CURRENT NANO DRUG DELIVERY STRATEGIES AVAILABLE FOR NOSE TO BRAIN DRUG TARGETING

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Abstract: Central Nervous System (CNS) disorder like HAND, multiple sclerosis, alzheimer's disease speak to a developing general medical problem because of the expanded future and aging population. The treatment of such disease is quite intricate and require the delivery of therapeutics to the brain in effective concentration to exhibit a pharmacological response. Effectiveness related issues emerge because of failure of macromolecule to cross the blood brain barrier (BBB) to elicit their significant delivery to the brain tissue and cerebrospinal fluid (CSF).The nose-to-brain delivery has developed effective route to bypass the BBB and deliver the medications to the brain. There are various nanotechnology drug delivery system approaches available such as nanoemulsion, nanosuspension, lipid nanoparticles, liposomal nanoparticle, magnetic nanoparticle delivery, macrophages carrier etc. Development of brain drug delivery is very tough task because of the presence of various physiological barriers called BBB and presence of efflux transporters puts restriction on the delivery of drug to the central nervous system. Since from last decade, intranasal route attracted wide attention of researcher as effective, noninvasive, reliable and safer route to achieve effective level of drug with faster rate in brain and CSF via olfactory and trigeminal pathway by passing blood brain barrier.

Keywords: Nose to brain, Blood brain barrier, Brain targeting, Nasal drug delivery, Delivery pathway.

1. INTRODUCTION

Drug delivery to the brain with safe and effective approach is required to protect its structure and function. Many existing pharmaceuticals are rendered ineffectual in the treatment of cerebral ailments because of failure in delivery or support their transport inside brain [7]. Different pharmacological agents have been utilized to open the BBB and direct intrusive strategies can introduce therapeutic active agent into the brain regions. It is critical to decide not just the net delivery of the therapeutic agent to the CNS yet in addition the capacity of the agent to get to the important target site inside the CNS [6]. Intranasal (IN) administration to target the therapeutic to the central nervous system (CNS) has numerous advantages in the treatment of neurological issues. The Blood Brain Barrier (BBB) limits the utilization of various therapeutics agent that have been created to treat memory misfortune and neurodegeneration since it limit CNS entrance, depends on drug size and efflux via transporter[5].

2. INTANASAL DELIVERY

2.1 Nasal cavity

Along with the oral cavity, nasal cavity includes an outer opening for the respiratory system giving a portal to the passage of air before its consequent flow to the lower airway routes. The nasal cavity plays significant role in fundamental physiological capacities, for example, dampness (humidity), temperature regulation of breathed in air, particulate residue filtration and olfaction forms [10]. The unpredictably organized nasal cavity broadens around 12–14 cm long and 5 cm in height, while its total surface and total volume are accounted in the range of 150–200 cm^2 and 13–25 cm^3 respectively [9]. During inward breath process, the air enter through the nostrils in to the nasal vestibule and is plan through the flexible nasal valve (the most impenetrable opening of the respiratory tract) into the essential nasal load. Total proof has recommended that only 10-20% of the breathed in air achieves the olfactory district, because of the anatomic configuration of nasal cavity [11].

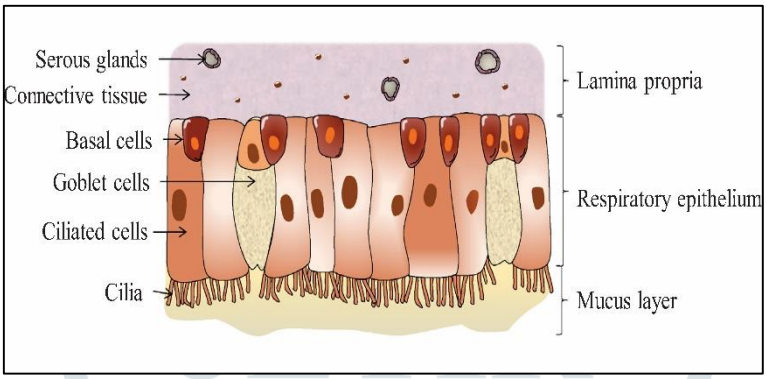
2.1.1 The respiratory epithelium

A ciliated pseudostratified columnar epithelium, called respiratory epithelium or schneiderian film lines the respiratory tract region which involves the best piece of the nasal cavity (~ 80-90% of the complete surface area) [11]. The respiratory epithelium (Fig. 1a) is the major site for foundational drug assimilation principally because of its enormous microvilli covers the surface area and level of vascularization [10 -12]. In fact, it gets blood supply from a blood vessel of the maxillary conduit [12].The respiratory epithelium is included by four morphologically distinct cell types, in particular the ciliated and nonciliated columnar cell, the basal cells and the challis cells, whose fundamental capacities lies in the planned sweeping movement of the cilia the water and ion exchange between cells, the procedure of bodily fluid discharge and freedom just as the regulation of the moistness of the mucosa [03]. The respiratory epithelium is secured by two fold layered body fluid gel, comprised of the low viscosity pericilliary layer, which expands 3-5µm in thickness and encompasses the motile cilia (2-4µm long) and the underlying viscous layer, which broadens 2-4µm in thickness [11,13,14]. The respiratory fluid is a viscoelastic gel, made out of a system of high atomic weight glycoproteins called mucins, water, salts, different protein and a little division of lipids fills in as a defensive boundary because of its viscoelastic and adhesive properties and speaks to the first line of barrier against breathed in particulate and aggravations [15].

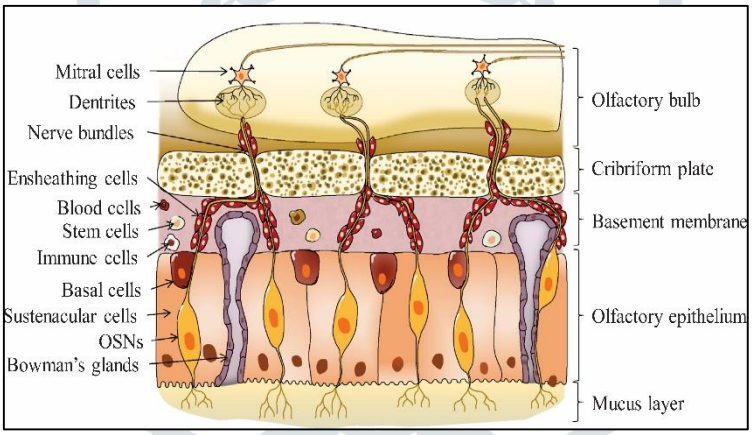
2.1.2 The olfactory epithelium

The olfactory framework has pulled in significant scientific interest among the segments of the nasal cavity, exclusively to the capacity of its neurons to recognize odorants and give the feeling of smells, yet additionally for its omnipresent capacity to give an entryway to guide delivery of brain [16]. From a basic viewpoint, the olfactory mucosa (Fig.2b) comprises of a ciliated

chemosensory pseudostratified columnar epithelium and is arranged on the prevalent turbinate and reciprocally on the nasal septum, while it is totally encompassed by respiratory epithelium. The olfactory mucosa includes the lamina propria, which is situated underneath the epithelial basement membrane and separated from a thick capillary network, contain lymphatic vessel, olfactory axon groups, autonomic nerve fiber, the maxillary part of the trigeminal nerve and the body fluid discharging Bowman's organs, which record for the emission of the overlying body fluid gel layer [16]. As opposite to the respiratory epithelium, the olfactory mucosa get its blood supply from ophthalmic vein branches, and the cilia of the olfactory epithelium are longer (> 50μm) and non-motile. In any case, in spite of the absence of movement, bodily fluid freedom is as yet practical, apparently because of constant bodily fluid discharge and shedding because of gravitational and mechanical powers just as because of a dissolvable drug effect, in spite of the fact that the overlying body fluid gel shows a very moderate turnover, in the request of a few days [17]. Barrier components incorporate the discharge of xenobiotic-metabolizing enzymes and antibodies of the immune system. The significance of the body fluid protective systems is evident in disease state, where olfactory keenness is significantly diminished as the clearance is prominently blocked because of the expanded fluid viscosity [3]. It ought to be noticed that the precise morphology and structure (e.g., olfactory surface area, cell composition) of the olfactory system and related structure may change significantly among species (see table 1), which reflect the major difference in the detecting capacity and olfaction between human subject and different species.



(a)



(b)

Figure1. Two distinct kinds of pseudostratified epithelia situated in nasal cavity: (a) the respiratory epithelium, which lines the upper aviation routes and is primarily included by goblet, basal and ciliated cells and (b) the olfactory epithelium situated on the top of the nasal cavity, which fundamentally contains the ciliated receptor neurons, the basal and the sustenacular cells [3].

Table 1. Surface area of olfactory epithelium [3].

Species	**Olfactory epithelium surface area (cm^2)**
Mice	1.25-1.40
Rat	4.2-6.8
Dog	170-380
Human	10 2-12.5

2.2 Olfactory and trigeminal pathways:

Intranasally administered therapeutics reaches the CNS by the means of olfactory and trigeminal neural pathways. Both the olfactory and trigeminal nerves innervate the nasal cavity, giving an immediate association with the CNS. Direct delivery of therapeutics from the nose to the brain was at first credited to the olfactory pathways [48]. More recently, the commitment made by the trigeminal pathways to intranasal delivery to the CNS has additionally been perceived, particularly to caudal brain areas and the spinal cord [18]. Extracellular delivery, as opposed to axonal transport, is unequivocally demonstrated by the brief span outline (≤ 10 minutes)

watched for intranasal therapeutics to achieve the brain concentration from the nasal mucosa. Potential mechanism of transport may include bulk flow and diffusion inside perineuronal channels, perivascular spaces, or lymphatic channels straightforwardly associated with cerebrospinal fluid or brain tissue [18].

3. Advances in brain targeting:

1) Nanoparticlulate drug carrier systems are observed to be better in the pharmacokinetic systems of the drug atom such as biodistribution, bioavailability and medication discharge qualities (drug release characteristics) in a controlled and powerful way with site specific drug targeting focusing to tissue or cell with limiting the toxic indication. So the utilization of nanotechnology in the field of pharmaceutical biotechnology helps in improving the delivery of drug technique including the pharmacokinetics and therapeutic index to deal with the delivery issues of some biotechnological therapeutic drug including the recombinant proteins and oligonucleotides [6].

2) Nanoparticles are believed to be efficient carrier in transporting of conventional therapeutic drug substance, recombinant proteins, vaccines as well as nucleotides [8].

3) The BBB itself utilized as the source of 'CNS drugs'. 'Bypassing' the BBB can be an intense system, particularly for some cases or circumstances. For e.g. Intrathecal administration for delivery of therapeutic substance to the brain is inefficient for small size drug, lipid dissolvable drugs [8].

The current challenges are to build up the active ingredient transporting carrier system, which most likely convey the medication across the BBB with a nontoxic and in compelling way.

3.1 Nanoemulsion:

Nanoemulsions (NEs) can be defined into various types of measurements structures like fluids, creams, gels, froths, and spray. NEs can be administered by various routes including oral, parenteral and ocular, addition to the nasal route [19]. NEs can be utilized to take care of issues of drug dissolvability as well as of drug stability (oxidation, pH, hydrolysis and enzymatic degradations at the mucosal dimension, under physiological conditions) [20]. Hydrophobic drug are relied upon to break down in the oily phase, and when the drug (broke down in the oily stage) is discharged from the NE and interacts with the encompassing fluid (aqueous) condition, a nano-precipitation can happen [22, 21]. This decides the arrangement of particles with an enormously high surface and an exceptional improvement of drug dissolution rate, as indicated by the Noyes–Whitney condition [21]. NEs can be utilized additionally to cover the severe or upsetting taste of drug and to convey results of characteristic natural origin [21].

NEs can be set up through various procedures that can be arranged into two general classifications: high-energy methods and low-energy methods (Fig.2). On account of high-energy method, for example, ultra-sonication and high pressure homogenization, the constitution of small droplet includes a mechanical devices that creates disruptive forces breaking up oil and water phase to prepare small oil drops, a procedure that expends critical energy. The device utilized are microfluidic, ultrasound or high pressure homogenizers [23].

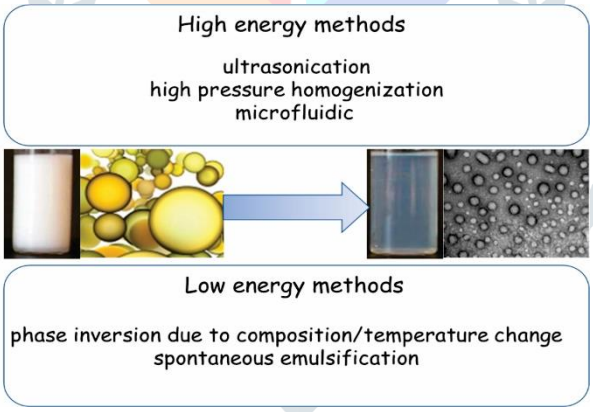


Figure 2. Preparation method of nanoemulsion [2].

Table 2. Research on nanoemulsion for nose to brain delivery

Drug	Therapeutic Approach	Name of the researcher
Curcumin	Mucoadhesive nanoemulsion of curcumin showed extraordinary transition crosswise over sheep nasal mucosa contrasted with fake treatment nanoemulsion what's more, medicate arrangement.	Sood et al., 2014 [50]
Ropinirole	Improved intranasal transition of chitosan-covered mucoadhesive nanoemulsion when contrasted with medication arrangement and better pharmacodynamics reaction.	Mustafa et al., 2012 [51]
Rivastigmine	Mucoadhesive formulation was free from nasal ciliotoxicity.	Shab et al., 2015 [52]
B-Asarone	Improved bioavailability	Zhang et al., 2014 [53]
Saquinavir mesylate	NEs for intranasal administration might be very promising methodology for delivering anti-retroviral agent in request to accomplish CNS targeting for the treatment of neuro-AIDS.	Hitendra S. Mahajan et al., 2013 [43]
Ziprasidone hydrochloride	Formulation was free from nasal ciliotoxicity and can be result in better brain take-up of the medication by nasal route than oral route, one of the significant limitations of commercially accessible preparation.	Shiv Bahadur et al., 2012 [44]

Yu et al. prepared a formulation that they characterized "submicron emulsion", containing an antiaging compound, ergoloidmesylate, which is established by methanesulfonate salts of the three alkaloids dihydroergocristine, dihydroergocornine and dihydroergocryptine [51]. Egg lecithin was utilized as the fundamental emulsifier. In vivo examinations were done on male Sprague–Dawley rats; Nasal administrations of ergoloidmesylate "submicron emulsions" were contrasted with nasal and intravenous administrations of therapeutic drug solution. The area under curve (AUC) and the absolute bioavailability in the cerebrospinal liquid (CSF) following intranasal administration of the "submicron emulsions" were higher than those got after nasal administration of the solutions [24]. These promising outcomes were accepted for instance for further examinations including drugs for the treatment of different CNS pathologies. Antiepileptic drug amiloride loaded mucoadhesive nanoemulsion for nose-to-cerebrum drug delivery was developed by Jain et al. [25].

3.2 Nanosuspension:

Nanotechnology can be utilized to solve the issues related with different methodologies portrayed before. Nanotechnology is characterized as the science and engineering which is carry out in the nanoscale that is 10^{-9}m. The drug microparticles/micronized drug powder is moved to drug nanoparticles by techniques like Bottom-Up Technology and Top-Down Technology as shown in fig.3 [28].

Nanosuspensions are submicron colloidal dispersion of nano sized drug particles stable out by surfactant. Nanosuspension comprises of the poor water- dissolvable drug with no lattice material suspend in scattering. These can be utilized to improve the dissolvability of drug that are poorly solubilize in water just as lipid media [27]. Because of expanded solvency, the rate of flooding of active compound increments and the most extreme plasma level is achieved faster. This methodology is helpful for particles with poor solvency, poor penetrability, or both, which represents a significant challenge for the formulators. The diminished molecule size renders the likelihood of intravenous administration of poor soluble drugs with no barricade of the blood vessels. The suspension can be lyophilized and into a strong lattice. Aside from these points of interest, it has the advantages of fluid formulation over others [27].

Bhavna et al.(2014) shows development of donpezil loaded nanosuspension utilizing the ionic cross linking technique. This formulation had the option to indicate higher drug concentration in brain and no mortality, heamatological changes, body weight varieties and histopathological changes in animals, when formulation was administer in various dosages when contrasted with normal saline administered intranasally [29]. In this manner it is presumed that donpezil loaded nanosuspension is fit for giving direct nose-to-brain delivery, consequently enhance the drug concentration in a brain. It is foreseen that the present original copy will help scientists in executing theutility of in vivo safety study which must be performed for various medications, immunization and challenge study for drug safety in the nasal mucosa while introduction through intranasal route [29].

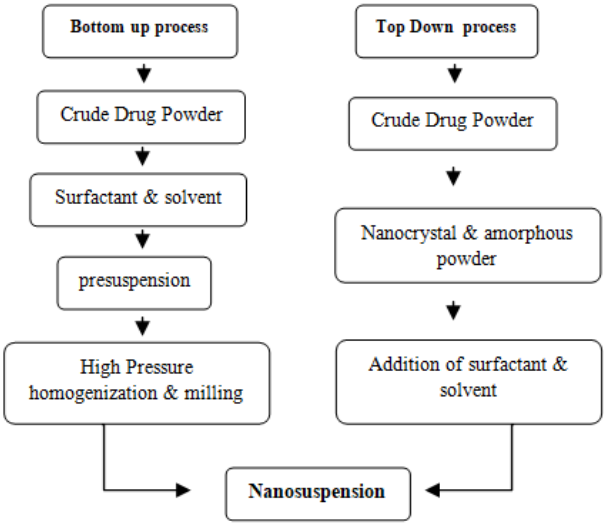


Figure 3. Preparation of nanosuspension [27]

Hydrocortisone nanosuspension was developed by Hany S.M. Ali et al. utilizing bottom-up technology [30]. The method included micronised fluidic precipitation process that influence the size of produced drug particles. Altered parameter included flow rated of drug medication arrangement and antisolvent, microfluidic channel measurements, microerector inlet angles and drug concentration. The trial result revealed that hydrocortisone nano-sized dispersion in the range of 80-450nm were gotten and the mean molecule size could be changed by adjusting the test parameters and structure of microerectors [30].

Sachin Kumar Singh et al. pepared the parameter of nanosuspension by top-down media processing to improve the dissolution of poor water-soluble or dissolvable glyburide [31]. From this investigation, it was reasoned that polymer concentration (proportion of polymer to drug) and processing speed (milling speed) plays a significant role in controlling the zeta potential of nanosuspension. Milling time and milling pace (speed) were viewed as significant variables, which influenced the mean particle sized d(90) of nanosuspension. The examination additionally helped in distinguishing certain formulation and processing parameter, such as, high polymer fixation(Concentration) and high processing velocity, which may influences the manufacturing of nanosuspension at higher scale [31].

Table 3. Research on nanosuspension for nose to brain drug delivery

Drug	Approach	Name of the researcher
Donepezil	This formulation has demonstrate higher drug concentration in brain and no mortality, hematological changes , body weight variations and histopathological changes in animals, when formulation was administered in various portions when compared with normal saline administered intranasally.	Shadab M db et al., 2014 [29]
Ezogabine	The Cmax revealed concentration of ezogabine in brain and plasma as 0.1812µg/ml and 0.183µg/ml, resp., for plain suspension and concentration of ezogabine in brain and plasma as 0.7885 µg/ml and 0.7483 µg/ml resp., for nanosuspension at same dose of 1 mg/ml when given intranasally	Pawar Anil et al. [45]
Olmesartan medoxomil	nanosuspension was converted into dry powder by lyophilization so as to build its stability.The lyophilized nanosuspension was observed to be stable when stored under refrigerating conditioned and take care of the problem of defining drugs with low aqueous dissolvability and poor systemic bioavailability.	Hetalparesh Thakkar et al., 2010 [46]

3.3 Liposome:

Liposomes are spherical, concentric bilayered, phospholipid vesicles made out of biodegradable and biocompatible lipid indistinguishable from the lipid present in biological layers/membranes (Phospholipids and cholesterol).The self-assemble into structures containing a aqueous core and a lipid bilayer having sizes extending from 50 nm to 100 µm. Hydrophilic and lipophilic medications can be delivered effectively utilizing liposomes. According to their structure, hydrophobic or amphiphilic compounds can be captured in the phospholipid bilayer and hydrophilic drugs can be encased inside the aqueous core [49]. Being highly lipophilic in nature, liposomes are promising brain focusing carrier systems.

As per the manufacturing procedure and phospholipids type, liposome may have uni-, bi-, or multi-lamellar structures and distinctive surface charges. Liposome are considered non-toxic and biocompatible because of their phosphiolipid nature and can shield the improve their therapeutic effectiveness [33].

Al Asmari and co-workers compared the brain and plasma pharmacokinetic profiles following brain to nose administration of a liposome formulation of donepizil in healthy male Wistar rats. The liposomes were found to have a smooth surface, round shape, and existed for the most part as a single unilamellar vesicles; although some were multilamellar, Liposomes were non-accumulated with a particle size (>90%) of 102±3.3nm. Intranasal administration of these liposomes fundamentally expanded donpezil delivery to the brain compared with the traditionally utilized products [34].

Li and colleagues prepared flexible liposomes through the lipid film hydration technique. The net size of galantamine loaded flexible liposomes was 112±8nm. High encapsulation effectiveness of the drug was attributed to the improved hydrophilicity of the lipi bilayer and high lamellarity of the vesicle core [35]. This examination demonstrated that the effectiveness of brain acetylcholineesterase inhibition by means of the intranasal course was enhanced by flexible liposomes (transferosomes), recommending the usefulness of this way to deal with improve brain targeting of drug [35].

Table 4. Research on liposome for nose to brain drug delivery:

Drug	Therapeutic Approach	Name of the researcher
Galantamine	Galantamine loaded liposomes effectively inhibit acetyl-cholinesterase following the Nose-to-Brain administration.	Zhou et al., 2012 [54]
Folic acid	Niosomal formulation of folic showed improved assimilation through the nasal cavity as contrasted with drug solution.	Ravouru et al., 2013 [55]
Rivastigmine	Demonstrated an enhanced ex vivo dissemination through goat nasal mucosa contrasted with rivastigmine solution, attributed to the lipoidic nature of the transporter. Higher conc. In hippocampus, cortex, and olfactory region.	Yang et al., 2013 [56]

3.4 Lipid nanoparticles:

Lipid nanoparticles are colloidal carriers which might be a substitute for some other larger colloidal transporters such as, polymeric NPs, liposomes and nanoemulsions. Depending upon their structure, lipid NPs may exhibit assurance against drug degradation, great loading of lipophilic drug, controlled drug discharge and low bio-toxicity [36]. Moreover, their lipophilic nature NPs could encourage penetration of the BBB through endocytosis. In any case, lipid NPs likewise represent a few restrictions; these incorporate poor loading of hydrophilic drugs, lipid type, poor in vivo stability, the need to utilize surfactant and metal contamination, which may happen when ultrasound is utilized during production [37]. Different limitations incorporate the production procedure using micro-emulsion and emulsification-evaporation, which may cause toxicity because of the residual organic solvent [37]. Lipid NPs involve first generation solid lipid nanoparticles (SLNs) and second generation nanostructured lipid transporters (NCLs). The SLNs are principally made out of a solid lipid matrix in which the drug is either dispersed or dissolved [38].

Table 5. Research on lipid nanoparticle for nose to brain drug delivery

Drug	Therapeutic Approach	Name of the researcher
Curcumin and Donepezil	Increased concentration of drugs in the Brain. Improve memory and learning in mice. More elevated amounts of acetylcholine in brain. Decreased oxidative damage.	Sood et al., 2013 [57]
Ropinirole	Enhanced stability, diminished dosing frequency.	Pardeshi et al., 2013 [58]

Pardeshi and associates prepared ropinirole-loaded polymer-lipid hybrid nanoparticles (PLN) and ropinirole hydrochloride-loaded SLNs for brain targeting through intranasal route. The PLN and SLN were synthesized by emulsification-solvent diffusion method and were characterized regarding in vitro mucoadhesion, mucosal toxicity and stability, and in vitro penetration studies. These authors discovered good retention with minimum detrimental consequences for the nasal mucosa, together with satisfactory pharmacodynamic results [39].

Zhao and associates documented the development of gelation nanostructured lipid carrier (GNLs) loaded with fundamental fibroblast growth factor (bFGF) utilizing the emulsion and freeze drying technique. The GNLs were administered utilizing the Nose-to-Brain course in a hemi parkinsonian rat model. The GNLs improved the levels of exogenous bFGF in the olfactory bulb and the striatum without any detriment to the mucus membrane. GNLs can be utilized as carriers for Nose-to-Brain drug delivery, especially for macromolecular drugs [40]. Table 6 listed some of the patents on intranasal drug delivery and table 7 listed current marketed products for intranasal delivery.

Table 6. Patents for nose to brain drug delivery

Inventor/Patent no./year	Drug/Method	Approach	Citation
Alam et al./ 17431920703064955355/ 2012	Thymoquinone(TQ)	Study in rats demonstrated that intranasal administration delivers TQ to the brain rapidly and more effectively.	https://patents.google.com/scholar/17431920703064955355
Stanley L. Gore/ CA2325106A1 / 2019	Compositions and methods	Intranasal delivery of active agent to the brain and is particularly concerned with composition and method for the intranasal delivery of active agent to the brain by means of neural pathways.	https://patents.google.com/patent/CA2325106A1/en?q=nose&q=brain&q=targeting&oq=+nose+to+brain+targeting
Zeenat I Khan/ CN105596293A/2016	Nimodipine	Tween 80 and poloxamer 188 may be active targeting brain increase the amount of the drug to the brain, reducing the side effects of drugs to other organs, improve the therapeutic effect of the drug.	https://patents.google.com/patent/CN105596293A/en
William H. Frey/ US9636312B2 /2019	Method of treatment of traumatic brain injury	Method of treating traumatic brain injury/head injury comprising administering metal chelators to the upper one-third of the nasal cavity.	https://patents.google.com/patent/US9636312B2/en?q=nose&q=brain&q=targeting&oq=+nose+to+brain+targeting

Table 7. Marketed nose to brain formulation

Name Of Formulation	Drug	Application	Manufacturer
Migranal Nasal Spray	Ergotamine	Anti-Migraine Drug	Novartis
Imigran Nasal Spray	Sumatriptan	Anti-Migraine Drug	GlaxoSmithKline UK
Instanyl 100mcg Nasal Spray	Fentanyl Citrate	Analgesia	Takeda UK Ltd.
Zomig Nasal Spray	Zolmitriptan	Anti-Migraine Drug	Grunenthal Ltd.
Butorphanol Nasal Spray	Butorphanol	Anti-Migraine Drug	Aalpharma Services Corp.

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