

## Recent Approaches of Intranasal to Brain Drug Delivery System

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### ABSTRACT

While the intranasal administration of drugs to the brain has been gaining both research attention and regulatory success over the past several years, key fundamental and translational challenges remain to fully leveraging the promise of this drug delivery pathway for improving the treatment of various neurological and psychiatric illnesses. In response, this review highlights the current state of understanding of the nose-to-brain drug delivery pathway and how both biological and clinical barriers to drug transport using the pathway can be addressed, as illustrated by demonstrations of how currently approved intranasal sprays leverage these pathways to enable the design of successful therapies. Moving forward, aiming to better exploit the understanding of this fundamental pathway, we also outline the development of nanoparticle systems that show improvement in delivering approved drugs to the brain and how engineered nanoparticle formulations could aid in breakthroughs in terms of delivering emerging drugs and therapeutics while avoiding systemic adverse effects.

**Keywords-** BBB, Intranasal route, drug delivery, brain disorder.

### I. INTRODUCTION

The brain is one of the most intricate and important organs in the body; it processes information received from the sense organs and controls the majority of the body's functions. Movements, both voluntary and involuntary, the release of hormones, the storing of memories, and the operations of many other organs are all under its command [1]. Because it plays such an important part in the functioning of the human body, the brain is guarded both on the outside and the inside. Cerebrospinal fluid (CSF), the CSF-blood barrier, and the blood-brain barrier (BBB) all work together to provide an additional layer of defense for the brain, in addition to the protection provided by the skull's multiple layers of membranes that prevent injury from

the outside environment. These barriers contribute to the homeostasis of the brain and help prevent any ill consequences, including damage to the tissue, infections, endotoxins, and other potentially dangerous substances [2,3].

The integrity of these protective mechanisms can be compromised by a variety of factors, including physical trauma, genetic mutation, and the natural process of aging, which can result in neurological diseases. Because the brain is the control center for the entire body, any damage to this regulatory center has a negative impact on both the physical and mental health of the individual. According to the World Health Organization (WHO), the number of deaths that were caused by Alzheimer's disease and other dementias more than doubled between the years 2000 and 2019, moving

it up to the position of the seventh top cause of death worldwide [4]. In many parts of the world, dementia and other neurological conditions, such as stroke, epilepsy, and Parkinson's disease, are major contributors to hospitalization and death rates. In 2016, neurological illnesses were the largest cause of disability-adjusted life-years (the total number of years of life lost combined with the number of years lived with a disability), and they were the second leading cause of death [5]. Patients who are afflicted with persistent neurological illnesses have an increased risk of developing depressive symptoms and having thoughts about ending their own lives [6].

These debilitating neurological conditions can be treated with a variety of various medicinal medicines that have been developed by researchers. However, the primary purpose of these medications is to slow down the progression of sickness; they are not capable of entirely reversing the condition [7]. The presence of the blood-brain barrier (BBB), which prevents more than 98% of neurotherapeutic compounds from entering the central nervous system (CNS) [8, is one of the primary reasons for this restricted therapeutic efficacy. Capillary endothelial cells, astrocyte end-feet that surround the exterior of brain capillary endothelial cells, and pericytes that are embedded in the capillary basement membrane are the components that make up the blood-brain barrier (BBB). [9] Because capillaries are non-fenestrated vessels with tight connections, the paracellular pathway that these therapeutic compounds can take through the capillary network is restricted. In addition, P-glycoprotein and other ATP-binding cassette transporters keep therapeutic medications from building up in the brain by pumping those molecules out of the organ [10,11]. The paracellular route of drug delivery is limited by tight junctions, so the most likely pathways for drug transport to the central nervous system are the transcellular route, receptor-mediated endocytosis, and carrier-mediated transport. The drug molecule must be highly lipophilic, and its molecular weight must be less than 500 da. However, in order to make use of these different pathways of drug entry into the brain, a drug or delivery vehicle needs to meet precise conditions in order for this to occur [12,13,14,15]. Additionally, circumventricular organs with permeable endothelial cells of capillaries as well as specialized permeability zones of the brain have the potential to also be utilized for the transport of medicines to the tissues of the brain [16]. In order to circumvent this physiological barrier, a number of researchers have developed alternate treatment methods, such as intracerebroventricular injections and intrathecal injections. By injecting neurotherapeutic chemicals intracerebrally or intracerebroventricularly, it is possible to achieve a high concentration of these molecules in the brain. However, in order for the injection solution and the drug itself can be injected directly into the brain structures, they must first fulfill a number of parameters, including those

pertaining to pH, volume, diluents, and preservatives. This presents a number of challenges for the use of alternative delivery channels for the brain [17]. Intrathecal injection is becoming more prevalent in the treatment of cancer in the central nervous system, particularly in oncology; nevertheless, its applicability in neurology is still limited. The implantation of electrodes in the brain, which is known as deep brain stimulation, is a treatment for Parkinson's disease that has demonstrated substantial progress. Having said that, this procedure is a technique that is both invasive and expensive [18]. There are also implantable drug reservoirs with sustained drug release that are employed for local brain administration [19,20]. One example of this would be the GLIADEL® Wafer.

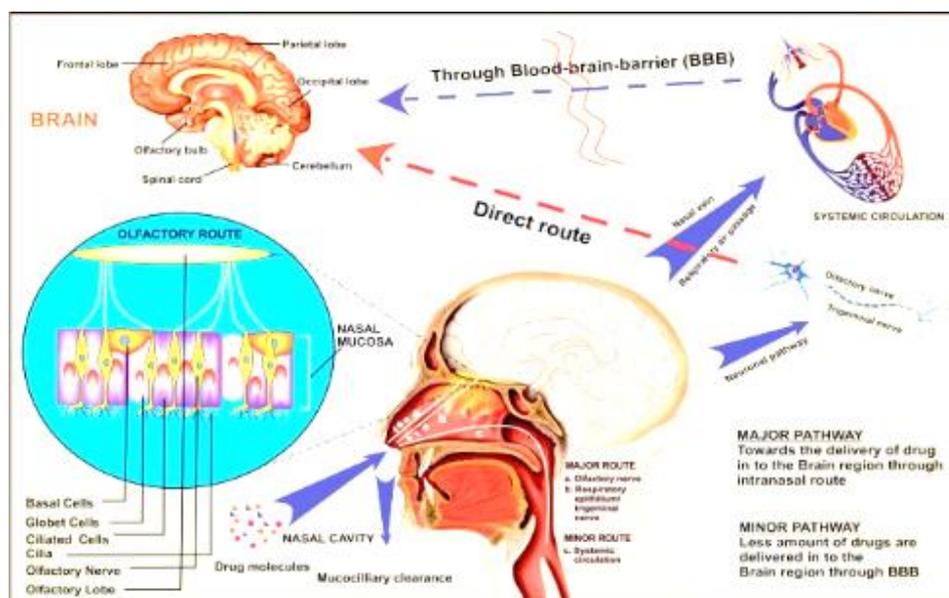
The intranasal delivery system has received attention as a potential method for drug delivery to the brain because all of the aforementioned techniques are intrusive and expensive. In the past, intranasal administration has been utilized to facilitate the production of local effects for the purpose of rhinitis or allergy treatment. In spite of this, intranasal delivery has also been utilized for systemic distribution since it possesses a number of advantageous qualities, such as the fact that it is non-invasive, that it has a high patient compliance rate, and that it is simple to administer. It has been demonstrated to be effective in the flu vaccine, pain and migraine management, smoking cessation, and other areas, which has led to an increase in the number of applications it is finding in the market [21]. Numerous studies have demonstrated that intranasal delivery of both small compounds and big molecules is capable of directly targeting the brain. The olfactory mucosa is the area that is not protected by the BBB, and it is in direct touch with the brain. Additionally, it has the ability to lessen the accumulation of therapeutic molecules in the major organs, such as the liver, spleen, and kidneys, which would lead to a reduction in the severity of the systemic adverse effects [22,23].

The current review provides a comprehensive synopsis and analysis of the current landscape of nose-to-brain (N2B) delivery for nanotherapeutics from a wide range of perspectives, including but not limited to mechanistic biology, transport kinetics, formulations, and clinical applications in both recent and historical context. In this article, we go into deeper detail on the anatomy of the nose, possible paths of N2B delivery, problems linked with those respective routes, fundamental pharmacokinetic characteristics, and expressions. In addition, the utilization of numerous nanotherapeutic strategies for N2B administration is evaluated in the context of neurological and other CNS illnesses.

Olfactory nerves continue to maintain a direct connection to the frontal cortex and specifically the olfactory bulb of the brain from the top area of the nasal cavity, which is known as an olfactory region. In addition to this, the sensory neurons of the trigeminal

ganglion and the blood arteries that supply them continue to be present in the center and the greatest part of the nasal cavity, which is known as the respiratory area. When a medicine is delivered into the nasal cavity, it must first clear the mucociliary barrier in the vestibular region before it can enter the nasal cavity. In addition, the drug molecule travels to the inside of the nasal

cavity, where it interacts with the neural network as well as the blood vessels that line the respiratory epithelium (olfactory and respiratory epithelium) (Crowe et al., 2018). The substance entered the systemic circulation from the blood arteries and was dispersed throughout the body in accordance with the relative volume of distribution.



**Figure 1: Transport of drugs from the nasal cavity to the brain happens in two ways: first, via the neuronal pathway, which travels through the olfactory and trigeminal sensory neurons; second, via the systemic circulation.**

This systemic bioavailability continues to be a secondary route of drug transport to the brain, with the BBB serving as the primary entry point for the drug into the brain. According to Lochhead and Thorne (2012), the direct neuronal pathway is another way that drugs can be delivered to the brain. This pathway is considered to be the primary way that drugs can be delivered to the brain. In this pathway, drugs follow intracellular and extracellular transport mechanisms to enter different regions of the brain via olfactory and trigeminal sensory neurons. Although it was anticipated to take the combined route to enter the brain, the precise process by which drugs are transported from the nasal cavity to the brain is still a topic of debate among experts. In addition, the drug transport mechanism is dependant on a variety of elements including the nature of the drug, the type of delivery system or dosage form, a device that is used for IN application, formulation parameters, experimental circumstances, and physiological conditions. It has been shown that the excipients included to the formulation in order to improve the drug retention time (such as a gelling agent and mucoadhesive polymers), a permeation enhancer, and the drug carrier system all have a major impact on the amount of drug that is present in the brain. In addition, the medicine is absorbed through the neural route more quickly if the formulation is aimed to the posterior upper region (olfactory region) of the nasal cavity. This is the case when the formulation is inhaled.

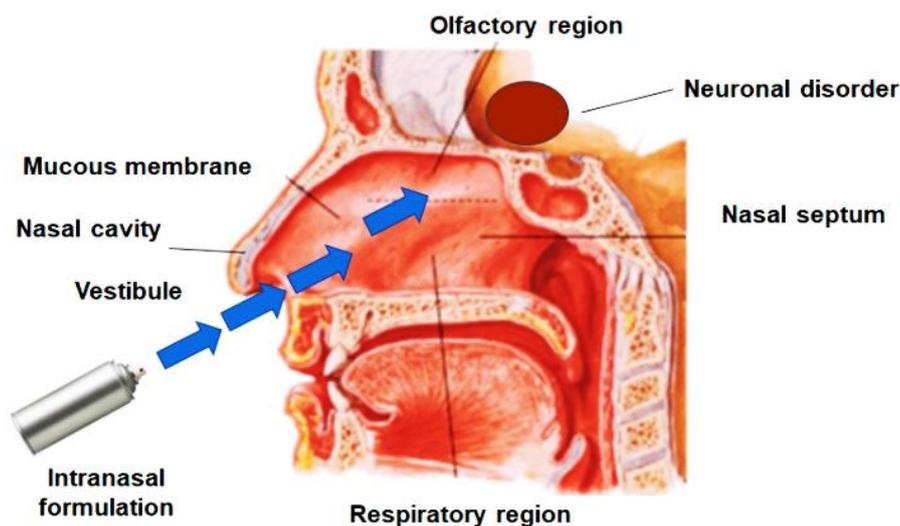
## II. PATHWAY OF DRUG DELIVERY SYSTEM THROUGH INTRANASAL ROUTE

In order for nasal drug delivery systems to be successful, it is critical to have a solid grasp of the anatomy and physiology of the nasal cavity. The vestibule, the respiratory region, and the olfactory region are the three distinct regions that can be found within the nasal cavity. Because of the vestibule region's limited surface area, the amount of medication that is absorbed here is negligible. After intranasal administration, the respiratory region, on the other hand, can offer systemic drug absorption and, as a result, indirect drug transport to the brain [11,12]. This is because the respiratory region has a high concentration of blood capillaries. [13] Research has shown that the trigeminal nerves, which are found in the respiratory region, can also function as a direct route for drug transport to the brain. For instance, it has been noticed that the respiratory region is the one that is most suited for the delivery of vaccinations by intranasal administration. This is because the respiratory region contains the most nasal passages. In addition to this, the olfactory area contributes significantly to the process of directly delivering drugs to the brain as well as the cerebrospinal fluid (CSF). It is important to note that the olfactory region is located in the upper section of

the nasal cavity; this may limit the amount of medications that are able to reach this permeability area [1,14].

The primary purpose of these different drug delivery channels is to transport the required amount of medicine to the location where it will have its effect. In addition, the breakdown of medications that occurs during metabolism can be slowed down, and physical clearance can also be reduced; an overview of drug transport can be found in Figure 2 [15]. Due to a high total blood flow, porous endothelium membrane, wide surface area, and the avoidance of first-pass metabolism, highly permeable nasal epithelium enables rapid drug absorption into the brain. This is possible because of the huge surface area. A wide variety of therapeutic medicines, both small compounds and macromolecules,

can be delivered to the central nervous system via the intranasal route. Several different medications have been demonstrated to be more effective in the central nervous system (CNS) when they are administered via the nasal route, meaning that lesser doses are required to achieve the desired therapeutic effects. In addition, the therapeutic agent does not need to be altered in any way, nor does the medicine need to be linked to any carrier in order to be administered via the nasal route. Nasal drug administration, which can take place via a variety of different pathways, has been and will continue to be an important development area for pharmaceutical as well as medical device firms because it offers significant advantages over other methods of drug delivery [16,17]. The routes that can be taken for delivery from the nose to the brain will be discussed in more detail below.



**Figure 2: Illustration of the path that drugs take on their way from the nose to the brain.**

Given the direct connection between the brain and the nasal cavity described above, IN delivery offers a unique way to circumvent many of the primary challenges around treating CNS disorders (i.e., the BBB and peripheral toxicity). However, delivery via the IN route also creates new challenges that need to be considered in the design and development of novel drug formulations for CNS disorders.

#### **Chemical Limitations**

Physicochemical properties of the drugs such as size, molecular weight, and lipophilic-hydrophilic balance significantly limit which drugs can be delivered intranasally and the efficacy of nasal drug absorption. Mucus comprises 90–95% water and thus represents a partitioning-based physiological barrier to the transport of many hydrophobic and highly lipophilic drugs (including many antipsychotics) as well as a diffusive barrier to the transport of larger molecular weight drugs to the nasal epithelium [40]. In addition, while small lipophilic drugs such as progesterone and dimethyl fumarate (DiF) are quickly absorbed through the nasal epithelia, the permeability of large molecules such as

peptides and proteins (> 1 kDa) is limited [41, 42]. In general, drugs with a molecular weight < 300 Da can sufficiently permeate the epithelium for direct CNS delivery while substances > 1 kDa tend to get stuck in the mucus [43]. Particle size also affects the amount of drug absorbed, as larger droplets are rapidly cleared given that they are more likely to cause irritation and reflexive sneezing [44].

#### **Biological Limitations**

The nasal mucosa represents a significant barrier against the transport of substances from the external environment to the brain. IN administration of liquid-based formulations can undergo rapid elimination by MCC in as little as ~ 12–15 min, while an additional (often significant) amount is lost due to drainage down the nasopharynx, which limits the contact time for drug absorption [24, 45]. The nasal mucosa also contains defensive metabolic enzymes that act to protect the nasal cavity from harmful xenobiotic substances [46]. However, these enzymes can also metabolize drug products and other small molecules administered intranasally [47], changing their solubility profile and/or

their chemical structure to alter drug activity and/or permeation properties [48]. Furthermore, analogous to the P-glycoprotein pumps in the BBB, p-glycoprotein pumps have been discovered in the nasal and olfactory epithelium, septum, sinonasal mucosa, inferior turbinate, and the olfactory bulb, in some cases reducing the absorption of low molecular-weight drugs [49–51]. Therefore, to maximize CNS absorption and minimize degradation, both slowing clearance and protecting the drug from enzymatic metabolism must be considered when developing and testing new drug-delivery vehicles.

#### **Local Tissue Damage**

Although, significantly less invasive than intracerebral injection for direct CNS administration [52–54], toxicity is a significant concern, especially for chronic conditions (like many CNS disorders) that require repeat treatment administration. Potential adverse effects include nasal irritation, itching, epistaxis, alterations in smell and taste, rhinosinusitis, and damage to the nasal and olfactory epithelium [54]. Maintaining the pH of IN-administered formulations around human nasal pH (5.5–6.5) is also critical for minimizing the risk of nasal irritation and tissue damage [55]; however, many antipsychotics including aripiprazole [56], clozapine [57], olanzapine [58], risperidone [59], and quetiapine [60] are moderately basic in solution, such that prolonged IN use could cause irritation and irreversible damage.

Toxicological considerations are relevant not only for the drug but also for the excipients within the formulations, including preservatives, surfactants and/or other absorption enhancers that may affect cellular contact [15]. In particular, drug formulations containing mucoadhesive agents that function to increase contact time with the nasal epithelium and/or penetration agents that disrupt cellular junctions within the nasal mucosa can pose increased risks of toxic effects. For example, tight junction modulators *Clostridium perfringens* enterotoxin (CPE) and *Zonula occludens* toxin (Zot) reversibly open tight junctions to facilitate paracellular drug absorption through nasal epithelia [61, 62], while the C-terminal fragment of CPE (C-CPE) disrupts tight junctions through modulation of claudins and has been used to increase absorption of human parathyroid hormone in rats [63]. However, toxicity is a major concern with such modulators, with repeated administration shown to increase C-CPE-specific serum IgG levels [64]. Hence, derivatives of these absorption enhancers have been synthesized to decrease toxicity and are currently being evaluated for IN administration in vivo [65, 66]. Some drugs can also affect the ciliary beat frequency (e.g. atropine) [67, 68] or inhibit ciliary movement (e.g. local anesthetics such as ketamine/xylazine and fentanyl) [69], increasing the potential for adverse effects.

Changes to or a loss of the sense of smell as a result of IN delivery can also be problematic since olfactory function contributes significantly to the flavour

of food and is essential for detecting external hazards such as gas or fire [70, 71]. Indeed, a zinc-containing nasal decongestant spray known as Zicam was withdrawn from the US market in 2009 after it was shown to cause anosmia in some users [72]. Olfaction dysfunction can also diminish the quality of life by decreasing appetite and general enjoyment of aromas [73, 74], reducing long-term patient compliance.

#### **Patient Heterogeneity**

Nasal tolerability depends on many individual factors such as pre-existing illness, allergies, or infections, and patient differences in pH and metabolizing enzymes, influencing how drug formulations interact with the nasal mucosa and their subsequent absorbance [15]. Infections can change the pH and enzymatic makeup of the nasal cavity, and thus affect drug absorption and toxicity; for example, chronic bronchitis can increase nasal pH to 7.6–7.8 [75]. Race and gender differences could also contribute to differences in drug delivery due to related differences in olfaction or respiratory function [76, 77]. Given that many controlled-release vehicles are pH-sensitive, such individual differences in nasal pH may affect how drugs are absorbed, introducing variability in dosing not seen with other routes of administration [55].

#### **Volume Limitations**

A major disadvantage of the IN route is the small nasal cavity size and small surface area for absorption compared with the gastrointestinal tract or the circulatory system. This limits the volume of drug formulation that can be administered to ~200 µL, significantly restricting the utility of IN delivery to only the most potent drugs. This is particularly true when factoring in the significant drug losses to systemic circulation, swallowing, inhalation, or other clearance mechanisms [18, 37]; for example, esketamine, the S-enantiomer of ketamine approved as a nasal spray under the trade name Spravato, shows a bioavailability of ~48%, significantly higher than that of oral esketamine (~8%), but still suggesting that the majority of the drug is cleared through other mechanisms [78]. Currently approved IN drugs for CNS diseases are available in milligram doses (e.g. esketamine, sumatriptan, diazepam, midazolam, and naloxone) (see Table 1), although only small doses in the nanogram range are actually needed for the therapeutic effect in the brain [16].

#### **Consistency of Administration**

Since the olfactory region has a small surface area (~5–10 cm<sup>2</sup>) and is located in the upper part of the nasal cavity, targeting this region can be challenging and result in improper dosing [79]. Drugs intended for the olfactory nerve pathway, if improperly administered, may be absorbed in the highly vascularized respiratory region, limiting the amount of drug reaching the brain and increasing peripheral side effects. Administration devices such as bi-directional nasal insufflators and nasal atomizers are designed to facilitate distribution to

specific regions of the nasal cavity while limiting lung deposition. However, the accuracy of these devices is complicated by patient-device interactions, which can result in significant variability in dosing. For example, while IN administration of insulin had been used in small-scale pilot studies to preserve cognitive performance in patients with AD and mild cognitive impairment (MCI) with great success [80], a larger phase 2/3 study revealed feasibility issues associated with the self-administration device. Of the 289 patients administered 40 IU insulin daily in the randomized, double-blind clinical trial, 49 used one administration device that was soon discontinued due to inconsistent dosing reliability; the remaining 240 patients used a new device that, while avoiding any apparent operational issues, resulted in no differences in cognitive (ADAS-cog-12), functional, or cerebrospinal fluid (CSF) markers between the insulin- and placebo-treated groups. This result was attributed to limitations in the consistency of administration between patients [81], and highlights the need for proper IN administration devices that are easy to use. Another recent study examining the quality of daily administration of IN corticosteroid sprays also found that most participants improperly administer the nasal spray according to the recommended steps, and concluded that administration techniques are inadequate in most patients [82]. As such, translational success of N2B delivery vehicles requires addressing this key point.

#### **Airway Flow**

For humans and most animals, the preferred airway is through the nose; as such, treatment of CNS disorders through the nasal cavity may interfere with natural breathing patterns. As almost half of an adult's total airway resistance is nasal, minor increases in nasal resistance can have significant effects on breathing [83]. Repeat use of nasal sprays or mucoadhesive agents can cause drug-induced rhinitis, inflammation, and congestion of the airways, either due to the drug itself or the additional excipients. In addition, the nasal cycle aims to keep the airway surface hydrated and enables each passageway to take turns in either predominantly undertaking the air-conditioning or mucus clearance functions; this can pose a dosing consistency challenge for drug doses that are not administered to both nostrils evenly [84].

#### **Animal Model Limitations**

Rodents are often used as test subjects in preclinical studies; however, differences in anatomy, limited volume, and administration techniques can limit the translatability of rodent results to humans. While the general structure of the rodent nose is similar to that of humans, the surface area of the olfactory epithelium (the primary contact point for nose-to-brain delivery) accounts for 50% of the surface area of the nasal cavity in laboratory rats but only 10% in humans [85]. The significant difference in relative target area in these models may overestimate the efficacy of many

formulations, leading to poor translational results. The small surface area of the rodent nasal cavity also greatly limits the amount of drug formulation that can be administered. In mice, the maximum volume of a drug solution that can be administered is 20–30  $\mu\text{L}$  (for formulations that do not persist in the nasal mucosa) in 1- to 2- $\mu\text{L}$  increments with a 3- to 4-min rest period between each inhalation, requiring between 30 and 45 min per animal [86]. The typical need for anesthesia for IN delivery in animals (again unlike with humans) further extends this required experiment time and may alter transport kinetics [87]. Devices engineered to allow for the IN administration of multiple mice simultaneously can increase feasibility; for example, a mouse-positioning device capable of holding four to eight anesthetized mice in head-down-and-forward position at a time was found to enable more efficient IN administration [86]. The typical use of pipetting for IN rodent delivery may also be a poor representation of practical IN administration techniques in humans that are almost uniformly based on aerosolization. Spray devices have been developed but pose challenges regarding variability in pressure uniformity and dose dispensed and effectiveness. The single-dose electronically pressurized spray device reported by Piazza et al. for IN delivery of nanoparticles to rats in part addressed this concern, with only 50–100  $\mu\text{L}$  of a haloperidol-loaded NP suspension inducing a cataleptic response in rats and transport to the olfactory bulb and striatum at a higher concentration than with a pipette [88]; however, such devices are not trivial to use and are designed for clinic-only use rather than at-home use. As such, not only the formulation but also the delivery mechanism of the formulation (in both animal models and human clinical use) is critical for successful IN delivery.

### **III. CONCLUSION**

AD was regarded as a primary cause of death in senior as well as young age populations all over the world by the healthcare organisations, and it was anticipated that the disease's severity would increase in the foreseeable future. Because of this, a treatment that is not only effective but also non-invasive and affordable would be really welcome. The intravascular drug delivery system offers a feasible method and is anticipated to be the therapy of the next generation for the treatment of brain diseases. In addition to receiving treatment, prevention is almost invariably regarded as the superior method for leading a healthy life. Because Alzheimer's disease is a complex disorder, its development is dependent on a variety of pathogenic factors (including genetic alterations, mutations, aging, and lifestyle factors associated with aging). Instead, it was found that a lower risk of AD is associated with living a healthy lifestyle and maintaining appropriate eating habits. In most of the world's industrialized nations, such as the United States and Europe, the

prevalence of AD is at an all-time high. Nevertheless, the risk of AD in some countries, such as India, continues to be lower. The consumption of a variety of antioxidants and neuroprotectants (such as curcumin, piperine, and quercetin) as spices in food on a regular basis, in addition to spending more time outside as opposed to living a machine-based lifestyle, is most likely the reason for this phenomenon. This is due to the fact that the lifestyle and dietary habits in question entail such things. To summarize, leading a healthy lifestyle can help prevent disease, but from a treatment standpoint, the IN route provides a direct, potentially effective, and convenient approach to treating brain diseases with the appropriate clinical studies. The administration of medication through the nasal passages directly into the brain presents an opportunity for the treatment of Alzheimer's disease (AD). The method is currently being researched, and so far, there have been a number of successful lab scale studies as well as significant obstacles to overcome before reaching the pharmacy counter. The researchers who are working in this stream have a fantastic opportunity to investigate the topic and conduct in-depth study in order to gain a deeper grasp of disease pathology, drug distribution in the brain, pharmacokinetic and pharmacodynamic factors, and experimental methodologies. We hypothesize that the development of a successful IN formulation will result from an all-encompassing investigation that takes into account and finds solutions for all of the potential stumbling blocks.

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