Review Article

NOVEL APPROACH FOR NOSE-TO-BRAIN DRUG DELIVERY BYPASSING BLOOD BRAIN BARRIER BY PRESSURIZED OLFACTORY DELIVERY DEVICE

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ABSTRACT

Although there is presence of a dense network of the cerebral vasculature, systemic delivery of therapeutics to the central nervous system (CNS) is infective for greater than 98% of small molecules and for nearly 100% of large molecules. This is imputable to the presence of the blood brain barrier (BBB), which prevents most foreign substances, even many beneficial therapeutics, from getting into the psyche from the systemic circulation. Certain small molecules, peptide, and protein therapeutics given systematically reach the brain parenchyma by crossing BBB but high systemic doses are required to reach a therapeutic level that contributes to adverse effects in the physical structure. The BBB is a system of layers of cells at the cerebral capillary endothelium, the choroid plexus epithelium, and the arachnoid membranes, which are linked by tight junctions (zonulae occludens) and which together separate the mind and the cerebro-spinal fluid (CSF) from the line. These tight endothelial junctions can be 100 times tighter than junctions of other capillary endothelium. Therefore, the barrier has many attributes similar to a continuous cell membrane, allowing lipid soluble molecule transport across the membrane where hydrophilic solutes demonstrate minimal permeation. Different strategies have been developed to cross the BBB have been involved, such as synthesis of small molecules to exploit existing Carrier-Mediated Transport (CMT) or re-engineering large molecules with molecular 'Trojan horse' delivery systems. These approaches may allow transport via Receptor-Mediated Transfer (RMT) systems in the BBB. An alternative approach is targeted intranasal delivery, which is potentially applicable which covers broader area of molecules, where the goal is to circumvent, rather than cross, the BBB.

***Keywords*:** Blood Brain Barrier, Peptide, Proteins, Hydrophilic Solutes, Permeation, Trojan Horse Delivery System

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INTRODUCTION

One of the significant indicators of Blood Brain Barrier (BBB) transport is drug distribution into Cerebro Spinal Fluid (CSF). The Blood CSF Barrier (BCSFB) is comparatively leakier as compared to BBB, and the rate of molecules entering CSF is inversely related to molecular weight. [1] The finding of drug penetration into the CSF is expected for any molecule, and does not provide information on rates of drug penetration across the BBB at the brain capillary endothelium. Therefore, drug distribution in CSF is simply a measure of shipping across the choroid plexus at the BCSFB rather than an index of BBB transport. The idea that CSF composition reflects BBB transport was first observed in Goldman's vital dye experiments in 1913 [2].

Before 1913, it found that certain acidic vital dyes, such as trypan blue, are precluded from entering into the brain following peripheral administration, and it was explained, not within the context of a barrier between blood and mind, but preferably because the brain lacked the 'receptors' that bind the dye and sequester the molecule inside the tissue. Goldman injected the trypan blue into the lumbar sac, or subdural space, of rabbits and it was assured that vital dye staining of spinal cord and brain tissue, respectively. Thus, the brain expressed vital dye binding sites. The failure to stain the brain following peripheral administration of the dye was hypothesized to be ascribable to a 'Blut-Gehirn schranke' or BBB. Notwithstanding, in 1913, it was believed that the pathway of nutrient flux from blood to brain took place across the choroid plexus. The anatomical site of the BBB was erroneously placed at the choroid plexus [2].

Until the 1990s, nose to brain transport was unnoticed when enhanced public attention to brain research encouraged scientists to identify and implement effective treatment strategies in an attempt to combat the upsurge of age-related neurodegenerative diseases and related neurological disorders in an increasingly elderly patient population. Difficulty in the treatment of brain disease and stroke is that many drugs known to mitigate the damaging effects of such pathologies are unable to enter the brain from the systemic circulation due to the blood-brain barrier (BBB). Nonetheless, because the olfactory sense organ cells are in direct touch with both the surroundings and the cardinal nervous system, the olfactory pathway offers a possible means of circumventing the BBB to deliver neuroprotective agents directly to the head. So, intranasal delivery of drugs targeting the CNS is now an alternative direction for drug administration [3, 4].

Depositing therapeutic drugs on the olfactory epithelium has been proven to lead to rapid and direct uptake into the psyche. This direct nose-to-brain delivery route bypasses the blood-brain-barrier, which holds a majority of drugs or drug candidates from reaching the brain in any significant concentrations. Despite its potential, direct "nose-to-CNS" distribution is underutilized in clinical settings because of lack of drug delivery devices to target olfactory region [5]. The olfactory epithelium, which is situated between the nozzle and the mastermind, is only 3–10% of the open region of the nasal cavity in humans [6, 7]. Its location in the upper nasal cavity with turbinate restriction makes consistent delivery of drug to this region challenging. Pressurized olfactory drug delivery device (POD) is an aerosol nasal spray having a narrow spray plume with circumferential velocity. The gimmick is planned to displace the residual olfactory air volume to deliver therapeutic compound in the olfactory area of the nasal cavity [8].

Pressurized olfactory drug delivery device is an aerosol nasal spray having a narrow spray plume with circumferential velocity. The gimmick is planned to displace the residual olfactory air volume to deliver therapeutic compound in the olfactory area of the nasal cavity. In one view, the pressurized olfactory drug delivery device comprises a container bearing a mixture of a pressurized fluid and a therapeutic compound, a delivery device defining a longitudinal axis connected to the container and causing an outlet opening at the nasal-proximal end, a cylindrical channel connected to the release of the container and stretching to the exit opening, and a plurality of discharge outlets radically disposed around the longitudinal axis, wherein each discharge outlet is oriented to discharge the pressurized fluid mixture in an axial and circumferential direction. The device further comprises a metering device for selectively releasing the pressurized fluid through the wall sockets, such that the outlets produce a relative majority of aerosol spray discharges comprising the therapeutic compound that converge into a single spray plume having a circumferential helical velocity [8].

In a second aspect, the pressurized olfactory drug delivery device includes a container comprising a assortment of a pressurized fluid and a therapeutic compound; a delivery device in communication with the container, the delivery device having a large number of longitudinal helical channels, each helical channel comprising an inlet and an outlet disposed at the nasal proximal-most end of the device; and a metering device for selectively releasing the pressurized fluid mixture through the helical channels. The releases are

configured to discharge a plurality of aerosol spray jets comprising the pressurized fluid mixture that converge into a single spray plume having a circumferential helical velocity as the spray leaves the device [8].

ANATOMICAL AND PHYSIOLOGICAL OBSTRUCTIONS HAMPERING THE DELIVERY OF FORMULATIONS TO THE NOSE

Various physiological and anatomical barriers which hinder the delivery of drug molecules to the nose includes nasal valve and aerodynamics, nasal cycle, nasal mucosa filtration and its clearance, nasal - sinus vascular and lymphatic system, the sensitivity of Nasal mucosa and enzymatic degradation through enzyme present in the nasal cavity.

Nasal valve and Aerodynamics

Nasal valve is narrow, constricted and is located approximately 2–3 cm from the nostril, with a mean cross-sectional area of only 0.5–0.6 cm^2 on each side [9]. The nasal valve is the narrowest segment of the entire respiratory tract, accounting for as much as 50–75% of the total airway resistance and represents an often underestimated hurdle for nasal drug delivery [10]. The nasal valve plays a key and dynamic role in carrying through a prime purpose of the nose as an air temperature regulator, a particle filter and an efficient scrubber to remove hazardous particles and gaseous/vapour phase pollutants, and protect the sensitive lower airways from hazardous exposures. In addition, vigorous nasal inhalation/sniffing – often undertaken in an endeavour to get air or medication deep into the nasal cavity – creates a negative pressure that actually causes dynamic narrowing and even crack up of the nasal valve, especially in the upper narrow regions of the valve. Therefore, simply a very minor fraction of the inspired air actually gets to the olfactory region during nasal breathing. Still, to increase olfactory air flow and optimize olfaction the valve collapse associated with sniffing can be at least partially neutralized by the voluntary activation of dilating muscles of the nostrils known as 'flaring' [11].

In the context of nasal drug delivery, and in particular for drug delivery to the upper portions of the nose housing the olfactory nerves, the small dimensions and dynamic inspiratory obstruction represent essential and often ignored obstacles for efficient nasal drug delivery of all types, and particularly for nose-to-brain drug delivery where access to the most superior and posterior sections of the nasal cavity is especially trusted.

Nasal Cycle

The turbinates and the medial (septal) and lateral walls of the nasal cavity contain richly vascular 'erectile' tissues that are responsible for a normally observed physiological cycle, switching between sides, of congestion and decongestion observed in 80% of healthy individuals [11, 12]. Due to this reciprocal 1–4 h autonomic cycling of mucosal swelling, at any given time one of the nostrils is generally considerably more congested with most of the air flow going through the other nasal passage while a stable total combined intranasal resistance is maintained [12]. The autonomic cyclic change in airflow resistance is primarily dependent on the blood content of the submucosal capacitance vessels that constitute the erectile component at critical sites, notably the nasal valve area. Furthermore, the erectile tissues of the septal and lateral walls and the turbinates respond to a diversity of stimuli, including physical and sexual activity and emotional states that can modify and override the basic cyclic rhythm [13]. The cycle may also cause accumulation of nitric oxide (NO) in the congested passage and adjacent sinuses and contribute to defense against microbes through direct antimicrobial action and enhanced mucociliary clearance [14]. Due to the cycle, one of the nostrils is considerably more congested than the other most of the time, and the vast

majority of the airflow passes through one nostril while the other remains quite narrow especially in the valve region. Accordingly, the nasal cycle contributes significantly to the dynamics and resistance in the nasal valve region and must be brought into consideration when the efficiency of nasal drug delivery devices is thought [15].

The Nasal Mucosa—Filtration and Clearance

The region anterior to the nasal valve called the foyer is lined by non-ciliated squamous epithelium that in the valve region gradually transitions into ciliated epithelium typical of the ciliated respiratory epithelium posterior to the valve region. Beyond the nasal valve, the nasal turbinate divides the nasal cavity into slit-like passages with much larger cross sectional area and open area. Hither, the predominantly laminar airflow is slowed down to velocities of 2–3 m/s and disrupted with eddies promoting the deposition of particles carried. The respiratory epithelium is cut through by a normal mucus layer which helps remove noxious gases and to trap particles smaller than 3–10 μm. Trapped particles and infectious agents behind the nasal valve are moved posterior by the beating cilia at a mean pace of 6–10 mm/min where they are shown to the abundant specialized lymphatic tissues of the nose and nasopharynx and ultimately swallowed (nasal mucociliary clearance). It leases approximately 10–20 min for a particle deposited at the principal of the inferior turbinate to reach the root of the tongue [14, 15]. The density and pulse frequency of cilia varies. However, contrary to common perception, recent gamma deposition studies suggest that the clearance from the upper nasal segment, including the olfactory region is as fast as from the other selected regions of the nose. Powder seems to be cleared somewhat slower, perhaps due to the time it accepts for the powder to dissolve; only in general particles have only minutes available for absorption or receptor binding. Excipients that slow or temporarily halt ciliary action may increase the residence time for a drug and may be beneficial for delivery of some drugs and in treatment for some indications, but may also introduce adverse effects on tolerability, reduce the surface covered by the drug, add complexity of formulation work, and possibly add to regulatory hurdles [13-15].

Nasal and Sinus Vasculature and Lymphatic System

The lymphatic drainage follows a similar pattern as the venous drainage where the lymphatic vessels from the vestibule drain to the external nose to the submandibular lymph nodes, whereas the more posterior parts of the nose and paranasal sinuses drain towards the nasopharynx and internal deep lymph nodes [14]. In the context of nasal drug delivery, perivascular spaces along the olfactory and trigeminal nerves acting as lymphatic pathways between the CNS and the nose have been implicated in the transport of molecules from the nasal cavity to the CNS.

For nasally delivered substances, the site of deposition may influence the extent and rate of absorption along with the target organ distribution. Branches of the ophthalmic and maxillary arteries supply the mucous membranes covering the sinuses, turbinates, meatuses, and septum, whereas the superior labial branch of the facial artery supplies the part of the septum in the region of the vestibule. The turbinates located at the lateral nasal wall are highly vascularized with a very high blood flow and act as a radiator to the airway. They contain erectile tissues and arteriovenous and anastomoses that allow shunting and pooling related to temperature and water control and is largely responsible for the mucosal congestion and decongestion in health and disease. Substances absorbed from the anterior regions are more likely to drain via the jugular veins, whereas drugs absorbed from the mucous beyond the nasal valve are more likely to drain via veins that travel to the sinus cavern, where the venous blood comes in direct contact with the walls of the carotid artery. A substance absorbed from the nasal cavity to these veins/venous sinuses will be outside the blood–brain barrier (BBB), but for substances such as midazolam, which easily bypass the BBB, this route of local “counter-current transfer” from venous blood may provide a faster and more direct

route to the brain. Subject fields in rats support that a preferential, first-pass distribution to the brain through this mechanism after nasal administration may exist for some, but not all small molecules [15].

Sensibility of the Nasal Mucosa as a Limiting Factor

In summation to the limited access, obstacles imposed by its small dimensions and dynamics, the high sensitivity of the mucous membrane in the lobby and in the valve area is really relevant to nasal drug delivery. Direct contact with the tip of the spray nozzle during actuation, in combination with localized concentrated anterior drug deposition on the septum, may create mechanical irritation and injury to the mucosa resulting in nosebleeds and crusting, and potentially erosions or perforation. The purpose of the high sensitivity of the nasal mucosa as a natural nasal defense is too frequently omitted when the potential of nasal drug delivery is discussed, in particular when results from animal studies, cast studies, and computer fluid dynamics (CFD) are measured. Exposure to chemicals, gases, particles, temperature and pressure changes, as well as direct tactile stimuli, may cause irritation, secretion, tearing, itching, sneezing, and severe pain. Sensory, motor, and parasympathetic nerves are affected in a bit of nasal reflexes with relevance in nasal drug delivery. Such sensory inputs and related reflexes are inhibited by the anesthesia and/or sedation often applied to lab animals, potentially setting the clinical predictive value of such works. Farther, the lack of sensory feedback and absence of interaction between the device and human subjects/ patients are important limitations of in vitro testing of air flow and deposition patterns in nasal casts and in CFD simulation of deposition. Consequently, deposition studies in nasal cast and CFD simulation of air flow and deposition are of value, but their predictive value for the clinical setting are all too often overestimated [14, 15].

Nasal Enzymatic Degradation

Another contributing (but normally considered less significant) factor to the low transport of especially peptides and proteins across the nasal membrane is the possibility of an enzymatic de-gradation of the molecule either within the lumen of the nasal cavity or during transit across the epithelial barrier. These sites both contain exo-peptidases such as mono- and diaminopeptidases that can cleave peptides at their N and C terminal and end-peptides such as serine and cysteine, which attack internal peptide bonds [16].

Pathways for Nose to Brain Drug Delivery

The olfactory epithelium is a pathway for substances entering the CNS and the peripheral circulation. The neural connection between the nasal mucosa and the brain is a unique pathway for the intranasal delivery of therapeutic agents to the CNS [17]. The olfactory neural pathway provides both an intraneuronal and extraneuronal pathway in the mind. The intraneuronal pathway involves axonal transport that takes hours to days for drugs to reach different brain areas. Whereas the extraneuronal pathway involves transport through perineural channels, which deliver drugs directly to the brain parenchymal tissue and/or CSF. The extraneuronal pathway shows faster pathway as therapeutic agents reach the CNS within minutes. Intranasal delivery of agents to the CSF is not surprising as CSF normally drains along the olfactory axon bundles as they traverse the cribriform plate of the skull and approach the olfactory submucosa in the roof of the nasal cavity, where the CSF is then diverted into the nasal lymphatic. The transfer of drugs across the nasal membrane and into the bloodstream may involve either passive diffusion of drug molecules through the pores in the nasal mucosa or some sort of non-passive transport [18].

In order to reach the neurons in the brain, substances in the blood must cross the tight endothelial barrier of the brain capillaries (the blood–brain barrier), or first cross the more ‘leaky’ barrier of the choroid plexus into the CSF and subsequently cross the barrier between the CSF and the brain interstitium (blood–CSF

barrier). The olfactory filaments penetrate the nasal mucosa of the upper portion of the nose and substances may be carried within the nerve axon (intracellular). Shipping across the mucosa also occurs between the cells (paracellular) or through the cells (transcellular). After crossing the mucous substances may follow channels surrounding the nerve bundles (perineuronal), be absorbed into submucosal blood and lymphatic vessels or move into the subarachnoid CSF where they may enter the brain interstitum via perivascular channels. The trigeminal nerve endings do not get across the mucosal surface. Substances must cross the mucous membrane and continue on the same transport routes as identified supra. A division of the ophthalmic branch (V1) innervates the upper anterior nasal segment with similar projections as the olfactory nerve. The maxillary branch (V2) provides sensory and parasympathetic innervation to the majority of the respiratory mucosa and projects to the brain stem [19].

FORMULATION CONSIDERATION FOR NASAL DRUG DELIVERY

Molecular weight and size

Molecular weight (MW) and size also controls the drug permeation through the nasal cavity. Bioavailability usually ranges from 0.5% to 5% for compounds with molecular weight around 1Kilo Dalton like proteins and peptides [20]. A direct relationship exists between the MW and drug permeation in case of lipophilic agents, whereas water soluble compounds show an opposite relationship. Further, it has been reported from various works, that the rate of drug permeation is highly sensitive for molecules with molecular weight >300 Dalton, while permeation for drugs having molecular weight <300 Dalton is not much influenced by the physicochemical properties of the drug because most of them permeate through the aqueous channels of the membrane [21, 22]. The particles having a size bigger than 10 microns can be administered through nasal administration because they could get lodged in the nasal cavity, whereas too fine particles having size below 5 microns should be warded off as they are inhaled directly into the lungs [23].

Lipophilicity

Being nasal mucosa primarily lipophilic in nature, the nature of the drug acts as an significant function in absorption. The lipid part plays a vital purpose in the barrier role of these membranes, although they have some hydrophilic characteristics. The permeation of the compound through the nasal mucosa normally increases with an increase in the lipophilicity of the drug [24]. Various lipophilic drugs like naloxone, buprenorphine, testosterone and estradiol are almost completely absorbed, when administered through the nasal route [25, 26]. However, the drug permeation through the wall also reduces when lipophilicity is too high because drug does not dissolve sufficiently in the nasal secretions. So a balance between the two factors is necessary [27].

$_{p}$Ka and partition coefficient

In general, the passage across biomembranes is affected not only by lipophilicity/hydrophilicity, but also by the amount of drug existing as uncharged species. This depends on the drug pKa and the pH of the absorption site (5.0-6.5 in human nasal mucosa). According to the pH partition theory, the non-ionized fraction of a drug is more permeable than that ionized. For the nasal mucosa, a range of studies evaluating the effect of lipophilicity and pH on the absorption of small drugs was performed. All of them demonstrated that nasal absorption of weak electrolytes depends on their ionization degree and the largest absorption occurs in the nonionized species. In this state, they present a higher apparent partition coefficient and, thus, they are more lipophilic. Nevertheless, drugs such as acetylsalicylic acid and benzoic acid showed some permeability across the membrane even in environments that they are expected to exist as the ionized species. Based on these observations, it was concluded that, for polar drugs, partition coefficient is the major factor influencing the permeability through nasal mucosa [28].

Solubility

Drug dissolution is a pre-requisite for any drug absorption, since only the molecularly disperse form of a drug at the absorption site may cross the bio membranes. Hence, before nasal absorption the drug must be dissolved in the watery fluids of the nasal cavity. Therefore, of the utmost importance is the appropriated aqueous drug solubility to allow enough contact with the nasal mucosa and posterior absorption. Withal, the absorption profile is influenced not only by drug solubility but also by the nature of pharmaceutical preparations, which have to guarantee the delivery of drug at therapeutically relevant doses. Due to the small size of the nasal cavity, the allowable volume of drug solution is low for intranasal drug administration [29].

Stability

During the development of new drug formulations biological, chemical, physical and drug stability studies must be a matter of the major importance in all process. As discussed before, the environment of the nasal cavity has the ability to metabolize drugs by defensive enzymatic mechanisms, which may reduce the biological stability of nasally administered drugs [29].

Osmolarity

The tonicity of the formulation also affects the drug absorption. The hypertonicity of the solution cause shrinkage of the nasal epithelium and also inhibits the ciliary activity. Hence, an isotonic solution is mostly chosen for optimum results [30].

Viscosity

The high viscosity of the formulation increases the time for drug permeation by increasing the residence time of the drug in the nasal mucosa. In gain, highly viscous formulations also interfere with the normal functions of the cilia like ciliary beating or mucociliary clearance and thus finally affect the drug permeability. Some studies suggested that by administering highly viscous formulations the residence time can be increased, but there could be diminished drug absorption due to decreased drug diffusion from the formulation. Further, it has also been reported that the viscosity of the solution provides a larger therapeutic period of the nasal formulations [31].

Dosage form

Nasal drops are the simplest and most convenient pharmaceutical dosage form, but the dose is not reproducible and often results in overdose [32]. Moreover, rapid nasal drainage with these drops makes them unsuitable. Solution and suspension sprays are preferred than powder sprays because the later cause mucosal irritation [33]. Nowadays metered dose gel devices are used that delivers the drug more accurately and gels also localize the formulation in the nasal mucosa, which enhances the drug residence time in the nasal cavity and diminishes mucociliary clearance and thus potentially results in better absorption [34].

POLYMERS USED IN NASAL DRUG DELIVERY

Cellulose Derivatives

Different cellulose derivatives are seen to be effective on enhancing the intranasal absorption of drugs such as Hydroxypropyl Methylcellulose (HPMC), Hydroxypropyl Cellulose (HPC), Methylcellulose (MC), and

Carboxymethyl Cellulose (CMC), and insoluble cellulose derivatives such as Ethylcellulose and Microcrystalline Cellulose (MCC).

Cellulose derivatives can markedly prolong the residence time of drugs in the nasal cavity due to their desirable mucoadhesive property. Additionally, due to their high viscosity following hydration in the nasal cavity, the celluloses can sustain the release of drugs. For these reasons, using celluloses as an absorption enhancer can lead to improved intranasal absorption and increased bioavailability. Many references show that the celluloses are effective in increasing the intranasal bioavailability of small hydrophobic as well as hydrophilic macromolecular drugs. For example, administered nasally with CMC, apomorphine can obtain a relative bioavailability of 102% compared with subcutaneous injection in rabbits. The peptide drugs, leuprolide and FD-4, when dosed with MCC/HPC through nasal route, turned over an absolute bioavailability of 34.9% and 35.5% in rabbits, respectively [35].

Polyacrylates

Polyacrylates have been investigated very frequently in many drug administration routes, like nasal drug delivery systems, due to their excellent mucoadhesive and gel-forming capability. Among the pharmaceutical polyacrylates, carbomers, and polycarbophil, which differ in the cross-linking condition and viscosity, are widely used in the nasal mucoadhesive drug delivery systems. Polyacrylates, capable of attaching to mucosal surfaces, can offer the prospects of prolonging the residence time of drugs at the sites of drug absorption, and ensure intimate contact between the formulation and membrane surface. Studies by Ugwoke *et al*. in rabbits reported that the use of Carbopol 971P in nasal dosage forms increases their residence time in the nasal cavity. The percentage of the formulations cleared from the nasal cavity at 3 hours was 24% for Carbopol 971P, while it was 70% for lactose. Prolonged release of drugs can also be obtained by using polyacrylates in nasal formulation, which result in a more stable blood concentration-time curve [34, 35].

Chitosan

Chitosan is a linear polysaccharide biopolymer produced by deacetylation of chitin, the main component of crustacean's exoskeleton. Due to its biodegradability, biocompatibility and bio adhesive properties associated to a low toxicity, Chitosan is widely used in intranasal formulations. It is believed that it interacts with the protein kinase C system and opens the tight junctions between epithelial cells increasing Para cellular transport of polar drugs. Moreover, it interacts strongly with nasal mucus layer enhancing the contact time for the transfer of the drug across the membrane. Finally; Chitosan also enhances the dissolution rate of low water soluble drugs. Consequently, Chitosan is used in several intranasal pharmaceutical forms, including powders, liquids, gels, microparticles and microspheres. For some drugs, it is well documented that the addition of Chitosan to nasal formulation increases drug bioavailability [36].

Cyclodextrins

Cyclodextrins are cyclic oligosaccharides composed of glucose units joined trough α-1, 4-glycosidic bonds resulted from bacterial digestion of cellulose. Structurally, they take in a hydrophilic counter surface and a lipophilic central cavity where polar drugs can be included. Cyclodextrins are used as complexing agents to improve nasal drug absorption by increasing the drug solubility and stability. They can work as absorption enhancers, since they interact with the lipophilic components of biological membrane changing their permeability. Although widely used in intranasal medicinal preparations; Cyclodextrins present some local and systemic toxicity. Moreover, alterations of nasal morphology, ciliary beat frequency, erythrocyte haemolysis and cytotoxic effects have also been reported [29, 34-35].

Lectins

Lectins are classified as a group of structurally diverse proteins that are found in plants as well as in the animal kingdom. Lectins have the capacity to identify and bind to specific sugar moieties. The sugar-binding moiety of most lectins is only a small part of the lectin, i.e., a major portion of lectin is not involved in the recognition and binding to the receptor. Lectins also cause agglutination due to their ability to cross link sugar containing macromolecules. The various lectins which have shown specific binding to the mucosa include lectins extracted from *Ulex europaeus I*, soybean, peanut and *Lens culinarius*. Lectins have the ability to stay on the cell surface or become internalized via a process called endocytosis if the adhesion is receptor mediated. Lectins have potential to be used in Nasal Drug Delivery; especially where internalization of the drug encapsulated nanoparticles is of particular importance such as DNA delivery [37].

Thiomers

Thiomers are mucoadhesive polymers that have side chains carrying thiols which lead to the formation of covalent bonds between the cystiene groups in the mucus and the polymer by thiol/disulphide exchange reactions or simple oxidation process. These adhesions are also known as disulphide bridges. These bridges sometimes improve mucoadhesion by 100 congregations. They also have a permeability enhancing effect and the ability to control the rate at which drugs are released. This property and increased mucoadhesion lead to higher residence time of the drugs administered in combination with thiomers hence improving their bioavailability. Thiolated polymers display in situ gelling properties due to the oxidation of thiol groups at physiological pH-values, which results in the formation of inter- and intramolecular disulfide bonds. This increases the viscosity of the formulation coupled with extensive crosslinking due to formation of disulphide bonds with the nasal mucosa, which increases the residence time of the formulation tremendously [37].

Alginate poly-ethylene glycol acrylate

Alginate Polyethylene glycol Acrylate is also recognized by the acronym Alginate-PEGAc. It has an alginate backbone with acrylated polyethylenglycol groups attached to it. This polymer meshes the properties of alginates (strength, simplicity and gelation) with characteristics specific to the acrylate functionality of PEG like mucoadhesion. PEG's have the ability to penetrate the mucus surface while the acrylate group of the polymer reacts with the sulphide group of glycoproteins present in the mucus. This solution in a potent interaction between the mucus and the polymer. It is expected to be cross-linkable by two different paths: chemically via the acrylate end groups and physically through the alginate backbone. Alginate is a mucoadhesive polysaccharide of 1 → 4 linked α-l-glucuronic acid and β-d mannuronic acid which binds to the glycoproteins in the mucus through carboxyl–hydroxyl interactions. It is anionic in nature. It is known to undergo ionic sol to gel transition (gelation) upon interaction with multivalent ions such as Ca^{2+}, Fe^{2+}, thus reducing its adhesion to mucosal tissues [34, 37].

Poloxamer (Pluronics)

Poloxamers are made up of non-ionic difunctional triblock copolymers containing a centrally located hydrophobic polypropylene oxide between hydrophilic polyethylene oxides. Aqueous solutions of poloxamers are extremely stable in the presence of acids, alkalis and metal ions. These polymers are readily soluble in aqueous, polar and non-polar organic solvents. Hence, they are widely preferred choice as excipients in formulations. Poloxamers are said to contain thermoreversible property and will convert from a liquid to a gel at body temperature, thus, causing in situ gelation at the site of interest preventing the drug to be removed from the nasal cavity due to mucociliary clearance. This vastly improves the bioavailability of the drug administered [34, 36].

PRESSURIZED OLFACTORY DEVICE (POD)

The device comprises a pressurized tank suitable for storing a pressurized fluid, such as a compressed gas or propellant. The compressed gas may be compressed air, nitrogen, or any other suitable non-toxic gas. The propellant may be a pressurized fluid such as chlorofluorocarbon (CFC) or hydrofluoroalkane (HFA). The pressurized tank is fluidically connected by tubing to a pneumatic solenoid. The pneumatic solenoid is fluidically connected by tubing to an air chamber. The air chamber is linked via an internal compartment to a nasal delivery device having an applicator with an orifice suitable for discharging an aerosol spray into the nasal cavity. The nasal delivery device comprises a generally elongated tubular housing having an exterior and interior and a first opening or orifice at one end (the nasal proximal end) that is radially aligned about the longitudinal axis of the housing, the housing being closed at the other end (the nasal distal end). The housing is preferably cylindrical in shape; however, any tubular shape may be practiced. The housing further comprises a conically shaped applicator at the proximal end adjacent to and surrounding the orifice. The housing surrounds a generally tubular, cylindrically shaped fluid reservoir that runs on an portion of the longitudinal axis of the housing. The fluid reservoir has a proximal second orifice disposed near the first orifice of the housing, the second orifice having a diameter smaller than that of the first orifice and being generally radially aligned about the longitudinal axis of the housing. The proximal end is conically shaped adjacent to and surrounding the second orifice. The proximal portion of the fluid reservoir has a diameter narrower than the diameter of the housing, thereby forming a channel extending from the distal portion of the reservoir to the orifice. The distal portion of the fluid reservoir has a wider diameter, such that the exterior surface of the fluid reservoir contacts the interior surface of the housing, creating a seal that prevents the flow of pressurized gas in a distal direction. The fluid reservoir further comprises an elongated needle whose long axis runs along the longitudinal axis of the housing and is moveable disposed within the interior proximal portion of the fluid reservoir. The proximal end or tip of the needle is configured to seal the second orifice of the fluid reservoir. The fluid reservoir preferably is provided with a vent to prevent a vacuum that would increase the pressure required to remove fluid from the second orifice [38, 39].

The housing further comprises a spin chamber defined by the space between the interior surface of the housing and the exterior surface of the fluid reservoir. The housing further comprises a compressed gas inlet that is in communication with the spin chamber and fluidically connected to the pneumatic solenoid. The spin chamber further comprises a coiled wire that wraps around the exterior of the fluid chamber, the coiled wire having a helical or corkscrew shape and extending from the gas inlet to the proximal orifice [38].

When a user determines to discharge the pressurized nasal spray, the pneumatic solenoid is activated by a programmable timer to release the pressurized gas from the tank for a predetermined amount of time. The pressurized gas released from the tank travels through tubing to the air chamber and through the air chamber into the gas inlet of the housing, thereby introducing the spin chamber of the nasal delivery device. The pressurized gas that goes to the spin chamber encounters the coiled wire, causing the pressurized gas to flow around the exterior surface of the fluid reservoir in a helical or corkscrew-shaped path, such that the gas acquires a circumferential helical velocity or vortex-like velocity having circumferential vector and axial vector components. The term circumferential velocity also includes tangential velocity, helical velocity, vortical velocity, and similar terms [38, 39].

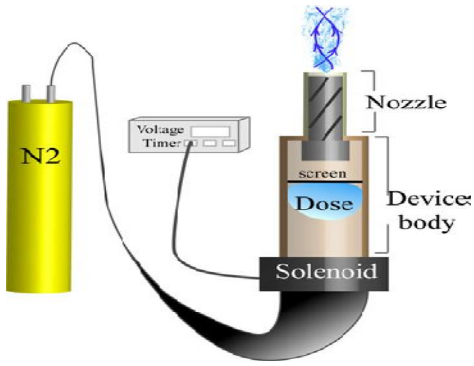

Figure 1 Schematic presentation of the pressurized olfactory delivery device. The pressurized nitrogen is controlled by a pneumatic solenoid which releases the gas in increments of 0.1 s. The gas gets the nozzle outlet and mixes with the liquid dose, which flows through the outlet producing a narrow flow with rotational velocity [39].

When the solenoid is triggered, the elongated needle disposed within the fluid reservoir is retracted from the orifice, thereby offering a narrow gap for the fluid within the fluid reservoir to escape. As the pressurized gas leaves the orifice, it produces a partial vacuum which pulls fluid out of the reservoir through the orifice. The fluid is aerosolized due to the slimness of the opening. The aerosolized spray is discharged from the nasal spray device as a spray plume having a circumferential velocity and axial velocity as the spray plume enters the nasal cavity. The circumferential velocity has the advantage that the aerosol spray penetrates the upper nasal cavity allowing direct deposition of aerosolized therapeutic compounds on the olfactory epithelium [38].

Patents on Pressurized Olfactory Device

Table 1 Patent on Pressurized Olfactory Device

Year	Title	Publication number	Applier	Reference No.
2014	Medical unit dose container	WO2014179228A1	Impel Neuropharma Inc	[40]
2014	Nozzles for nasal drug delivery	EP2707146A1	Impel Neuropharma Inc	[41]
2012	Nasal drug delivery device	WO 2012119153 A2	Impel Neuropharma Inc	[42]
2011	Circumferential aerosol device	US 20110048414 A1	Impel Neuropharma Inc	[38]

EVALUATION OF PRESSURIZED OLFACTORY DELIVERY DEVICE (POD)

Actuation Volume

A fluorescence assay was used to determine if the total desired volume was dispensed from the device with each actuation. A solution of 50 µg/ml fluorescein was dispensed from the device into a well in a 24-well plate that was profiled with 1 ml deionized H_2O. After collection of the aerosol, the solution was mixed by pipetting up and down several times. Three volumes 5, 10, and 25 µl which could be used for rat nasal delivery were tested at two different pressures, 20 and 30 pounds per square inch. The fluorescence of the solution was measured on a PerkinElmer 1420 multivariable fluorescence plate reader. The fluorescence signal of the collected volume was compared with the expected signal to estimate the percentage of drug

expelled from the device with each actuation. The device produced consistent volume, suitable for targeting the dispensed aerosol. At 10 µl doses, the device dispensed the set volume with 99.3±2.6% accuracy [43].

Spray Rate

The spray rate was tested by changing the driving pressure from 1 to 6 pounds per square inch and the diameter of the orifice. The spray rates were reproducible and within the desired range for human application, namely less than 50 microliters per second [38, 43].

Particle Size

Particle size distribution was determined by spraying water from the device into viscous oil at a distance of 2 cm and 4 psi. A total of 199 measurements was made. The distribution showed that the device produced particles having diameters of from 5 to greater than 50 microns, and that the majority of the particle diameters were between 5 and 20 micrometers, with an average diameter of 11.2 microns [43].

Similarly the aerosol droplet size distributions of the POD device were determined by a Phase Doppler Particle Analyzer using 200 mW argon laser emitting beams of 488 and 514.5 nm. Initially, the measurement volume was struck across the aerosol stream to determine the edges of the spray. Then, sizing measurements were determined at 1-mm intervals across the width of the spray, taking 30,000 measurements at each interval. Sizing data are presented as a volume weighted mean and span, defined in Equation below where Dv is droplet frequency distribution [43].

$$\text{Span} = \frac{¼\,Dv90 - Dv10}{Dv50}$$

The volumetric mean aerosol diameter of the solution using the POD aerosol device was 29.18 µm with a span of 9.5 µm using a device input pressure of 20 psi [43].

Nasal Cavity Deposition Testing

Dye deposition within the rat nasal cavity was determined after delivery with the POD device. When using 10 µl of dye, the POD administration resulted in deposition primarily in the olfactory epithelium area of the nasal cavity. The dye was found primarily in the posterior two-thirds of the olfactory turbinates and within the folds of the turbinates as well as deep within the nasal cavity along the cribriform plate region of the nasal cavity [43].

In the radiolabel drug experiments, it was quantified that relative amount of drugs on the respiratory and olfactory epithelia 30 min after delivery got a quantitative indication of the relative deposition on the respiratory and olfactory epithelia after nasal drug delivery. After POD administration, 68.3±7.1% of drug in the nasal cavity was found in the olfactory epithelium and 31.7±6.8% were found in the respiratory epithelium 30 min after drug administration [43].

Data Addressing Human Model for Nose to Brain Transport by Pressurized Olfactory Delivery Device

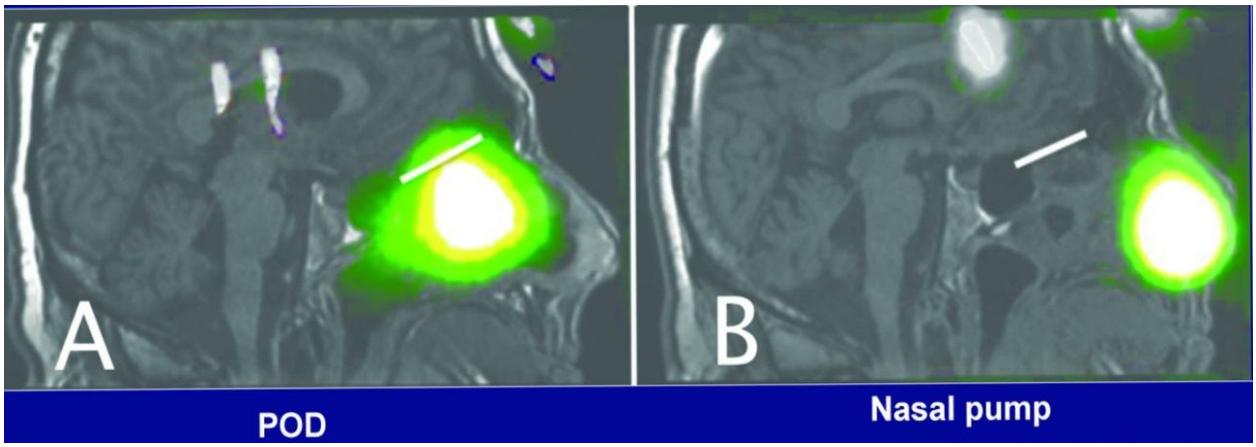

Figure 2 2D SPECT sagittal image showing the nasal deposition of the POD device (A) as compared to a standard nasal pump (B).The white bar identifies the cribriform plate where the nasal cavity is in direct contact with the CNS. [44]

The information piled up (John Hoekman, *et.al* poster presented at AAPS, 2013) showed increased drug targeting to the upper nasal cavity and lead to increased CNS concentrations and direct nose-to-brain delivery. Seven subjects were enrolled in this study. MAG-3 (mercapto acetyl triglycine), a technetium-99m labeled peptide, was presented as the radiotracer. This study investigated MAG-3 administration with Impel's POD nasal device in comparison with a traditional nasal pump. Imaging was performed on two separate days, one week apart. After tracer administration, 2D SPECT imaging was performed for 5 minutes. Then, 3D SPECT was acquired for 8 minutes begining at 10 minutes after tracer administration. An MRI was also acquired to provide detailed anatomical information. Pixel analysis of the nasal region of interest was applied to measure the radioactivity in each target nasal deposition region [44].

CONCLUSION

The intra nasal route has been an effective route for delivery of drugs directly to the brain, bypassing the blood brain barrier through the olfactory route. Different experiments provide evidence of effectiveness of the route. Although the route is effective it is still under clinical studies due to the lack of proper delivery device to target the olfactory region. Pressurize olfactory delivery Device has been shown to effective in delivering the drug to the target site. Different studies in animal and human model suggested that the deposition of the radiolabelled drug substances sprayed by the device deposited in the olfactory region in higher concentration as compared to traditional Nasal sprays. Similarly, higher drug concentration was also visible in the brain areas. These studies indicate that the device is effective for delivering therapeutics to the brain by passing the blood brain barrier. Future prospective of device will leads to the development of new types of biological CNS drugs, expand the number of potential clinical compounds, improve safety of existing drugs enable new drugs for Alzheimer's, Parkinson's, Brain Cancer etc.

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