

# Nanotechnology-based Intranasal Drug Delivery Systems: A Review

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## ABSTRACT

An experimental study has focused on developing a different approach to systemic oral along with parenteral administration in order to overcome their common drawbacks, including hepatic first-pass, which reduces drug bioavailability following oral administration, off-target effects, low patient compliance, along with a slow onset of pharmacological action through first-aid cases. Novel drug delivery systems (DDS), mostly composed of polymers and biocompatible lipid materials, have significantly boosted this sector in recent years. The previously intranasal (IN) method of delivery is an acceptable non-invasive option. It is ideal for self-administration since the medication quickly enters the circulation, eliminating the initial pass effect, and it may additionally reach the brain's cortex directly by crossing the blood-brain barrier (BBB). The combination of the IN route alongside DDS can, therefore, become a successful method for regulated drug administration, particularly when a rapid impact is sought or required. This study seeks to analyze the scientific literature on IN-DDS and its various routes for consumption (systemic, topical, pulmonary, and nose-to-brain). In this regard, the intranasal route offers a *viable* pathway for medication delivery reaching the brain because of its distinct anatomical characteristics. Nanoparticle-based technologies, in particular, have proven a remarkable ability to overcome the limitations of the intranasal route to induce drug accumulation throughout the brain despite avoiding systemic dissemination.

**Keywords:** Novel drug delivery systems, Intranasal, Advantages, Nanotechnology and Methods.

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## INTRODUCTION

Scientific research has lately focused on developing an alternate mode of delivery to oral and parenteral routes in order to address the objections that a medicine receives after administration. The oral route is commonly utilized in chronic situations for the management of several disorders.<sup>1</sup> The previously well-known disadvantages of oral delivery, such as limited absorption *via* the gastrointestinal mucosa along with the hepatic first-pass impact, frequently reduce the total bioavailability of a medication. As a result, the medicine must be provided at a greater dose to have the intended therapeutic effect, which may lead to an increase in adverse effects. This needs to be taken into account because it is impossible to deliver the medicine directly if the patient remains unconscious, such as during a seizure.<sup>2</sup> During such emergency instances, rapidity of action is critical, which oral administration cannot provide; hence, injections are frequently required in acute conditions. Parenteral administration, therefore, proves particularly valuable in first-aid medicine due to the early

beginning of pharmacological activity, increased absorption, and capacity to be used on unconscious or recalcitrant patients. If the drug's target site is the brain's primary nervous system (CNS), crossing the blood-brain barrier (BBB) must also be considered. The BBB inhibits the administration and transport of therapeutic agents and medications, limiting permeability and the uptake of drug molecules; as a result, there are relatively few therapies effective for medicinal purposes of the majority of CNS diseases.<sup>3</sup> Several intrusive procedures have been used to briefly expose the tightly bound BBB connections to the medications by disrupting the BBB briefly due to biological, chemical, or physical stimulation. However, all of these techniques are limited by tissue harm and uncontrolled drug dispersion from the injection site. As a result, intranasal administration is the quickest and potentially least intrusive method of transporting therapeutic cargos that concentrate on cells in the brain. As soon as medications enter the airway epithelium, they go to the brain *via* olfactory neurons, which is the simplest and fastest route for nanocarriers to make it to the

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CNS. Nanotherapeutics can be administered intranasally to the central nervous system *via* the olfactory as well as trigeminal nerves.<sup>4</sup> The respiratory and olfactory regions are extremely well-vascularized and coated with mucous membranes, making them very intriguing for medication delivery and absorption. The trigeminal nerve route can be carefully designed to provide consistent medication delivery through the brain. Intranasally given medicines can reach the CNS *via* the olfactory nerves located in the olfactory bulb and travel through the olfactory neuroepithelium to the piriform cortex, amygdala, as well as hypothalamus. Before reaching the CNS, drugs absorbed enter the systemic circulation and must overcome the BBB through blood-cerebrospinal fluid (CSF) blood-CSF barriers.<sup>5</sup> As a result, the nose vasculature may serve as a sink for particular intranasal drugs. Therapeutic drugs can enter the CNS through the nose passage *via* the olfactory nerve fibers of the olfactory bulb. Intranasal (IN) administration provides an appealing method of achieving high drug levels throughout the brain, and has been proposed as an alternative to established parenteral as well as oral routes enabling drug delivery to the brain. The nasal cavity has distinct anatomical properties for drug administration, providing a minimally invasive route, permitting a speedy commencement of action, and minimizing hepatic first pass-effect.<sup>6</sup> Considering a surface area of approximately 160 cm<sup>2</sup> (96,000 cm<sup>2</sup> that includes microvilli), the IN pathway has been widely explored for topical and systemic therapies. Meanwhile, the sense of smell region, which provides direct communication with the brain, covers approximately 5 cm<sup>2</sup> (3,000 cm<sup>2</sup> for the microvilli). Furthermore, the IN cavity has a dense microvascular network contributing to medication absorption and distribution. However, nasal physiology presents significant problems that should be considered when creating medication formulations utilizing this route.<sup>7</sup> The restricted amount of formulation that may be placed into the nasal passages, mucociliary clearance, the existence of a mucus layer, including local enzymes are all variables that might impede medication absorption *via* the IN route. In light of this objective, nanoparticle-based drug delivery methods have been demonstrated to be a significant tool for promoting drug accumulation throughout the CNS through greater permeability over the olfactory area.<sup>8</sup> In this essay, we will critically overview recent advancements in creating nanoparticles (NP) that enable medication delivery to the central nervous system *via* the IN route. Special attention will be given to the nanocarrier nature, which includes polymer, lipid, inorganic nanoparticles, and drug nanocrystals.<sup>9</sup>

#### **Advantages, Problems, and Obstacles of Nose-to-brain Medication Administration**

The intracranial (IN) route constitutes a non-invasive, minimally invasive method of administering drugs to the CNS that is more effective either intravenous (IV) or oral routes. This route directly to the CNS may circumvent the BBB while decreasing systemic adverse effects. Drugs administered *via* different parenteral or oral methods must first pass multiple barriers to enter systemic circulation before crossing the

BBB and reaching the CNS. Furthermore, IN prevents hepatic first-pass metabolism and drug degradation through the gastrointestinal system, making it an alternate route to supply parenteral administration, particularly when dealing with biopharmaceuticals (such as proteins and peptides).<sup>10</sup> Consequently, IN injection can provide direct drug transport to the brain, mostly *via* the sensory neuronal route, or indirectly by passage across the blood-brain barrier (BBB) compared to systemic circulation. The previously vestibular, respiratory, and olfactory regions are the three primary areas of the nose cavity.<sup>11</sup> The initial section is the nasal cavity's outermost surface, which is coated with ciliated hairs, including a layer of mucous that prevents foreign particles, antigens, and infections from entering. The respiratory area is then furnished with trigeminal sensory neurons and blood vessels. Subsequently, the olfactory area is positioned on the top of the nasal canal, with an epithelium composed of supporting and basal cells, including olfactory sensory neurons. This area is in intimate touch with the olfactory bulb (OB) from the brain through olfactory nerves, resulting in are located beneath the plate known as the cribriform of the skull's surface.<sup>12</sup> In turn, this region contains trigeminal nerves. Conversely, the respiratory area is highly vascularized, making systemic medication absorption easier. Smaller lipophilic molecules can enter the bloodstream and traverse the BBB more easily than hydrophilic or higher Mw molecules. Once the medication reaches the nasal blood arteries, it can reach the arteries that supply the carotid artery, the cerebral cortex, and the vertebral column.<sup>13</sup> The traditional method is less recommended due to the limits imposed by the BBB on medication access to the CNS as well as the undesirable peripheral effects that might result from systemic administration. Notwithstanding the benefits and promise of the nose-to-brain delivery route, medications must overcome considerable difficulties reaching the CNS, including the intended site's anatomical, physiological, and biochemical properties.<sup>14</sup> One of the most significant challenges is the presence of mucus within the mucosa of the nose, as well as ciliary movement because these are among the initial barriers to overcome whenever drugs are delivered *via* the IN route, as these two variables can limit the duration of retention of the drug dosage create in the nasal cavity as well as molecule movement regarding the CNS. Furthermore, the small amount available for formulation distribution in each nostril may hinder effective brain medication delivery.<sup>15</sup> Another major constraint of this method is the physical position of the olfactory epithelium, which must be accessible before the dosage form can be administered. Metabolic enzymes found in the mucosa of the olfactory bulb must also be addressed when developing a formulation that supports the nose-to-brain pathway. As a result, IN formulations must be constituted of biocompatible and odorless excipients to avoid fast removal owing to mucociliary clearance and enzymatic degradation.<sup>16</sup> Additionally, they must have a proper viscosity, physiological tonicity, as well as pH that is compatible regarding the nasal mucosa. As a result, many solutions have been developed

to address the difficulties associated with this mode of administration. Most of these treatments tried to improve molecular absorption in addition permeability by expanding the dose form's duration in the nose's mucous membrane and improving drug concentration throughout the CNS.<sup>17</sup> These tactics may involve the use of permeation as well as absorption enhancers, cell-penetrating molecules, mucoadhesive along with mucopenetrating agents, enzyme inhibitors, hydrogel systems, nanoparticulate systems for drug delivery, as well as a combination using these strategies. Nanoparticulate-based methods, in particular, have proven an impressive ability to overcome the limitations of the IN pathway and achieve drug accumulation throughout the brain while avoiding systemic dissemination. The latest advancements in this discipline are listed below.<sup>18</sup>

### **Nose-to-brain is an Efficient Brain-targeting Pathway**

The issues encountered in administering anti-epileptic medications by traditional methods (oral, intravenous, intramuscular), particularly inadequate bioavailability, have prompted researchers to investigate alternative delivery routes. Drug delivery to the brain *via* the nasal route represents a promising, effective, and safe method of transporting medications to the brain's nerve cells. The potential use of continuous nose-to-brain conveyance addresses enhanced therapeutic targeting while minimizing systemic adverse effects.<sup>19</sup> However, low-soluble, labile, low-permeant, and possibly less powerful medications may require a formulation different than the typically used dose forms, including solutions as well as suspensions. The employing of nanotechnology enabling nose-to-brain transport protects the medication against degradation by numerous enzymes, which improves brain utilization of the drug molecule through the olfactory mucosa.<sup>20</sup> Nanotechnology is frequently regarded as an appropriate strategy since it protects medications from metabolic or chemical degradation, increasing their solubility and allowing transit through biological membranes. The previously olfactory area located inside the nasal cavity transports medicinal substances directly from the nose to the brain. Intranasal injection of the medication can carry the drug towards the brain through numerous methods, both direct and indirect.<sup>21</sup> Intranasal administration represents a new method of medication delivery towards the treatment as well as management of several CNS illnesses, particularly Alzheimer's, Parkinson's, depression, anxiety, Huntington's, psychosis, and schizophrenia. Nose-to-brain delivery, when combined with nanomedicine, has recently been found to be useful for managing epilepsy.<sup>22</sup> Many variables influence medication nasal transport throughout the brain, including quick nasal mucociliary clearance and drug concentration. According to increasing data, when delivered nasally, pharmacological molecules of any size can bypass the BBB across the olfactory neuroepithelium. Several studies have shown a variety of potential benefits of nose-to-brain delivery. Some consist of the ease in approachability regarding the nasal passageway permitting self-administration, decreased patient

in compliance, short duration of action, greater surface area over absorption, lessened systemic exposure along with minimized peripheral side effects, permeable endothelial membrane, as well as avoiding the impact of the first pass.<sup>23</sup> intranasal medication transfer therapy potential can be expanded by researching and creating more successful formulations and administration systems. Nanoparticulate drug delivery shows considerable promise in drug transport through the blood-brain barrier *via* many routes. Nanotechnology's intrinsic qualities, such as nano-size, the capacity to tailor/modify the outermost layer, solubility improvement, and release modification, help increase bioavailability, effectiveness, and targetability.<sup>24</sup> Polymeric as well as lipid nanoparticles with a carrier particle diameter less than 200 nm are commonly used for brain administration. Lipid-based nanoparticles have several benefits over polymeric nanoparticles in terms of brain-focused drug administration, including quick absorption by the nervous system, biocompatibility, biodegradability, and low toxicity. One of the distinguishing characteristics of nanoparticles of lipids is that organic solvents may be avoided throughout the manufacturing process. The only limitation to intranasal medication administration is mucociliary clearance as well as the tendency of different proteins, peptides, and other compounds to degrade. This can be avoided by encapsulating the therapeutic molecule into a suitable carrier system, such as the construction of PEGylated nanoparticles.<sup>25</sup>

### **Nanotechnology-based Techniques for Reaching the Brain from the Nose**

Nanotechnology-based formulations offer the advantage of protecting the therapeutic payload while also increasing and/or extending its interaction through the olfactory system. Before developing a successful nose-to-brain delivery system, it is critical to carefully evaluate a variety of aspects. These concerns include formulation considerations, physiological and anatomical aspects of the nose-to-brain pathway, and medication or dose form-related issues. Formulation-related parameters include pH, medication concentration, viscosity, particle size, osmolality, along with particle size.<sup>26</sup> The pH of the intended formulation should be kept within the nasal mucosal pH, which is 5.5 to 6.5, along should be consistent with the drug's solubility and stability. The medicine's concentration level in the formulation is also important for enhancing the drug's nasal bioavailability.<sup>27</sup> The basic justification for choosing a good drug delivery system is its potential to increase the medication's bioavailability and duration, hence improving its therapeutic efficacy. Employing nano vehicles in drug delivery through the CNS results in specific properties such as prolonged or delayed release, maintenance on the solubilized form of pharmaceuticals, and greater penetration owing to surface changes, all of which contribute to increased efficiency *via* nose-to-brain administration.<sup>28</sup> Mucoadhesive polymers utilized in nose-to-brain delivery systems include cellulose derivatives that include hydroxyl propyl methylcellulose (HPMC), hydroxyl propyl cellulose (HPC), microcrystalline cellulose (MCC), starch, polyacrylates, carbomers, and

chitosan, among others. The attachment mechanism that promotes extended drug retention is essentially the same at nasal and gastrointestinal tract locations; however, the functionalization that occurs in the polymers leads to enhanced tissue/organ selectivity.<sup>29</sup> Consequently, mucoadhesion enables the formulation to give extended drug release. Mucus can act as an effective barrier towards nanoparticle transport over the mucosae. Factors that may limit intranasal delivery reaching the brain include medications with a molecular weight larger than 20 kDa, increased ionization, and increased hydrophobicity of molecules. Furthermore, the nasal cavity has several constraints, such as low dosage administration, mucociliary clearance, enzymatic degradation, and limited penetration into the mucous membrane of the nose.<sup>30</sup> As a result, using permeation enhancers combined with mucoadhesive polymers to extend the medication's residence duration in the nasal cavity has been shown to improve drug penetration through the mucosa of the nose.

### **Nanotechnology-based Methods to Deliver Through the Nose**

A major need for nanoparticulate brain administration is that the tiny particles used for medication delivery be both biocompatible and quickly biodegradable. Various nanocarriers are constructed and functionalized to target brain locations by changing the ability to penetrate of the BBB.<sup>31</sup> The modification of nanoparticles containing surfaceactive ligands aids in the circumvention from the BBB through nanocarriers. Because the BBB contains transport molecules, including as insulin, growth hormones, and transferrin, NPs are expected to function as medication carriers in epilepsy mapping efforts. The utilization of standard medications loaded into unique and experimental nanocarriers might aid in the treatment of epilepsy and other neurological illnesses. Nanoparticles (NPs) may theoretically protect medications against metabolic breakdown, increasing the residence duration at the desired delivery location.<sup>32</sup> Furthermore, NPs can boost medication absorption through cells from the nose that travels to the brain *via* the axons that run through the olfactory and trigeminal nerve. The fundamental benefit of using drug nanocarriers is their capacity to disguise drug molecules before transporting them into the brain parenchyma and crossing the BBB. Nanoparticles' tiny size and high mobility allow for better diffusion through the blood-brain barrier. It is unclear how these systems boost drug absorption, but it is assumed that transportation of the encapsulated drug across the membrane, extending the retention time, and increasing stability all contribute to absorption. However, the results of these nanotechnology-based technologies have proved exceedingly promising when paired with nasal administration.

### **Emulsomes**

Emulsomes become nanocarriers made from lipid cores that are either solid or liquid crystalline at 25°C and covered through a phospholipid bilayer. These nanocarriers have the features of both lipid spheres (polar core) and liposomes (hydrophilic

surface). Emulsomes can entrap large quantities of lipophilic medications while significantly increasing the solubility and bioavailability of poorly soluble pharmaceuticals. Emulsomes were shown to have greater  $C_{max}$  and AUC compared to the corresponding IV dose.<sup>33</sup> According to 2016, nano-spherical emulsomes containing oxcarbazepine (OX) were produced utilizing several triglyceride (TG) cores (Compritol(®), tripalmitin, tristearin, and triolein) containing soya phosphatidylcholine in varying ratios. They created bespoke emulsomes by adjusting particle size overall surface charge characteristics, resulting in a stable system with a longer release profile and overall residence period. The trials, therefore, shown effective direct nose-to-brain OX delivery within rats.

### **Nanoemulsions**

Nanoemulsions (NEs) comprise emulsions containing nanosized droplets that range in size from 20 to 200 nm. Such multicomponent systems seem transparent or translucent before the human eye and exhibit long-term physical stability. Brownian motion between droplets prevents creaming, sedimentation, and coalescence.<sup>34</sup> Small droplet size prevent flocculation, allowing the system to stay disseminated without phase separation. NEs have recently received much interest in potential drug delivery systems since they are thermodynamically inert and form spontaneously by mixing the various components. A study utilizing risperidone-loaded intranasal nanoemulsions for brain targeting found that risperidone was transported into the rat brain more quickly and extensively. A range of medicines, including as sertraline hydrochloride, amiloride, and morphine, were explored as NEs because of their nose-to-brain targeting capability.<sup>35</sup>

### **Nanoparticles**

Nanoparticulate devices are being investigated to improve medicine or vaccination delivery using IN drug administration. NPs comprise compact colloidal particles that range in size from 1 to 1000 nm. They are composed of macromolecular components and can be employed therapeutically as an adjuvant in vaccines or as carriers for drugs in which the active ingredient dissolves and is entrapped, encapsulated, adsorbed, or chemically linked. NPs may have various benefits due to their tiny size; however, only the smallest NPs permeate the membrane of the mouth *via* the paracellular pathway and in limited quantities since the tight junctions have temperatures on the order of 3.9 to 8.4 A°. The use of NPs for the intravenous administration of medicinal medicines has shown controversial results.<sup>36</sup>

### **Nanogels**

Nanogels (NGs) also comprise high-viscosity systems that incorporate nanoparticles (NPs, microcapsules, NEs, etc.) embedded in a polymer network. These systems were not very interesting until the recent advancements in precision dosage devices. The benefits of NGs include reduced mucociliary clearance because of increased viscosity, reduced taste effect due to decreased post-nasal drop into the nasopharynx,



reduced discomfort due to soothing/emollient excipients, and targeted distribution to the mucosa for improved absorption. The route of delivery influences the deposition of NGs within the nasal cavity, since higher viscosities reduced these systems respond to the effect of reduced deprived spreading capacities.<sup>37</sup> Well-designed application devices are essential for appropriate NG distribution. Without specific applicators, they only have a small distribution area throughout the nasal cavity and are administered directly. *In-situ*, gelling substances are introduced into NG formulations to address spreadability issues.

### Liposomes

Liposomes are made up of phospholipid bilayers that surround several aqueous compartments that are where medications and other things can be ingested. Liposomal drug delivery methods have several benefits, including the effective encapsulation of tiny and bulky molecules with a wide hydrophilicity range. According to certain studies, liposomes enhance nasal consumption of peptides, including calcitonin, *via* increasing membrane permeability. The increased absorption is ascribed to the extended retention duration of peptides, protection of encapsulated peptides against enzymatic deficiency, and increased mucosal membrane distraction.<sup>38</sup>

### Microspheres

Microspheres are widely used as effective formulations for medicinal administration *via* the nasal route. To counteract mucociliary clearance, mucoadhesive polymers such as chitosan, gelatin, alginates, etc., are used during formulation, resulting in prolonged contact duration and greater drug absorption. Furthermore, microspheres are an excellent delivery mechanism for medications that are susceptible to enzymatic degradation, and they can offer prolonged drug release if needed. Gelatin microspheres containing insulin revealed a strong hypoglycemia impact in rats following nasal administration, contrasting dry powder form, contrasting the solution of insulin.<sup>39</sup>

### Carbon Nanotubes

Carbon nanotubes (CNTs) are emerging technologies in nanomedicine, including nanobiotechnology. This is due to their ease of manipulation and modification, which may be accomplished by biopolymer encapsulation or covalent attachment of solubilizing groups to exterior walls and tips. CNTs are made entirely of carbon atoms arranged in a sequence of condensed benzene rings that have been rolled up into a tubular form. CNTs are categorized into single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNs). CNTs can also be examined for nose-to-brain targeted medication administration by contemplating surface engineering methods to boost the bioavailability and therapeutic efficacy of medicinal drugs that are otherwise difficult to administer by any other route.<sup>40</sup>

### Quantum Dots

A so-called quantum dot (QD) represents a nanocrystal made up of semiconductor components that display quantum

mechanical features due to their nanoscale size. The success of QD applications in imaging, sensing, and detection has prompted the scientific community to expand this platform toward drug delivery studies. Because of their ability to clarify the pharmacodynamics and pharmacokinetics of therapeutic drugs, the creation of traceable drug delivery carriers constitutes one of the most promising uses of QDs for establishing design principles for drug carrier development. Cadmium QDs have been shown to have neurological effects, but a recent study found that they have the potential for direct nose-to-brain transport. This work demonstrates the fast absorption of QDs through the brain/olfactory bulb *via* axonal transport followed by short-term inhalation.<sup>41</sup>

### Polymeric Nanoparticles

The decision about the kind of polymer is critical for medication absorption due to the relationship between the polymeric matrix and the mucus protein chains. Polymer hydration causes swelling that prepares the polymer, enabling interaction with water and reducing polymer-polymer interactions. As a result, polymeric chains can interact by binding to the nasal membrane's mucus proteins. The polymer can temporarily restrict mucociliary movement, preventing the medication from being washed away and extending the duration the drug spends in contact with the nose tissue. At the same time, it protects the medicine from interacting with degrading enzymes. According to a recent study, galantamine (GAL), an inhibitor of acetylcholinesterase used in Alzheimer's disease, was incorporated within hierarchical porous carbon (HPC) for the reason that it improved drug loading up to 30% during nanoencapsulation along with the dissolution of the drug by its protection, considering that the drug has become water-soluble.<sup>42</sup>

### Transferosomes

Transferosomes are a relatively novel carrier technology used for regulated and potentially targeted medication delivery. It is a specialized category of vesicular drug delivery system that contains phosphatidylcholine as well as an edge activator. An edge activator is often a single-chain surfactant that destabilizes the lipid bilayers of vesicles, increasing their deformability. The existence of a potential direct association between vesicle elasticity as well as the amount of medication reaching the brain intranasally has been documented by Wong *et al.*<sup>43</sup> Throughout their investigation, transferosomes were created with phosphatidylcholine (PC) provided the lipid matrix as well as sodium deoxycholate (SDC), Span® 60, Cremophor® EL, Brij® fifty-eight, and Brij® 72 provided surfactants.

### Smart Gels

Smart medication delivery systems that respond primarily to physiological inputs have developed as novel medicinal drug delivery methods. Gel-based medication delivery systems have been created to treat various neurological illnesses that may be delivered intranasally. This non-invasive method improves medication absorption while reducing systemic side effects and

**Table 1:** Drugs as well as nanotechnology-based technologies, are being investigated for nose-to-brain delivery

Medication	Distribution system	References
Amiloride	Nanoemulsion	
Doxorubicin	Niosomes	
Didanosine	Nanoparticles	
Lidocaine HCl	Nanogel	
Lorazepam	Microparticles	
Melatonin	Gel suspension	
Methylprednisolone	Liposomes	
Odorranalectin	Cubosomes nanoparticles	
Neurotoxin-1	Nanoparticles	47-50
Olanzapine	Transfersomes nanoparticles	
Rivastigmine	Nanoemulsion nanoparticles	
Sumatriptan	Micellar nanocarriers	
Tacrine	Nanoparticles	
Tramadol HCl	Microspheres	
Valproic acid	Nanostructured lipid carriers	
Ziprasidone HCl	Nanoemulsion	
Zolmitriptan	Micellar nanocarriers	

bypasses the BBB. The extended residency of a medication formulation within the nasal canal is critical to effective intranasal drug delivery. *In-situ* gelation can be triggered by a variety of factors, including temperature, pH, and ionic-based. Someone *in-situ* gel composition can be a beneficial technique for nasal delivery of medicines produced carbamazepine (CBZ) gel utilizing 2% carbopol 974P to test the effectiveness of the medication in reaching the brain subsequent intranasal administration.<sup>44</sup> Following intranasal administration, the amount of CBZ in the cerebral cortex was considerably much greater than that in the plasma. *In-vivo* experiments found that administering CBZ-loaded nanoemulgel intranasally significantly delayed convulsions and protected animals against both chemical and electrical stimulations. The findings show that intranasal administration of CBZ-laden nanoemulgel might be a potential alternative for the treatment of epilepsy.<sup>45</sup>

**Nanoemulsions**

Nanoemulsions (NEs) are somewhat dispersions around two immiscible liquids employing an average diameter of 100 nm that are frequently stabilized by a surfactant(s). The systems in question are isotropic and thermodynamically stable. NEs utilized for nose-to-brain administration are usually O/W emulsions. Surfactants are a key constituent within a nanoemulsion system because they minimize surface tension while avoiding phase separation as well as the formation of globules. Surfactants are substances have also been demonstrated to improve permeability by functioning as permeation enhancers. However, lowering the surfactant content might be one way to lessen the risk of toxicity.

Mucoadhesive polymers are sometimes included in their formulation to impede nasal clearance. Nanoemulsions also address the issue underlying nasomucosal clearing. Iqbal and colleagues created a nanoemulsion enabling the nose-to-brain transfer of letrozole (LET) to reduce the peripheral adverse effects of LET<sup>46</sup> Table 1.

**Inhalation Devices Readily Accessible in the Market**

As has been widely discussed, intranasal administration is a viable alternative to therapies that need brain action since the power source, the ophthalmic nerve exists in direct touch with the outside world within the nose cavity. This method allows the medicine to come into contact with the facial nerve, but it must be delivered in the upper section of the nasal passageway. This was a difficulty for many researchers, but great progress has been made in the creation of effective nasal delivery systems suitable for N2B administration of medicinal drugs. Dr. Djupesland proposed the Xhance exhalation delivery system (EDS). It consists of a device incorporating fluticasone propionate intended to enhance intranasal medication therapy. Xhance uses optinose technology to administer a liquid medicine formulation for nasal congestion and polyp therapy. This gadget contains two spouts: one to be put in the mouth while the other to the nasal cavity.<sup>51</sup> Whenever, the patient exhales *via* the spout, the medicine is discharged through the highest section of the nasal cavity because of the pressure imposed upon it by the expired air, and the resulting action forms a hermetic grip on the soft palate, isolating the nose traveling the mouth and lungs. As a result, the medicine is delivered unidirectionally to the brain, leaving no sadness in other sections. The drug’s direct influence on the brain *via* this EDS is currently investigated using oxytocin. Xhance is intended for adult patients, but its safety among pediatric patients is still being investigated due to the corticosteroid’s side effects, such as reduced growth in children. The European Union recognized the prospective of this strategy and awarded a multidisciplinary consortium funding in 2017 for a project titled “nose to brain delivery of an API through the power source olfactory region to facilitate the regenerative treatment regarding multiple sclerosis utilizing novel multifunctional biomaterials combined with an innovative medical device”. The goal of this research is to build an N2B-patch containing a hydrogel matrix that is in touch with the epithelium that lines the nose and releases the medication into the brain towards multiple sclerosis therapy, however, the device may be altered to deliver additional classes of pharmaceuticals.<sup>52</sup>

**CONCLUSION**

The IN route appears to be a potential method of administration due to several benefits, offering a *viable* alternative to more typical systemic administration routes. A number of pharmaceutical businesses are thus focusing their efforts on this treatment method. The field of science is actively investigating IN-DDS, including polymeric along with lipid-based microparticles as well as nanoparticles, in order to optimize these systems over systemic, local, pulmonary, as

well as N2B action, with the primary goal of delivering drugs to a particular point of action and controlling their release to reduce the amount of administration. The present article is intended to update the scientific literature regarding IN-DDS, highlight major achievements made to date, and provide researchers with fascinating information that will help to build more efficient IN-DDS. The previously intranasal drug delivery system, which has been researched for a variety of different CNS illnesses, can be used as a platform technology and applied to epilepsy therapy approaches.

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