



## **Brain Targeting Through Intranasal Route: An Overview**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. Authors SVA and MV designed the study, performed the statistical analysis, wrote the protocol, author JR wrote the first draft of the manuscript. Author SS managed the Collection of data. All authors read and approved the final manuscript.*

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### **ABSTRACT**

Brain targeting has always been challenging due to the presence of physiological barriers by Changing the integrity of these barriers, so as to allow the toxic substances, bacteria and viruses into the brain, Which may severely damage the central nervous system .This problem can be reduced by delivering drugs through the intra nasal route, which by passes the blood brain barrier and reaches into the brain. Nasal route is a non-invasive type, widely used for the local treatment as well as used for systemic therapy as drug delivery directly goes in to systemic circulation. Nasal route provides good absorption of small molecules compared to that of large molecules, absorption of small molecules and large molecules can be increased by absorption promoters. Different drug delivery devices are developed for nasal administration like liquids, semi-solid and solid formulation are consider to deliver the drugs to treat most of the CNS diseases (i.e. Parkinson's, Alzheimer's disease) because it requires specific targeting of drugs to the brain. This review highlighted the challenges, approaches for brain targeting and various drug delivery systems developed with different drugs targeting to brain through nasal administration.

**Keywords:** Brain targeting; CNS diseases; blood brain barrier; drug delivery devices; nasal route.

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## 1. INTRODUCTION

In Targeted drug delivery system the medicament is selectively delivered to the particular site of action without reaching to the non target organs. It is a method of delivering medication to a patient that increases the concentration of drug in body parts and to reduce the side effects [1]. Targeting to brain is a major challenge because it is separated from the circulating blood by a unique membranous barrier called as blood brain barrier. which is a highly semi permeable membrane [2]. Any disorder (or) diseases related to brain are difficult to control because it is covered by the blood brain barrier. Which doesn't allow the 100% of large molecules and 98% of small molecules [3]. The blood brain barrier consists of tight junctions around the capillaries and actively transport the metabolic products such as glucose crosses the barrier with specific proteins [4]. There are different factors responsible for crossing the blood brain barrier like binding of the drug to a transporter, opening and closing of ion channels, lipophilicity, enzymatic degradation of drugs, higher molecular weight of drugs and the presence of functional groups. These are the factors which determine the blood brain barrier permeability of any drugs [5].

### 1.1 Objectives of Brain Targeting

Central nervous system disorders are one of the leading cause of illness requiring more extended care and hospitalization. It has been estimated that around 10 million people in the world are living with Parkinson's disease and the number of central nervous system related disorders are rising day by day [6]. Treating central nervous system diseases such as Parkinson's disease, Alzheimer's disease, Schizophrenia, Stroke, Epilepsy, Brain tumours is extremely difficult due to the presence of various barriers mainly the blood brain barrier which restricts the passage of drug into the brain. Investigating a suitable drug delivery system which could allow the drug to bypass the barriers and enter the drug into brain for the management of brain diseases is a big challenge [7].

## 2. METHODOLOGY

### 2.1 Approaches for Brain Targeting

Actual treatment of CNS disorders, such as brain tumours, psychological disorders and neuro degenerative disorders depends on successful

delivery of drug to the brain. Lipid soluble molecules with a molecular mass under 400-600 Da can easily enter through the tight junction of the blood brain barrier [8]. However, water soluble molecules with a mass of less than 600 Da may enter into the brain through carrier mediated transport, receptor mediated transport (or) absorptive mediated transport. The three different approaches currently used to deliver the drug into brain without systemic toxicity are Invasive Approach, Pharmacological Approach and Biological (or) physiological approach [9].

### 2.2 Invasive Approach

The invasive approach is a physical approach in which peptides and nutrients having poor bioavailability in the brain after intravenous (or) oral administration are made bioavailable by using different techniques like intra cerebral ventricular infusion (drug is directly injected into the cerebral lateral ventricles resulting in diffusion of drugs into the brain through the cerebrospinal fluid) [10]. Convection enhanced delivery (In which the drug is delivered directly into brain parenchymal cells, with the help of stereotactic apparatus) [11]. Intra cerebral injection (or) brain implants (It is a direct method to deliver drug into target site of brain) The drugs such as Nitrosourea, Methotrexate, Mitoxantrone, Carmustine were used for brain targeting by using invasive approach [12,13].

In certain cases the blood brain barrier is mechanically reached by applying osmotic shock, MRI guided focused ultrasound blood brain barrier disruption [14].

### 2.3 Pharmacological Approach

The pharmacological approach is used for lipid insoluble, high molecular weight drug molecules by chemical techniques with the modification of the chemical structure of the drug to improve lipophilicity, (or) by converting into prodrug form to reach the active site in the brain. The other pharmacological approach is development of colloidal drug carriers such as nanoparticles, micelles, liposomes, emulsions and dendrimers to effectively transport the drugs across the blood brain barrier by various trans cellular mechanisms. Paclitaxel loaded micelles, Doxorubicin loaded liposomes, Quercetin loaded solid lipid nanoparticles, Lamuvidine loaded dendrimers were developed for brain targeting by using pharmacological approaches [15].

## 2.4 Biological (or) Physiological Approach

Biological (or) physiological approaches are based on the transport of different molecules by specific transporters such as insulin receptors, transferrin receptors etc. These physiological approaches are a) Cell penetrating peptide mediated drug delivery ( amino acids with a positive charge are used to transport the drug molecules into the cytoplasm by different mechanisms). Methotrexate was used for brain targeting through cell penetrating peptide delivery. b) Receptor mediated drug delivery (Receptors such as transferrin receptor and insulin receptor are targeted by specific ligands and antibodies which will transfer the drugs into the brain). Loperamide was used for brain targeting through receptor mediated delivery [16]. c) Adsorptive mediated drug delivery (Various peptide vectors are developed for adsorption endocytosis to deliver peptides and proteins for treating brain tumours). Cisplatin was used for brain targeting through adsorptive mediated drug delivery [17].

## 2.5 Intra Nasal Route

Drugs and its delivery systems are administered through different routes based on different approaches like oral, injections and nasal route etc. Intra nasal route has been considered as a important route to achieve faster drug absorption because nasal mucosa is permeable to different compounds than the gastro intestinal tract due to lack of pancreatic and gastric enzymatic activity, neutral pH of the nasal mucosa and less dilution unlike by gastro intestinal contents. Many drugs have been shown to achieve better systemic bioavailability through nasal route than by oral administration. The nasal route avoids hepatic first pass elimination and is easily available with self-medication .Rapid drug absorption and quick onset of action are achieved with the nasal route. The bioavailability of larger drug molecules can be improved by using absorption enhancers [18]. Drugs having more than 300 Daltons molecular weight are suitable for nasal administration and better nasal permeability. P<sup>H</sup> of the nasal formulation should be adjusted to 4.5-6.5 to avoiding nasal irritation.

### 2.5.1 Brain targeting by intra nasal route

The movement of molecules from the nasal cavity to the brain parenchyma occurs along with the olfactory nerves. Once the molecules are

delivered to the origin of the nerves in the cerebrum and they are able to distribute through the brain. This process occurs via two pathways intracellular and extra cellular mechanisms. Intra cellular mechanism involves internalization of the molecule by an olfactory neuron, movement of the endocytic vesicle with in the cell to the neuron projection site and finally release via exocytosis. Where as extra cellular pathway involves crossing of drug through the nasal epithelium to the lamina propria by bulk flow process. The axon leads into the central nervous system, where the drug is distributed further via fluid movement [19].

## 2.6 Pharmaceutical Approach

For intra nasal administration of drugs, four basic formulations are considered i.e. solution, suspension, emulsion, gels and dry powders [20]. These are administered through nose using different devices like catheters, nebulizers, squeezed bottles, insufflators, dry powder inhalers and metered dose inhalers. There are different particulate (nano, micro) novel drug delivery systems are being developed for targeting to brain through nasal route to improve bioavailability with fast action. These include nanoparticles, nano emulsions, solid lipid nanoparticles, liposomes etc [21].

## 3. DISCUSSION

The present review is focusing on different novel (nano and micro particulate) drug delivery systems developed with various drugs for brain targeting by intra nasal administration to treat CNS disorders as given in Table 1. Based on the Table 1, it was found that, 50% of developed delivery systems belong to nano drug delivery systems, 20% micro particulate systems and remaining include gels, micelles etc. Among nano drug delivery systems, 27% of Solid lipid nanoparticles (SLNs), 18% of Nanoparticles, 9% of Nanoemulsion and 2% of Nano liposomes were developed for intra nasal administration as shown in Fig. 1. Based on the table, it was demonstrated that 20.31% drugs (Astaxanthin, Galanamine hydrochloride, Donepezil, Venlafaxine, Valproicacid, Thymoquinone, Hyaluronic acid, Rivastigmine) were selected for the treatment of Alzheimer's disease, 18.75% for the treatment of Epilepsy and status epilepticus, 12.5% for the treatment of Schizophrenia and 9.4% for the treatment of Depression by intranasal administration. Most of the reports identified that higher concentration of drug in

**Table 1. List of drugs developed into nasal drug delivery systems for brain targeting**

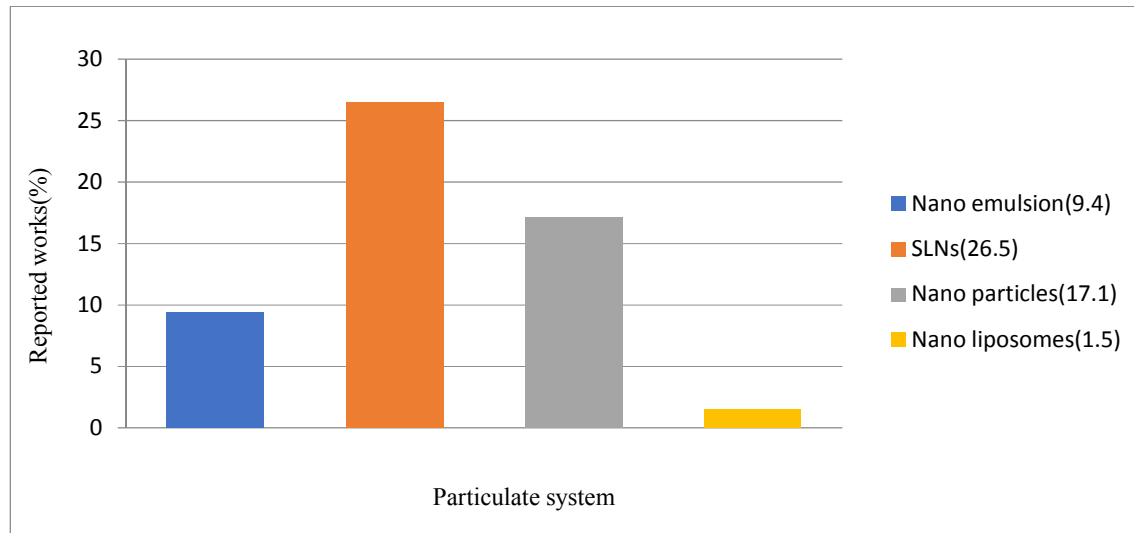
S. No	Drug name	Drug delivery system	Name of the disease	Result	Reference
<b>Nano drug delivery systems</b>					
1.	Arthemether	Nanoparticles	Cerebral malaria	Exhibit sustained release and higher concentration of drug in brain upon intra nasal administration was observed.	[22]
2.	Astaxanthin	SLNs	Alzheimer's & Parkinson's Disease	Improved brain targeting efficiency of drug was observed.	[23]
3.	Agomelatine	SLNs	Depression	Enhanced absolute bioavailability and successful brain targeting by the intra nasal route was estimated.	[24]
4.	Almotriptan malate	SLNs	Migraine	Enhanced the nasal residence time and formulation was safe for nasal administration.	[25]
5.	Bromocriptine	Nano particulate formulation	Parkinson's disease	Enhanced drug bioavailability and direct targeting to the brain was observed.	[26]
6.	Carbamazepine	Polymeric hybrid Nanoparticles	Epileptic seizures	Good targeting efficiency and improved bioavailability was observed.	[27]
7.	Diazepam	Nanoparticles	Status epileptics	Significantly higher brain uptake of drug was observed.	[28]
8.	Duloxetine	Nano structured lipid carriers	Depression	Increased nasal residence time and higher amount of drug in brain were found.	[29]
9.	Donepezil	SLNs	Dementia	Achieved sustained release and increased brain targeting potential was observed.	[30]
10.	Donepezil	Nano emulsion	Alzheimer's Disease	Increased penetration of drug through nasal mucosa and improved brain delivery was observed.	[31]
11.	Donepezil	SLNs	Alzheimer's disease	Drug delivery system with sustained release and localization of drug in brain was observed.	[32]
12.	Doxorubicin	Lipid nano carriers	Glioblastoma	High quality, safety and efficacy of the developed delivery system was observed.	[33]
13.	Efavirenz	SLNs	HIV/AIDS	Increased concentration of drug in brain was observed.	[34]

S. No	Drug name	Drug delivery system	Name of the disease	Result	Reference
14.	Embellin	Nano structured lipid carriers	Epilepsy	Achieved sustained release and higher concentration of drug into brain was found.	[35]
15.	Galantamine hydrochloride	SLNs	Alzheimer's disease	2 fold improvement in the bioavailability of the drug was observed.	[36]
16.	Haloperidol	SLNs	Schizophrenia	Controlled and sustained release with better brain targeting efficiency was estimated.	[37]
17.	Hyaluronic acid	Nano emulsion	Alzheimer's Disease	Nano emulsion was safe on intra nasal administration and increased amount of drug in the brain was observed.	[38]
18.	Lorazepam	Polymer nanoparticles	Epilepsy	Gamma scintigraphy studies showed that high uptake of nanoparticles in to brain.	[39]
19.	Lorazepam	Nanoparticles	Epilepsy	Increased patient compliance for the easy and non-invasive route of administration was observed.	[40]
20.	Olanzapine	Nanoparticles	Schizophrenia	The results proved that the drug concentration increased in brain was observed.	[41]
21.	Pramipexole dihydrochloride	Nanoparticles	Parkinson's Disease	Increased dopamine levels in brain was observed.	[42]
22.	Quetiapine fumarate	Nano structured lipid carriers	Schizophrenia	Achieved sustained release and Blood brain ratio showed 10 fold increase for NLCs administered through nasal route was observed.	[43]
23.	Quetiapine fumarate	Nano liposomes	Schizophrenia	Maximum efficiency was observed and formulation shown better potential to deliver drugs to the brain.	[44]
24.	Risperidone	Nano emulsion	Depression	Brain blood ratio of 0.617, 0.754 at 0.5h was increased.	[45]
25.	Risperidone	Solid lipid Nanoparticles	Psychotic disorders	Better brain targeting delivery was observed.	[46]
26.	Resveratrol	Nano emulsion	Parkinson's disease	Pharmacokinetic studies showed the higher concentration of drug in brain.	[47]
27.	Rosmarinic acid	SLNs	Huntington's disease	The sustained release and better brain	[48]

S. No	Drug name	Drug delivery system	Name of the disease	Result	Reference
28.	Rivastigmine	Nano structured lipid carriers	Alzheimer's Disease	targeting efficiency was observed. Initial fast drug release followed by prolonged release over 48 h was estimated.	[49]
29.	Saquinavir mesylate	Nano emulsion	Neuro AIDs	Nano emulsion with better brain targeting efficiency was observed.	[50]
30.	Safranal	Nano emulsion	Cerebral malaria	The developed targeted formulation is safe and reached into brain.	[51]
31.	Thymoquinone	Nanoparticles	Alzheimer's disease	Reducing the systemic exposure and delivery of drug to the brain rapidly and more effectively was observed.	[52]
32.	Teriflunomide	Nanoparticles	Multiple sclerosis	Increased nasal residence time and formulation was safe for nasal administration.	[53]
33.	Valproic acid	Nano particulate system	Alzheimer's disease	Brain/ plasma concentration ratio was increased to about 20 times was observed.	[54]
34.	Valproic acid	Lipid nano carriers	Bipolar disorders	Better drug delivery into the brain was observed.	[55]
35.	Zolmitriptan	SLNs	Migraine	Formulation reached the brain with increased bioavailability and localized for 24h.	[56]
<b>Micro particulate drug delivery system</b>					
36.	Amisulpride	Micro emulsion	Schizophrenia	Nasal drug solution showed significantly high activity.	[57]
37.	Asenapine maleate	Micro emulsion	Schizophrenia	Increased bioavailability and controlled targeting of drug to the brain was observed.	[58]
38.	Clonazepam	Micro emulsion	Acute status epilepticus	Rapid delivery of drug to the brain was observed.	[59]
39.	Carbamazepine	Micro emulsion	Epilepsy	A Formulation free from nasal ciliotoxicity was developed and proved.	[60]
40.	Diazepam	Micro emulsion	Status epilepticus	Antiepileptic activity was improved.	[61]
41.	Nimodepine	Micro emulsion	Senil dementia	Increased retention time of the formulation and enhanced brain delivery was observed.	[62]
42.	Nimodepine	Micelles	Global ischemia & epilepsy	Improved brain bioavailability was observed.	[63]

S. No	Drug name	Drug delivery system	Name of the disease	Result	Reference
43.	Olanzapine	Micro emulsion	Schizophrenia	Enhanced permeation of drug through nasal route was observed.	[64]
44.	Paliperidone	Micro emulsion	Schizophrenia	Achieved desired therapeutic activity and delivered drug directly to the brain by nasal administration was observed.	[65]
45.	Rizatriptan	Microspheres	Migraine	Effective concentration of drug for brain targeting was observed.	[66]
46.	Tramadol HCL	Microspheres	CNS targeting	Localization of drug in brain was observed.	[67]
47.	Valproic acid	Micro emulsion	Epilepsy	Better brain bioavailability was found.	[68]
<b>Nasal gels</b>					
48.	Agomelatine	Insitu gels	Depression	Enhanced nasal retention time and successful brain targeting by the intra nasal route was observed .	[69]
49.	Carbamazepine	Nasal gel	Epilepsy	Fast and pronounced drug uptake in the brain was observed .	[70]
50.	Doxepine	Biogels	Mild & moderate depression	Effective drug delivery to brain by nasal route was observed.	[71]
51.	Geniposide	Insitu nasal gel	Alzheimer's disease	More residence time and release of drug is controlled by gel was observed.	[72]
52.	Methotrexate	Nano gel	Primary CNS targeting	Increased methotrexate concentration in brain was observed.	[73]
53.	Naringenin	Insitu gel	Brain ischemia	Enhanced brain bioavailability was observed.	[74]
54.	Rasagiline mesylate	Nasal gel	Parkinson's disease	Four to six fold increased bioavailability of the drug was found .	[75]
55.	Sumatriptan succinate	Insitu gel	Migraine & cluster headache	Enhanced nasal residence time and drug reached to the brain by nasal pathway.	[76]
56.	Temozolamide	Hydrogel formulation	Meta static melanoma & glioma	Increased residence time on nasal region was observed.	[77]
57.	Tramadol HCL	Insitu gels	Depression	Increased locomotor activity.	[78]
58.	Venlafaxine hydrochloride	Insitu gel	Alzheimer's disease & depression	Estimated pharmacodynamics properties and proved more effective anti-depressant by nasal route.	[79]
59.	Vinopectin	Insitu gel	Dementia	Enhanced bioavailability was observed.	[80]

S. No	Drug name	Drug delivery system	Name of the disease	Result	Reference
<b>Other drug delivery systems</b>					
60.	Carbamazepine	Niosomes	Epilepsy	Improved invitro drug release was observed.	[81]
61.	Donepezil	Liposomes	Alzheimer's disease	The bioavailability of drug in brain was increased significantly.	[82]
62.	Dioleoylphosphatidyl choline	Cationic liposomes	Alzheimer's disease	Improved therapeutic efficacy was observed.	[83]
63.	Haloperidol	Dendrimer	Catalepsy	Improved delivery of insoluble drugs to the brain was established.	[84]
64.	Resveratrol	Transferosomes	Alzheimer's disease	Enhanced permeation through nasal mucosa was observed .	[85]
65.	Zolmitriptan	Niosomes &novasomes	Migraine	Constituted advances in the management of migraine.	[86]



**Fig. 1. Different intra nasal Nano drug delivery systems**



brain and enhanced bioavailability by intra nasal route compared to intravenous and oral route of administration. Reports concluded that the dose required for nasal administration is less than the dose required for other route of administration. The present review highlighted the CNS disorders treated by intra nasal administration using various novel drug delivery systems which helps to have a pharmaceutical strategy for nasal administration to cross BBB.

#### 4. CONCLUSION

Nasal drug delivery system is an alternative route of administration for the systemically acting drugs to improve patient acceptability and compliance compared to parenteral administration of drugs. Nasal drug absorption can be increased by using different approaches like increasing the nasal duration of drug, use of absorption enhancers and decreasing the mucociliary clearance. The nasal drug delivery system is beneficial in conditions like Parkinson's disease, Alzheimer's disease, (or) pain because it shows specific targeting of drugs to the brain. Nasal application of nanocarriers like solid lipid nanoparticles, liposomes and emulsion etc. to achieve efficient and safe approach for the treatment of CNS disorders. In near future, that more drugs will be introduced in the market in the form of nasal formulation with reduced doses and reduced cost of total treatment.

#### CONSENT

Not applicable.

#### ETHICAL APPROVAL

Not applicable.

#### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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