AN OVERVIEW ON CARRIER MEDIATED NOSE TO BRAIN DRUG DELIVERY SYSTEM

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ABSTRACT

One of the most exciting applications in the field of nasal medication administration is nose-to-brain delivery, which directly addresses the central nervous system while avoiding the blood-brain barrier. Lower doses and direct brain administration of strong drugs are among its advantages, resulting in fewer systemic side effects. Nasal insulin administration showed promising results in Alzheimer's disease clinical trials. Nanomedicines may be able to aid in the realisation of nose-to-brain delivery. While technologies to allow formulation deposition in the upper region of the nose are still needed, surface modification of nanomedicines appears to be the most effective method for increasing medication delivery from the nasal cavity to the brain. This work will describe and critically examine nanomedicine delivery to the nasal epithelium based on particle engineering using surface electrostatic charges, mucoadhesive polymers, or chemical moieties. The mechanism of delivery is nose-to-brain.

KEYWORDS: Nanoparticles, Nose-to-Brain Delivery, CNS Disorders, Mucoadhesion, Neurodegenerative Diseases, Alzheimer’s Disease, Parkinson’s Disease.

INTRODUCTION

Brain cancer, Alzheimer's disease, Parkinson's disease, stroke, and multiple sclerosis are among the most frequent disorders, and their prevalence is rising as the older population increases. However, due to the brain's complexity, treatment for brain disease is currently insufficient in comparison to other sections of the body. Longer durations and more complex clinical trials are also required for drug development for brain illnesses. The blood-brain barrier is a critical barrier to therapeutic drug delivery to the brain. It is a selective
permeability mechanism that functions as a local gateway against circulating foreign medicines. The physiological structure of the blood-brain barrier, on the other hand, is a major impediment to the delivery of prescription pharmaceuticals to the brain, and it is the primary cause of difficulties in existing treatment approaches, according to various scientific research. The research and development of innovative drug-delivery methods for the treatment of brain disorders. Nanotechnology-based brain delivery approaches, such as nanoparticles, liposomes, dendrimers, micelles, and carbon nanotubes, may, however, provide the key to better brain therapeutics.[2] The nose-to-brain channel allows medications to be delivered directly to the brain, bypassing the BBB and eliminating the first-pass effect. The upper section of the nasal cavity contains the trigeminal and olfactory nerves, which provide direct access to the brain via the nasal passage.[3]

Pathways and Mechanism For Nose To Brain Delivery
Nose-to-brain (ntb) delivery, in contrast to systemic administration, is a prospective approach for therapeutic drugs to enter the CNS without passing through the BBB. NtB is a non-invasive technology that directly accesses the CNS via the olfactory or trigeminal nerve, in contrast to standard drug delivery methods. In the rat and squirrel monkey, Frey was the first to show that horseradish peroxidase administered intranasally travels quickly across intercellular connections of the olfactory epithelium, reaching the CNS olfactory bulbs in 45–90 minutes. The exact pathways and transport methods by which medications reach various areas of the CNS via the nasal tube are yet unknown. The main conduit is assumed to be the olfactory nerve, which starts in the olfactory region at the top portion of the nasal cavity. Regular exposure to exogenous unpleasant compounds causes the olfactory neurons to regenerate every 3–4 weeks. As a result, enzymes, proteins, and transporters found in other epithelial cells in the nasal airways may not function effectively. This turnover creates a 'leaky' barrier that drug molecules can easily get past.[4] The transmission of information from the nose to the central nervous system can take many different forms, including paracellular, transcellular, and neuronal transport. A paracellular route is formed by strong connections between sustentacular cells or the so-called clefts between sustentacular cells and olfactory neurons. This is a slow and passive route for transporting hydrophilic medicines, with a rate dependent on the drug's molecular weight. The vehicle of lipophilic pharmaceuticals that show a rate reliance on their lipophilicity is accountable for transcellular measurement. Sustentacular cells, specifically, more likely via receptor-mediated endocytosis, fluid phase endocytosis, or passive diffusion. It moves rapidly and at a fast rate. Endocytosis or
pinocytosis processes gather up a substance into a neuronal cell, which is then transported to the olfactory bulb via intracellular axonal transport.[5]

**NASAL DRUG ADMINISTRATION FOR CNS TARGETING**

- Intranasal drug delivery to the CNS
  1. Olfactory pathway (Bulbus olfactorius)
  2. Respiratory pathway (Brainstem, pons)

**Formulation Strategies for N2b Transmission**

The use of the nose-to-brain delivery channel to bypass the BBB is a necessary and non-invasive method of medicine delivery. Indeed, it is commonly acknowledged that the nasal cavity and the CNS have an intranasal direct anatomical link, indicating the development of nasal formulations for brain-targeted therapy. Many strategies, including nanomedicine and various types of nanocarriers, such as polymeric nanoparticles, nano-emulsions, dendrimers, and nano-micelles, have been developed for nose-to-brain medication delivery. It's also conceivable to use bioadhesive systems. The development of novel nasal systems for controlled medicine targeting and delivery is a substantial challenge.[6]

**The Dosage Form That's Used To Make The Formulation**[7]

The dose type chosen is influenced by the medicine being used, the intended indication, the patient population, and, last but not least, marketing preferences. The following are some of the more noticeable properties of several of these distribution methods:

1. **Nasal Drops**

Nasal drops are one of the most basic and practical methods of nasal administration ever developed. Nasal drops may not be suitable for prescription medications due to this system's lack of dosing accuracy.
2. Nasal Sprays

Both solution and suspension formulae can be used to make nasal sprays. A nasal spray can deliver a precise dosage ranging from 25 to 200 L thanks to the availability of metered dosage pumps and actuators. The pump and actuator assembly selection is influenced by the drug particle size and shape (for suspensions), as well as the viscosity of the formulation. Because powder produces mucosal irritation, solution and suspension sprays are recommended over powder sprays.

3. Nasal Gels

Nasal gels are viscosity-high thickened liquids or suspensions. This was the case until the recent invention of precision dosing. The public was not interested in this system. Reduced post-nasal drip due to high viscosity, reduced flavour effect due to less swallowing, less anterior formulation leaks, reduced discomfort due to soothing/emollient excipients, and focused distribution to the mucosa for enhanced absorption are some of the advantages of a nasal gel.

4. Nasal Powders

This dosage form may be devised if solution and suspension dosage forms are not possible to produce, for example, due to a lack of pharmaceutical stability. Nasal powder dose forms have two advantages: they don't contain a preservative and the formulation is more stable.

5. Nano Emulsion

Nano emulsions are dispersions of two immiscible liquids stabilised by an appropriate surfactant. They can be oil-in-water (O/W) or water-in-oil (W/O) (s). NEs can be produced into a variety of formulations, including liquids, lotions, gels, foams, sprays, and more, and can be administered orally, parenterally, or ocularly in addition to nasally. Nano emulsion formulations were generated by establishing pseudo-ternary phase diagrams with lipophilic and hydrophilic surfactants and water. Different ratios of pluronic PF 127/PF 68 were used to generate thermo reversible nano emulsions. Several mucoadhesive agents were investigated in order to generate thermo triggered mucoadhesive nano emulsions. In nano emulsions have exhibited higher targeting (AUC=302.52 g min/g) than IV delivery of the medication (AUC=109.63 g min/g), according to a study by R. S. Bhanushali and M. M. Gatne.

To improve the formulation's residence time and overcome nasal clearance for better mucosal absorption, NEs can be transformed into mucoadhesive systems. The nano emulsion
formulation has proven to be effective in the treatment of epilepsy, depression, schizophrenia, Parkinson’s disease, Alzheimer’s disease, migraine, brain tumours, CNS infection, and other neurological disorders.[12]

6. Hydrogel
Hydrogels are water-soluble polymer cross-linked networks that can hold a lot of water.[14,15] Slabs, films, in situ hydrogels, nanogels, microparticles, nanoparticles, and other physical shapes are all possible.[13,14] They have pores that can be controlled by crosslinking density and can be altered with various functional groups. Their porosity aids medication loading and release at a rate dictated by the macromolecule diffusion coefficient throughout the hydrogel network. Hydrogels are particularly biocompatible due to their high-water content and physiochemical features that are similar to the original extracellular matrix.[14,15] They can also be distorted to fit the curvature of the surface on which they’ll be used. They're manufactured in a variety of ways, and the method determines pore size, rate of degradation, mechanical strength, and drug release mechanism. Because of their particular physicochemical properties, they were developed for nose-to-brain transfer.

7. In-Situ Gels
Systems that transform from sol to gel at the time of injection into the body are known as in situ-based gels. When administered, they are liquid and undergo a sol-to-gel transformation while exposed to external stimuli such temperature, pH, ion change, or magnetic field, or when in the biological environment. They have properties that make them useful for drug shipping, such as: they're particularly compatible with a wide range of drugs, including soluble, insoluble, low, and high molecular weight drugs; they're much less invasive and can be used to achieve high drug concentrations on the desired webpage of movement with fewer systemic side effects; biocompatibility.[13,16] Chitosan[17], Pluronic PF127[18], Poloxamer 407[19], Poloxamer 188[20], Pluronic F-127[18], Sodium alginate[21], Hydroxyl methyl propyl cellulose[22], Deacylatedgellanum[23], Carbopol 934, and NaCMC (Sodium carboxymethylcellulose)[24] were among the gelling agents utilised.

8. Liposomes and Lipid-Based Formulations
Lipid-based carriers such as mono-, di-, triglycerides, fatty acids, and waxes reduce medicine toxicity and can be used for long-term drug release. Lipid nanoparticles are extremely stable and can hold both hydrophilic and hydrophobic drugs. Lipid-based drug transport systems can easily cross the blood-brain barrier.[25,26] Combinations of solid and liquid state lipids
make create lipid carriers with nanostructures. Due to their distinct characteristics, they have high drug load capacities and maintain drug stability.\textsuperscript{[25,27]} Zheng and colleagues\textsuperscript{[28]} investigated the efficacy of nasal administration of the -amyloid protein breaker H102 peptide as a liposome formulation. They started with systemic pharmacokinetics: 5 minutes after intravenous administration of H102 solution containing BSA and chitosan (as an absorption enhancer), H102 was undetectable in plasma, in line with the reported short plasma half-life (2 min), whereas both H102 solution and liposome administered intranasally were detected at the same time. Liposomal H102 had a slower systemic Tmax than H102 solution (30 min vs. 5 min), indicating that liposome encapsulation causes systemic absorption to be delayed. H102 liposomes had a slightly higher systemic Cmax than H102 solution, and liposomal H102 stayed in the systemic blood circulation for longer than H102 solution. After intravenous administration, H102 was undetectable in the brain, demonstrating that the peptide cannot cross the BBB. Nasal administration of solutions or liposomes, on the other hand, resulted in significant H102 brain absorption, particularly in the olfactory system among the four brain regions (cerebrum, cerebellum, hippocampus, and olfactory bulb).\textsuperscript{[28]}

Yang and colleagues looked at the possibility of liposomal nasal delivery of rivastigmine, an alzheimer's medicine that is now only available in oral form. Liposomal compositions were compared to solutions. Poloxamer 188 is used as a permeation enhancer. The authors first looked at the differences in plasma rivastigmine concentrations 15, 60, and 240 minutes after intravenous or intranasal treatment, and discovered that (i) the intravenously given solution group had the lowest drug level plasma, which appears to be linked to fast medication absorption in the kidneys, and (ii) the intranasally administered liposome group had the highest drug level plasma, which appears to be linked to slow medication absorption in the kidneys.\textsuperscript{[29,8]}

**Developing Liposomal Nasal Formulations: Pharmaceutical Considerations**

The various qualities of nanoparticles as drug carriers are widely recognised to be influenced by their physicochemical characteristics (e.g., size and surface charges).\textsuperscript{[30,8]} In the research field of developing nanoparticles as a nasal formulation, the impact of surface charge on the nasal residence time of drugs/nanoparticles has been demonstrated, and it appears that cationic particles have a longer nasal residence time due to electrostatic interactions between nanoparticles and the mucous layer.\textsuperscript{[8]} In systemic circulation, liposome surface modification has been found to increase liposome binding to target regions or the half-life of encapsulated
Surface attachment of cell-penetrating peptides or RGD or PEGylation of liposomes have been tested in some studies.\[33\]

In a study with positively or negatively charged polymeric nanoparticles, anionic nanoparticles preferred the olfactory pathway, whereas cationic nanoparticles preferred the trigeminal pathways\[34\], suggesting that nanoparticle surface charge may play a role in determining the major drug transport pathway reaching the brain.\[8\] Overall, liposome compositions and/or surface modification appear to be critical factors in determining the efficacy of liposome formulations for medicine delivery from the nose to the brain. Permeation enhancers in the medication solution have previously been shown to improve nasal absorption of weakly permeable medicines by transiently boosting epithelial cell tight junction opening.\[35\] The usage of permeation enhancers has been restricted due to their nasal toxicity. Nasal toxicity following liposome intranasal delivery has been demonstrated to be minor in a number of studies.\[36\] This opens the way for improved liposomes to be developed as a nontoxic, safe nasal drug carrier for intranasal administration.

9. Nanoparticles
Medicinal drugs can be supplied in a controlled and site-specific manner using nanoparticles as drug delivery devices. Because nanoparticles encapsulate the medication, they can protect it from biological and chemical degradation, as well as help it avoid drug-efflux mechanisms such as the P-glycoprotein transporter in the blood-brain barrier\[37,25\]. To ensure content delivery to the site of action, nanoparticles can be linked to specific targeting ligands.\[37,38,25\]

According to Pardeshi et al., nanoparticles should be non-toxic, biocompatible, and biodegradable; physical stability; cost-effective production process and scale-up; and compatible with small molecules, proteins, peptides, and nucleic acids in order to effectively distribute N2B. Additionally, turning the medication into nanoparticles increases its stability and reduces pharmacological modifications caused by excipients. Particulate formulations can provide controlled drug release patterns, reducing medicine administration frequency while also increasing patient compliance.

Three methods for customising nanoparticle uptake are available for N2B transport. To increase the time that nanoparticles interact with the mucosa, the first step is to improve mucoadhesion. This enhances the likelihood that the medicine will pass past the epithelium and reach the brain. The second factor is the ability of diverse materials used in particle
formulations to diminish the barrier function of tight junctions. These particles would be able to open up tight connections in the nasal mucosa for a short time, allowing the drug to pass through. The final option is to make nanoparticle endocytosis more likely. After being endocytosed, the nanoparticles may release their pharmacological payload, which would subsequently be delivered to the brain.\textsuperscript{[26,37,39]} The use of nano- and microparticles for drug delivery provides a number of advantages, including controlled and sustained drug release as well as environmental protection. This is critical when spreading proteins and peptides. Surprisingly, particles can have ligands or molecular imprinting on their surfaces that guide them to a disease site.\textsuperscript{[25]} Nanoparticles must adhere to mucus in order to maximise medication absorption, but they must also be able to pass through mucus to avoid trapping and drug clearance.

Some of the nanocarriers that can be used are polymeric, lipid, and inorganic nanoparticles. Chitosan, hydroxy propyl cellulose, carboxymethylcellulose, and carbopol have mucoadhesive properties, while hyaluronic acid and polyacrylic acid are also effective.\textsuperscript{[40,41]}

**Nanoparticle Biodistribution in the Human Body**

After intravenous injection, polymeric nanoparticles come into direct touch with plasma/serum proteins before reaching the target cells. The interaction of polymeric nanoparticles with phagocytes is regulated by the balance between two serum components – opsonin, which stimulates phagocytosis, and dysopsonin, which suppresses it. Reticuloendothelial cells recognise polymeric nanoparticles because opsonin binds to their surfaces (RES).\textsuperscript{[42,43]} Polymeric nanoparticles are rapidly absorbed by RES located in the liver, spleen, and bone marrow following intravenous injection and rapidly disseminated throughout the liver (60-90 %), spleen (2-10 %), and bone marrow (to a lesser extent).\textsuperscript{[43,44]} A small concentration of nanoparticles can infiltrate the brain because of their absorption by RES following intravenous administration. To overcome phagocytosis difficulties and boost medicine concentration in the brain, several approaches based on surface modification of nanoparticles are being developed.

**METHODOLOGIES FOR NANOPARTICLE SURFACE MODIFICATION**

1. **Coated Nanotechnology**

   Coated nanotechnology involves coating nanoparticles with polymers or surfactants. Molecular simulations that would normally be carried into the brain are now possible. Nanoparticles are coated using the incubation method. This procedure involves adding the
coating solution to the prepared nanoparticle formulation and stirring or incubating the mixture overnight. Coating chemicals for polymeric nanoparticles\textsuperscript{[45]} are discussed in the sections below.

**Polysorbate 80:** Several drugs have been reported to be delivered to the brain efficiently using polysorbate 80 as a coating material. Polysorbate 80 is used to coat nanoparticles, which is done by mixing 1\% v/v polysorbate 80 with drug-loaded polymeric nanoparticles for 30 minutes. The delivery of Nerve Growth Factor (NGF) using polysorbate 80 coated PBCA nanoparticles as a carrier was also explored. The blood-brain barrier prevents NGF from reaching the brain, which is necessary in age-related neurodegenerative illnesses like forgetfulness and Parkinsonism. NGF-loaded PBCA nanoparticles coated with polysorbate 80 may efficiently transfer NGF to the brain\textsuperscript{46}, according to a pharmacokinetic model. Gallic acid was efficiently given to the brain for antidepressant effects using polysorbate 80 coated chitosan nanoparticles.\textsuperscript{[47,43]}

**Glutathione:** Glutathione is recommended as a coating material over Polysorbate 80. Aside from polysorbate 80, glutathione is a non-toxic peptide that occurs naturally in the body. Using glutathione as a coating material, an attempt was made to distribute Paclitaxel across the BBB. Glutathione-coated Polylactide-co-glycolide (PLGA) nanoparticles are a suitable transporter for Paclitaxel to the brain, according to the PgpATpase test. Glutathione is reported to impede the Pgp efflux transport mechanism.\textsuperscript{[48,43]}

Doxorubicin has a low permeability to the brain due to its weak lipophilicity, large molecular weight, and efflux via Pgp. The Pgp efflux transport mechanism is inhibited by glutathione, which is coated on Doxorubicin adsorbed on PLGA PEG nanoparticles, allowing Doxorubicin to reach the brain.\textsuperscript{[43,48]}

**Polyethylene glycol (PEG):** Unlike polysorbate 80, which is adsorbed to the polymer, a PEGylated polymeric nanoparticle penetrates the brain better than a polysorbate 80 coated nanoparticle because the covalent attachment of polyethylene glycol (PEG) to the polymer prevents PEG desorption from PEGylated polymeric nanoparticles. Numerous drugs have been successfully targeted to the brain using coated nanotechnology.\textsuperscript{[43,49]}
2. **Ligand Nanotechnology**

By covalently attaching ligands to polymers or nanoparticles, this approach increases receptor-mediated endocytosis or transporter-mediated transcytosis. Typical ligands include transferrin, lipoprotein, insulin, and thiamine, though synthetic or natural peptides can also be used. The ligands are bound to the nanoparticles or polymer surface using two techniques.

**A. Covalent Chemical Conjugation**: The ligand is first thiolated, then interacts with a maleimide-functionalized drug or nanoparticle to form a stable thioether bond, which is the most extensively used chemical conjugation approach. By treating a thiolated drug or vector with a free cysteine or reduced disulfide bond, a disulfide-bonded drug-nanoparticles conjugate can be created. A chemical spacer (CH2)5NHCO(CH2) 5NHC0 or polyethylene glycol (PEG) moiety can be placed into the connection to reduce steric hindrance and ensure the vector and protein function.

**B. Noncovalent Streptavidin/Biotin Linkages**: To monobiotinylate lysine residues in medications, biotin hydrazide or N-hydroxysuccinimide (NHS) analogues of biotin can be utilised. Streptavidin can be linked to the targeted vector via a thioether linkage. To construct a BBB targeted treatment, combine the biotinylated therapeutic with the streptavidin-functionalized targeting vector. The use of a PEG linkage is also an option.

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**Advantages and Limitations Of Intranasal Drug Delivery System**

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<th>ADVANTAGES</th>
<th>LIMITATION</th>
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<tr>
<td>The availability of needle-free drug delivery without the need for trained personnel makes self-medication easier, which improves patient compliance.</td>
<td>Mucocilliary clearance permits pharmacological substances to be quickly removed from the nasal cavity.</td>
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<td>Low-molecular-weight medicines, particularly lipophilic medications, permeate the nasal mucosa well.</td>
<td>Absorption enhancers used in formulation may cause mucosal toxicity.</td>
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<td>Increases bioavailability by avoiding drug degradation in the gastrointestinal tract, first-pass metabolism, and drug gut-wall metabolism.</td>
<td>This technique of medicine administration may be hampered by nasal obstruction caused by a cold or an allergic response.</td>
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<td>Avoidance of hepatic first-pass metabolism, which allows for a lower dosage when compared to oral delivery.</td>
<td>Variation in concentration levels in different parts of the brain and spinal cord.</td>
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<td>Direct medication delivery to the central nervous system through the olfactory system, thereby bypassing the blood-brain barrier</td>
<td>It’s perfect for powerful medication because only a small amount needs to be sprayed into the nasal cavity.</td>
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<td>Vaccine distribution to lymphatic tissue and secretory immune response activation at the proximal mucosal area</td>
<td>The nasal mucosa is damaged and irritated when this procedure is used on a regular basis.</td>
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<tr>
<td>An absorption enhancer or another approach can be used to increase the bioavailability of larger drug molecules.</td>
<td>The mechanics of drug transport are still unclear.</td>
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Conclusion and Future Perspectives
The science of nose-to-brain communication is fascinating. The employment of nanocarriers appears to be an asset in the quest for a non-invasive, efficient, safe, and maybe revolutionary breakthrough in the treatment of CNS difficulties and brain illnesses, with multiple benefits but also a few drawbacks.[1]

The development of nanoparticle formulations targeted at enhancing medicine transport from the nose to the brain has shown great promise for the future. Because of their great permeability, liposomes and other nanoparticles have gained favour as a formulation for delivering drugs to the brain via the nasal route.[8]

Drug targeting and delivery to the brain are difficult due to the presence of the blood-brain barrier, which protects the brain from outside chemicals. In order to progress in the successful treatment of brain cancer, neurodegenerative sickness, and stroke, which are all relatively common conditions, novel strategies for enhanced blood-brain barrier transit must be created. Nanotechnology-based approaches, such as nanoparticles, liposomes, dendrimers, micelles, and carbon nanotubes as nanocarriers, are now being researched to breach the blood-brain barrier and deliver the right amount of medicine to the specific brain region. More research is needed to better understand and control the crossing of the blood-brain barrier, as well as to improve the efficacy of nanotechnology-based brain delivery systems.[2]

REFERENCES
1. Fabio Sonvico, Adryana Clementino, Francesca Buttini, Gaia Colombo, Silvia Pescina, Silvia Stanisçuaski Gutterres, Adriana Raffin Pohlmann, and Sara Nicoli; Surface-Modified Nanocarriers for Nose-to-Brain Delivery: From Bioadhesion to Targeting; Pharmaceutics, 2018; 10: 34.
3. Maria Cristina Bonferoni, Silvia Rossi, Giuseppina Sandri, Franca Ferrari, Elisabetta Gavini, Giovanna Rassu and Paolo Giunchedi; Nanoemulsions for “Nose-to-Brain” Drug Delivery; Pharmaceutics, 2019; 11(84): 1-17.
5. Angela Bonaccorso; Nanocarriers for nose-to-brain delivery: a novel strategy for the treatment of CNS disorders, PhD Thesis, Department of Biomedical and Biotechnological Sciences, University of Catania – Medical School, 2016; 41-44.

6. Paolo Giunchedi, Elisabetta Gavinia and Maria Cristina Bonferoni; Nose-to-Brain Delivery; Pharmaceuticals, 2020; 12: 138(1-5).


8. Soon-Seok Hong, Kyung Taek Oh, Han-Gon Choi and Soo-Jeong Lim, Liposomal Formulations for Nose-to-Brain Delivery: Recent Advances and Future Perspectives; Pharmaceuticals, 2019; 11(540): 1-18.


12. Blessing AtimAderibigbe; In Situ-Based Gels for Nose-to-Brain Delivery for the Treatment of Neurological Diseases; Pharmaceutics, 2018; 10: 40.


