different routes of administration for letrozole solution for comparison, it showed some neuroprotective effect by decreasing 17β-estradiol, an enzyme that has neuronal excitability and seizure enhancing activity.[86-88]

Polymer-Based nanoparticles

Polymeric nanocarriers, either natural or synthetic polymers, have been used for N2B delivery to increase stability, control the drug release pattern and modify the surface of nanoparticles.

Natural Polymer-Based Nanoparticles

Chitosan (CS) has been widely used for preparing different nanoparticles. Chitosan is a polysaccharide of D-glucosamine, and N-acetyl-D-glucosamine obtained from the deacetylation of chitin, which is the building material of insects and crustaceans.[89] The pKa value of chitosan is around 6.5, so it becomes protonated in acidic ph. The pH of mucus is between 5.5–6.5, which makes chitosan positively charged and increases its stability.[90,91] Since both the olfactory and respiratory epithelium are negatively charged, chitosan-based NPs stay longer in the olfactory and respiratory mucosa and increase the bioavailability of the encapsulated drug for the brain. Also, it acts as a permeation enhancer that helps open the tight junctions between epithelial cells and allows the paracellular transport of materials. It can translocate proteins that consist of the tight junction, ZO-1, and CLs, from the cell membrane to the cytosol by modulating protein kinase C.[92,93] Chitosan-based nanoparticles are degraded by different enzymes such as chitosanase, cellulases, pepsin and lipases.[94]

Even though chitosan has very promising characteristics for N2B delivery, there are some limitations of this material. Chitosan is insoluble under physiological pH and positively charged only in an acidic environment, which may interfere with bio adhesion.[95] Due to these limitations, many researchers have modified chitosan derivatives for N2B delivery. One example is trimethyl chitosan (TMC), which has a better water solubility than naïve chitosan, and high positive charge under physiological Ph.[96,97] Kumar et al. formulated TMC nanoparticles and loaded leucine-enkephalin, an analgesic neurotransmitter, for pain management. The permeability and brain accumulation of leucine-enkephalin TMC NPs IN were significantly higher than leucine-enkephalin solution IN.[98]

Another modification of chitosan, thiolate-chitosan (TC), can increase Mucoadhesion by forming disulfide bonds between the thiol group and mucus glycoproteins.[99,100] Singh et al. formulated selegiline-loaded TC NPs for the treatment of depression. The concentration of selegiline in the brain was significantly higher in TC NPs IN than the selegiline solution IN and unmodified chitosan-coated NPs IN. Behavior assessment in mice with TC NPs showed a more favorable response than unmodified chitosan-coated NPs in an immobility stress evaluation and sucrose preference test. Also, TC NPs successfully decreased oxidative stress and repleted the mitochondrial complex activity.[101] These results show that TC could be a valuable option for N2B delivery.

Alginic acid is a natural polysaccharide that is present in the cell walls of brown algae. The salt form, sodium, or calcium alginate are the primary forms that are currently used for drug delivery. It is hydrophilic and becomes viscous, and easily forms a gel when hydrated, which helps design-controlled drug release.[102]

Haque et al. loaded venlafaxine, a serotonin-norepinephrine reuptake inhibitor, into alginate NPs for the treatment of depression. The particle size was 173.7 ± 2.5 nm with ZP of +37.4 ± 1.74 mV, PDI of 0.391 ± 0.045, and EE of 81.3 ± 1.9%. Behavioral tests, such as forced swimming and locomotor activity tests, were measured in depressed rodents. The rodents treated IN with venlafaxine alginate NPs had similar behavioral tests results compared to non-depressed rodents and better results than venlafaxine solution and tablet groups. The drug targeting efficiency (DTE) and drug transport percentage (DTP) from venlafaxine alginate NPs IN were higher than those from venlafaxine solution IN (425.77% vs. 268.38% and 76.52% vs. 62.76%, respectively).[103] It showed that alginate could be a useful carrier for N2B delivery.

Mechanism of drug delivery from nose to brain

There are three mechanisms underlying the direct nose to brain drug delivery, one is intracellular transport mediated route and two extracellular transport mediated routes. The intracellular transport mediated route is a relatively slow process, taking hours for intra nasally administered substances to reach the olfactory bulb. The two extracellular transport mediated routes could underlie the rapid entrance of drug into the brain which can occur within minutes of intranasal drug administration. In the first extracellular transport-based route intranasally administered substances could first cross the gas between the olfactory neurons in the olfactory epithelium which are subsequently transported in to the olfactory bulb. In the second extracellular transport-based route, intranasal administered substances may be transported along trigeminal nerve to bypass BBB. After reaching the olfactory bulb of trigeminal region the substances may enter in to other regions of brain by diffusion, which may also be facilitated by perivascular pump that is driven by arterial pulsation. Delivery of drugs to the central nervous system (CNS) remains a challenge in the development of therapeutic agents for central targets due to the impenetrable nature of the drug through blood-brain barrier (BBB). The BBB obstruct the substrate penetration based on several characteristics, including lipophilicity, molecular size and specificity for a variety of ATP-dependent transport systems. Injection of dyes in the ventricles of rabbits and

monkeys showed that the cerebrospinal fluid (CSF) is drained via the olfactory neurons into the olfactory neurons, originating from the olfactory bulb; connect the brain with the nasal cavity by penetrating the cribriform plate, which brings the neurons into the nasal mucosa. This coined the idea that this transport route could also exist in the opposite direction, which would imply direct access from the nasal cavity to the brain, thus circumventing the BBB.[104] It has been a promising approach for the rapid-onset intranasal delivery and the optimized nasal formulation showed effective absorption in terms of in-vitro release through excised goat nasal mucosa.[105] Brain drug level following the nasal administration are the results of double absorption pathway that is direct transfer through olfactory region and absorption into the systemic circulation and then transport across the blood brain barrier (BBB).[106]

Therapeutic application of nose-to-brain delivery

Epilepsy

Epilepsy is a chronic neurological disease that causes seizures and can be manifested at all ages, though the highest numbers of new cases occur in childhood and the geriatric population.[107] Epilepsy affects more than 65 million people globally, and about 4.6 million people are diagnosed each year.[108,109] According to the International League Against Epilepsy, there are six etiologies of epilepsy: (1) structural, (2) genetic, (3) infectious, (4) metabolic, (5) immune, and (6) unknown.[110] The cause of epilepsy is not limited to one specific etiology, as they can be combined. Also, the most common causes are different according to population and area. For example, children are more likely to suffer seizures from genetic disorders, whereas from the older generation it can be from an acquired injury. These physiological changes alter the number and properties of voltage or ligand-gated ion channels in the neuronal membrane and lead to hyperexcitation of neurons and, ultimately, a seizure.[111] The symptoms of epilepsy can differ based on the region of the brain and types of seizures. The symptoms include motor symptoms, such as twitching or shaking, sensory symptoms, such as numbness and tingling, and loss of consciousness. If the clinical and/or electrographic seizure lasts more than 5 min, it is called status epilepticus. This serious condition can cause severe morbidity and mortality.[112] Moreover, the elderly population can develop multiple complications such as fractures, depression, and anxiety. The general approach to treat epilepsy is antiseizure medications and benzodiazepines, but these agents are symptomatic treatments only.[113] Typical antiepileptic agents have many drug-drug interactions, as they can modify hepatic enzymes such as CYP3A4 and CYP1A2. This is significantly more problematic in the geriatric population, as they usually take multiple medications to control their chronic disease.[114]

Nasal administration of antiepileptics is attractive since it can be administered relatively easily and has good compliance by avoiding parenteral injection. Also, it can decrease drug interactions, hepatic degradation and reduce systemic side effects. One of the challenges to delivering these antiepileptics and benzodiazepines is that they have limited water solubility, which may prevent effective doses to the brain.[115] Many different formulations have been studied to avoid this obstacle, but only nanoparticles were reviewed in this article. summarizes various applications of nanoparticles for the treatment of epilepsy.

CONCLUSION

A successful drug delivery system is one which offers commercial applicability to pharmaceutical industries for large-scale production. CNS drug delivery is complex due to limitations imposed by the BBB. Direct nose to brain drug delivery system is a potential strategy to overcome the obstacles presented by the BBB. Intranasal delivery bypasses the BBB to target CNS, reducing systemic exposure of drug, thereby reducing the systemic side effects. It is an attractive option of drug delivery due to its non-invasiveness. A variety of neurotherapeutic agents including small drug molecules, proteins, peptides, hormones and biological cells such as stem cells can be delivered by this route, thereby yielding new insights into prevention and management of different neurological disorders. It is uncertain, however, whether the drug is being released from the carrier system in the nasal cavity and transported to CNS, or the carrier system is transported along olfactory and/or trigeminal nerve pathways into the CNS where the drug is released. Thus, more basic research is required to determine the possible transport pathway of therapeutic carrier to the CNS and their further fate into the biological system. Again, delivery of surface engineered carrier systems through passive or active targeting approach would be desirable for further progress in the field.

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