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PULSATILE *IN SITU* GEL FORMULATIONS OVERVIEW TO OVERCOME CHALLENGES RELATED TO NOSE-TO-BRAIN DRUG DELIVERY

Rohit Sharma [1], Dr. Monika [2]*, Rupa Mazumder [3], Avijit Mazumder [4], Rashmi Mishra [5] and Malakpogu Ravindra Babu [6]

[1, 2, 3, 4, 5] Noida Institute of Engineering and Technology (Pharmacy Institute) 19, Knowledge Park-2, Industrial Area, Greater Noida, Uttar Pradesh, India.
[6] Lovely Professional University, Jalandhar.
*Corresponding Author Email: madhra1282@gmail.com

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Abstract

Smart polymer-based in situ gelling devices triggered by stimuli have gained popularity in the past ten years as a promising method of giving bioactive to treat a range of neurological conditions, from the nose to the brain. When exposed to a physiological stimulus, the polymers utilized to create pulsatile in situ gel tend to change from the solution phase to the gel. Studies have shown that by extending the native duration in the nasal fossae, the addition of mucoadhesive-ness substances enhances medication absorption through the nasal epithelium. By reducing mucociliary removal and enzymatic degradation and lengthening nasal residence time, in-situ mucoadhesive gel overcomes the drawbacks of nose-to-brain direct transport. This delivery method increases the bioavailability of medications to the brain as well as nasal absorption. This method can be used to deliver a variety of substances intranasal to a range of medicines including proteins, antibodies, peptides, vaccines, large and small-size lipophilic as well as hydrophilic compounds, genes, and Ribonucleic acid.

Keywords: Blood-Brain Barrier, Nasal Drug Delivery, Mucociliary Clearance, Nose To The Brain, Olfactory Transport, Alzheimer's Disease, Parkinson's Disease, Drug Delivery.

INTRODUCTION

According to the WHO[1], neurological illnesses are the number one global public health threat [1]. According to a Lancet Neurology report on GBD[2], neurological disorders are the leading cause of weakness, thereby affecting a population of almost 276 million, and are the second most deadly condition after heart problems. According to GBD, depending on the age and gender variations, how bad the illness can be described regarding passing away, DALYs, YLD, and YLL [2,3]. Every year, the number in terms of disease prevalence rises. There is a growing need for affordable, effective therapeutic approaches due to the rising number of neurological problem patients, particularly in underdeveloped countries where people cannot afford pricy and luxurious therapies [4]. There is currently a lot of study data available that claims to lessen the growing burden of CNS problems. However, due to the fact that absolutely no proven curative procedures (apart from those for AD, stroke, and idiopathic epilepsy) have been introduced into clinical practice to address the risk factors of neurological illnesses, all scientific assertions are still only valid on paper or in the laboratory [2]. As the population ages and diseases become more prevalent, there is a greater need for a tough robust system of risk management that includes affordable and effective courses, support, and rehabilitation networks. Contrarily, the poor facilities for treating the load of neurological illnesses necessitate the development of novel treatments and preventive measures, which calls for new understanding and tactics [5].

The typical CNS conditions are AD, PD, seizures or epilepsy, brain tumors or gliomas, migraines, MS, trauma to the brain, schizophrenia, cerebral palsy and strokes, Central nervous system infections, and many other psychiatric conditions like anxiety and depression [6]. Treatment options for CNS illnesses include surgery, deep brain stimulation, and rehabilitative therapy, and oral, topical, and IV dose forms [7]. Through neural transmission, including olfactory and trigeminal nerves, the IN way creates a contact link with the outside world and with the brain. It depicts a painless method of brain drug delivery in contrast to IN administration and surgical operations. It also gets around the oral pathway drawbacks by rejecting or avoiding the first-pass metabolism effect and GI drug deterioration [8, 9]. Additionally, the intranasal method also avoids BBB and delivers the medication to the brain directly to the cellular and trans-neural route [10]. It is a patient-friendly method for treating chronic illnesses due to its quick beginning of action, non-invasive therapy, non-invasiveness, and the convenience of administering and taking medication [11, 12]. The most associated problems with IN drug delivery, include mucociliary leeway, slow penetration of deliquescent substances, enzymatic deterioration, and poor residence time. Utilizing pulsatile mucoadhesive in situ gelation can overcome these restrictions [13, 14]. Smart polymers were used to create the pulsatile in situ gel; these compounds have a tendency to change uniformly in regard to physiological changes. When administered to the nasal cavity, the in situ gels formed with these compounds first take the form of a solution that goes through an alteration in phase (from sol to gel) in regard to heat stimulation, ionic concentration, and pH. The first solution form makes the formulation easier to handle both before and after giving. In contrast, the hard(gel) form lengthens the duration that the drug remains in the nose and makes it easier for it to pass past the nasal epithelium, which ultimately enhances the bioavailability of the API in the brain [15, 16, 17].

IN SITU GELATION

Numerous innovative technologies, including systems of nanocarrier, adhesive agents, and systems made of hydrogel or gel, has thoroughly researched to address the difficulties of nasal API administration, enhance nasal absorption, and increase the systemic circulation of neurotherapeutic drugs. Among these, in situ, gelations stand out as a potential method that lengthens the time that drugs are retained in the nasal cavity, decreases the amount of medication that is expelled through mucociliary clearance, prolongs the time that they are released, and increases the amount of medication that is absorbed [7, 18]. When administered into the bodily cavity, pulsatile in situ gel, a brand-new medication, displays a sol-gel transformation in response to the altered physiological environment. It starts off as a clear soln of compound(s) or a poor-viscosity liquid, but any external stimuli, such as a change in temperature, pH, an ionic change, in a magnetic field, a biological setting or an electrical signal, can cause it to turn into a viscous gel [19]. The two main categories of trigger mechanisms for the phase transformation of the pulsatile in situ gels are physical cross-linkage and chemical cross-linking. Physical crosslinking is typically chosen over chemical cross-linkage for in situ gelations owing to its simplicity of manufacture and safety profile. It is a common technique for in situ gelation that uses changes in pH, ionic modulation, and temperature as triggers [20, 21].

- **Thermo-Responsive System**

The term "thermoreversible in situ gel" refers to an apparatus that reacts to temperature changes and changes from solution to gel at a particular range of temperatures. It is made up of thermosensitive polymers that exhibit sol-gel transition between 25 and 37 degrees Celsius. In addition to this temperature extent, sooner or later gelation may happen; which is, a decreased temperature produces soln form or poor viscosity liquid, while an increased temperature causes the outer layer to gel instantly with soln trapped inside. Sooner gelation (soln form) makes administering and operating more challenging, while delayed gelation increases the risk of inside drug leakage [18, 22].

- **Poloxamer**

A Poloxamer is a tri-block, linear copolymer of the ABA type made up of hydrophilic PEO33 end-groups and a hydrophobic PPO34 core group [8]. It is commercialized under the name Pluronic and is frequently used as a thermoresponsive gelling agent and non-ionic surfactant. At a temperature of 25 °C, a thermoreversible gel is created by the concentrated solution of poloxamer [13, 23]. It is frequently employed in the pharmaceutical sector for the creation of innovative dosage forms due to its special gelling ability and harmlessness nature [24]. There are several different forms of poloxamers with different qualities that are accessible dependent on the height and makeup of the polymeric series, such as Poloxamer 181 (Pluronic L61), P407 (PF127), and P188 (PF68) [25].

- **Chitosan**

A naturally occurring, linear polysaccharide with cationic properties, chitosan is taken out of crustacean shells. It is made up of N-acetylated-D-glucosamine and deacetylated. It is a thermoresponsive polymer that is frequently employed in the pharmaceutical sector as a drug delivery system. Chitosan has a crystalline, stable compound structure that can be dissolved in an acid soln. By protonating the amine group in the chitosan structure, the acid soln causes the production of + charged molecules [26–28].

- **EHEC**

EHEC is an unusual mixture of irregularly disbursing water-loving and water-hating units in the compound backbone, making it an amphiphilic, non-ionic polysaccharide. The thermal nature of the EHEC is remarkably affected by the addition of an ionic surfactant e.g., SDS, cetyl triammonium bromide, etc. The EHEC interacts with the ionic surfactant and changes from a non-ionic state to a polyelectrolyte state [29, 30].

- **pH-responsive System**

Using polymers that go through phase transformation when the pH changes, pH-stimulated gelation is achieved. The principal pH-responsive substance that exhibits sol-gel transition in reaction to a considerable pH variation environment is carbopol (934 and 940). The nasal cavity has a pH of about 6.2. The carbopol-based series are originally kept between a pH of 4 and 5.5. Such a series experiences conformational changes in the presence of nasal fluid, forming a 3D network and undergoing soln-gel transmission [20, 31]. (Figure 1) provides an excellent explanation of the pH-triggered soln-gel transformation.

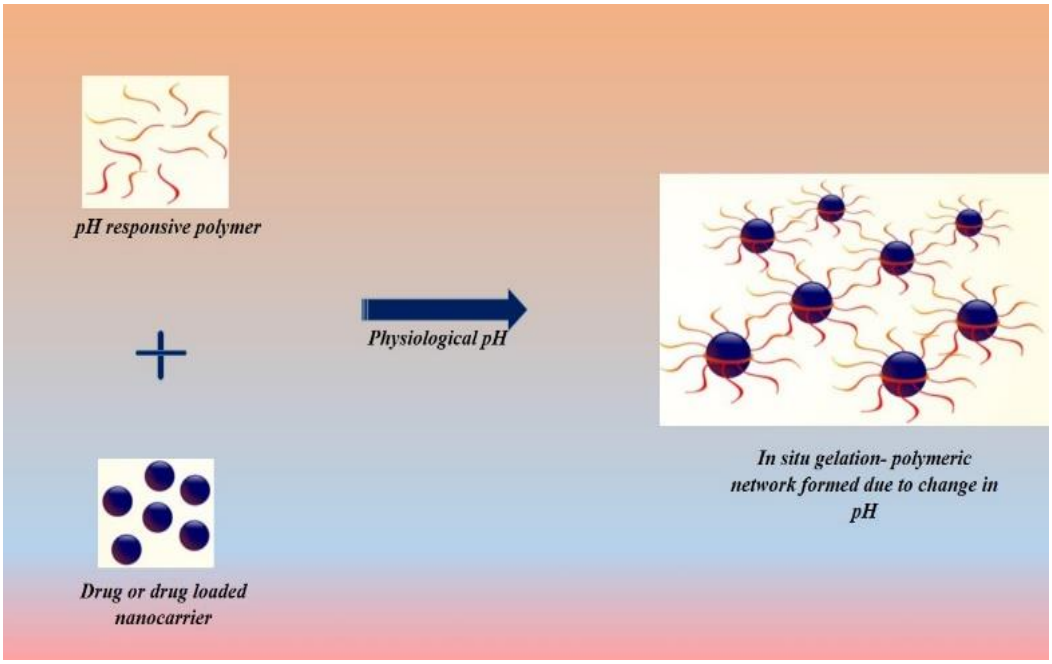

Figure 1: A Conformed Shift in the Compound Network was seen as the Formulation was Put to the Nasal Area as a Result of a Considerable pH Value Change. This Alteration Causes the in Situ Gel Network of the Viscous to Develop

- **Carbopol**

The high molecular weight chemical carbopol is made up of a poly (acrylic acid) cross-linked network. In contrast to poloxamer, it is a pH-responsive compound that exhibits soln-gel transmission when the pH of an aqueous solution changes. As the pH rises above 5.5 pKa, gelation begins to occur [32].

- **Ion-responsive System**

The in situ gelling systems show a soln-gel transition in response to the ionic stimuli. It comprises an ion-sensitive compound that gels in a physical setting. The most popular ion-sensitive gelling ingredient for nose formulations is gellan gum. It reacts with cations found in the physical fluid, such as sodium+, potassium+ calcium++, and Magnesium++, and produces a two helical junction zone. It is an anionic polysaccharide. Additionally, cationic complexation between these double helical units causes a reaction that results in the development of a 3D network structure. When the gellan gum-based series is injected into the nostrils, positive ion complexation and compound reaction take to occur, leading to the sol-gel transition since the nasal mucosa is rich in + ions like Calcium++. The resulting gel optimizes medication absorption, regulates drug release, and increases nasal retention [33]. Pectin is a further naturally occurring ion-sensitive polysaccharide that has been mentioned in the review for the creation of in situ intranasal gel. Pectin undergoes phase shift by + ion complexation with its functional groups, much like gellan gum, and forms a 3-dimensional network as a result [34]. In (Figure 2), the soln-gel transformation caused by ionic contact is diagrammatically depicted.

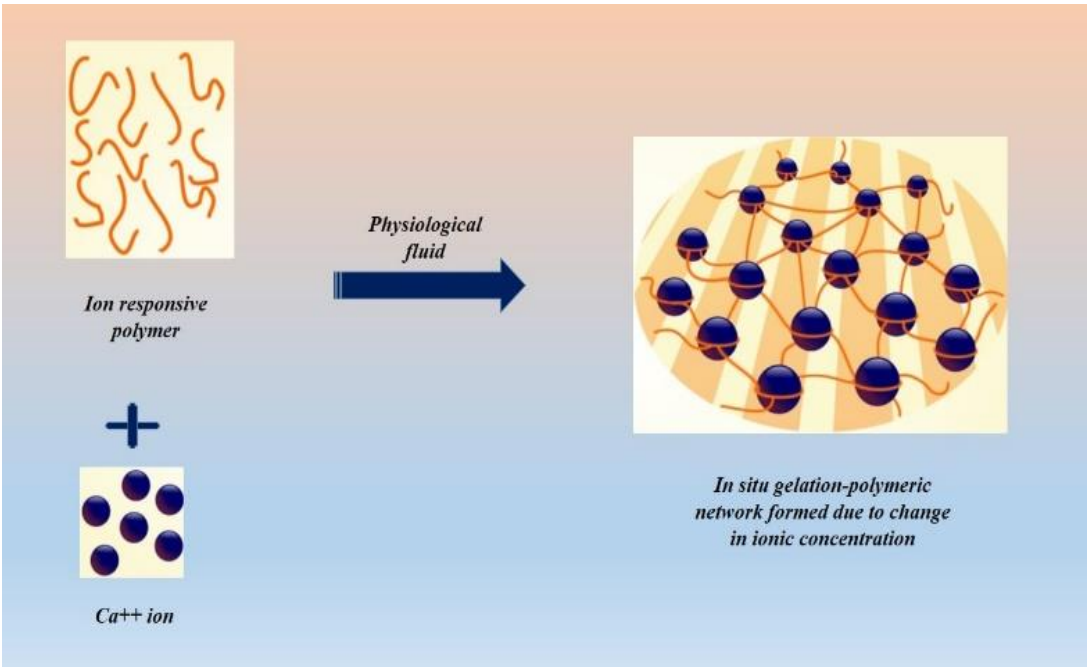

Figure 2: When Gellan Gum And Other Ions-Responsive Are Brought In Light To The Increased Conc Biological Fluid DGG, Which Simulates Nose Mucosa, They Undergo Constitutional Changes That Respond İn The Formation Of İon-İnduced İn Situ Gel

ANATOMY OF THE NOSE

The nasal cavity is a key organ for filtering impurities arising from inhaled air and acting as an immune system. The scent of sense, which is closely in connection to taste perception, is produced when the inspired air makes touch with the olfactory nerves [35]. Nose bone and cartilage add to the nasal outside entrance. The nasal area runs from the mouth to the outside entrance of the nasal [36]. The nose septum, which split the nose area into the left and right sides, is part of the nose's internal structure [35]. The facial bones that make up the paranasal sinuses, which encircle the nasal cavity, are hollow. They are categorized as maxilla, frontal, cranium, and sphenoidal sinuses because they are lined by epithelium [36]. The longest paranasal sinuses are pinpointed to the left and right of the nasal area and are called the maxilla sinuses. They have a tiny opening that joins the nose canal and gives air to flow between them [36]. A small layer of bone divides the nasal area from the frontal sinuses. The nose canal is not connected to them [36]. The term "air cells" also applies to the ethmoidal sinuses. Varying persons have varying numbers and sizes of them. Round and coming in different sizes are the sphenoidal sinuses. The vestibular, turbinate, and olfactory areas of the nasal cavity are separated from one another [36]. The vestibular area is pinpointed on the front of the nasal. It is a tiny area of the nasal area and has vibrissae that help in extracting out airborne particles more than 10 m [37].

- **Mechanism of Nose-to-Brain Drug Delivery**

When differentiate from oral medication delivery, the nasal area has become a useful target tissue for APIs delivery due to its ease of access and robust blood flow, wide large area, spongy endothelium membrane, and capacity to evade first-pass [38, 39]. However, the precise medication delivery mechanisms for nose-to-brain transport are

not well known. Bioactive substances have been shown to be carried from the nasal area to the brain via pathways including cerebrospinal fluid, the vasculature, and the lymphatic system (Figure 3). The characteristics of the medicines and delivery method, however, may lead to one predominant pathway [40]. The medication enters the circulation after being deposited on the respiratory epithelium and subsequently travels to the central nervous system (CNS). Olfactory neurons or olfactory epithelial cells use paracellular or transcellular transport to carry drugs that have been agglomerated on the olfactory epithelia to the (CNS) central nervous system. The trigeminal nerves provide another pathway for APIs delivery from the nasal area to the brain. The brain and nose area are joined by the olfactory and trigeminal nerve systems. [41].

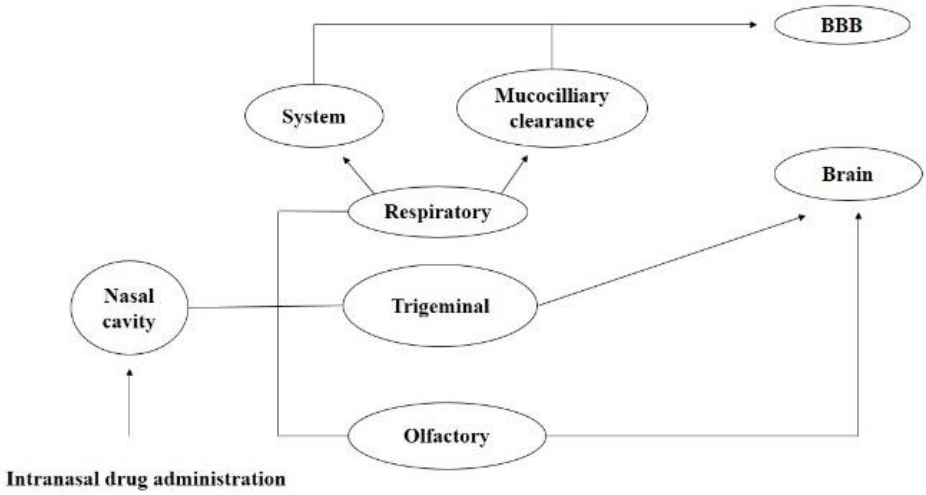

Figure 3: Diagrammatically Represent The Mechanisms From Nose-To-Brain Drug Delivery

- **Nose-To-Brain Transport-Related Anatomical Elements**

The transformation from the IN to the brain involves some anatomical components (Figure 4). The respiratory mucosa's cilia move the nasal area and it has a pH range between 5.5 and 6.5. The amount of sputum in the nasal area may have an effect on how well an API is absorbed [42]. The initial obstacle that medications given orally must overcome before moving between cells, whether paracellularly or transcellular [43]. Drugs are transferred across epithelial units, which can be stuck together by a diversity of junctions as well as tight junctions, adherent junctions, and gap junctions [43, 44]. The paracellular delivery is affected by the junctions' never-ending state. Some medications can facilitate nose-to-brain delivery by opening these connections, which is a quick pathway [43]. It is imp to note that the size of the APIs affects the drug transfer method. It has been found that potentials of more than 20 nm are delivered transcellular. [43, 45].

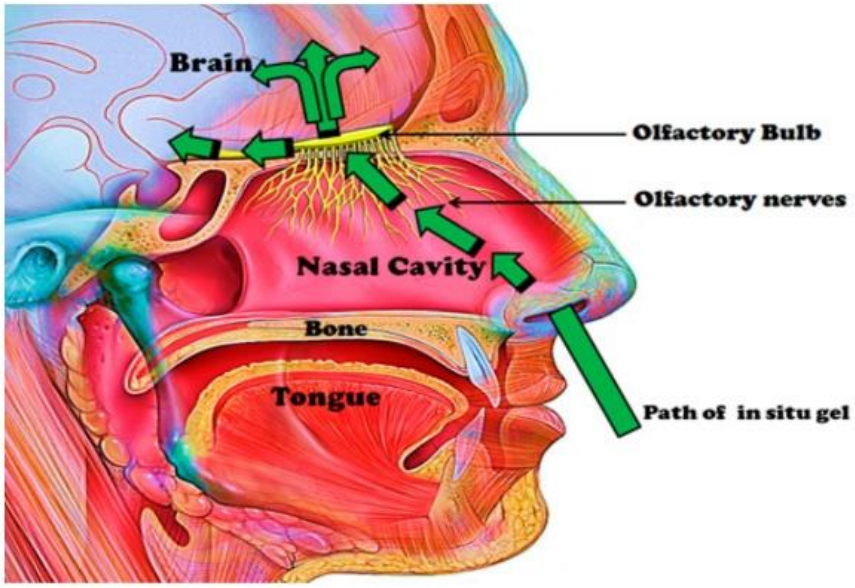

Figure 4: Nose-To-Brain Transport-Related Anatomical Elements

In olfactory nerve fibers of the olfactory bulb can carry bioactive substances to the central nervous system. The entorhinal cortex, the anterior olfactory nucleus, the hypothalamus, the olfactory tract, the amygdala, and so forth. are only a few of the areas of the brain to which the olfactory bulbs project. When a medication is administered intranasal, these projections allow for intra- and peri-neural transport [43]. The trigeminal nerves, project into the nose area to supply the respiratory region with nerves. These branches create access directly into the rostral and caudal regions of the brain by entering the cribriform plate and the lacerated foramen [43]. Another characteristic helpful in the transport from the nasal area to the brain is the vascularization of the olfactory area, which develops from tiny branches of the ophthalmic artery. Drugs given orally reach the blood flow through this vascularization, crossing the (BBB) on the way to the brain. Tiny and lipophilic APIs fall within this range [43, 46].

BIOFATE OF NEUROTHERAPEUTICS

- **Drug Absorption**

Drugs must first travel through mucus in the nasal cavity in order to be absorbed. Big and charged units find it more challenging to cross the (BBB) this barrier, but small, uncharged molecules can move through it with ease. The primary protein in mucin has the ability to bind with the substances and the presence of difficulty in diffusion. Natural factors like pH change or temperature can cause structural changes in the mucus layer. The main barriers to medication absorption across nasal mucosa include possible nose area metabolism before getting to the target location and short nasal cavity residency times [47].

- **Drug Distribution**

Drug disposition in the nasal area has a major impact on how effectively nasal absorption is accomplished. The way a medicine is administered may have an impact on how it is distributed in the nasal cavity, which can then influence how much of a

drug is absorbed. Particle deposition in the nose is connected to an individual's nasal mucosa's ability to restrict airflow. Almost all units with an aeronautics particle size between 10 and 20 m are gathered on the nose area when breathing through the nose. Particle size and breathing patterns influence how particles are gathered in the respiratory system. Additionally, to improve therapeutic outcomes and boost patient compliance, drug delivery systems, and formulations must be improved through the use of integrated DDD(drug delivery devices)[48–50].

CHALLENGES OF NOSE-TO-BRAIN DRUG DELIVERY

The nose passage offers a comparably small area than the oral area, which decreases its many benefits and lowers the APIs conc in the body [51]. Furthermore, it is shielded by the mucosal membranes and gives defensive enzymes that stop the body from absorbing such antigens or non-native substances, which also has an impact on how well drugs are absorbed [52, 53]. Bad contact time, bad drug retention, nasal mucosa annoyance or injury, enzymatic degeneration, and mucociliary clearing are also regarded as major obstacles to intranasal medication administration [54, 55]. These elements lower medication absorption and, hence, therapeutic potency. Below are some of the difficulties with intranasal medicine delivery to the brain.

- **Mucociliary Clearing And Deficient Drug Retention**

The mucociliary clearing is the body's main defense mechanism, preventing the admission of pathogens, poisons, allergies, antigens, and other foreign particles. The nasal cavity's cilia and mucus work together to create this effect. Typically, liquid or powdered formulations have a 15-20 minute clearance half-life [56]. Drug absorption is limited by such quick evacuation and short APIs period times in the nasal area. Therefore, to prevent such quick clearance and increase the APIs retention period in the nasal cavity, bioadhesive/mucoadhesive systems made with suitable mucoadhesive polymers, such as HPMC23, viscosity increasers; pulsatile in situ nasal gel; etc. are used. Such cutting-edge methods promote medication absorption through the nose [57]. In addition, by reducing mucociliary clearance, instillation to the posteriormost section of the nose area, also known as the olfactory region, also promotes increased drug absorption to the brain region. [58].

- **Enzymatic Degradation**

Exopeptidase and endopeptidase enzymes are in charge of breaking down various proteins and peptides in the epithelial barrier and lumen of the nose area [59, 60]. The bioavailability of peptide/protein-based bio-actives is constrained by the appearance of peptidase impulse, which clear them. In order to safeguard the bioactive and increase their bioavailability going forward, innovative drug carrier systems, enzyme inhibitors, and prodrugs are utilized [61].

- **Poor Permeation And Low Bioavailability Of Drugs**

A thin layer of mucus that is naturally lipophilic surrounds the nasal cavity. Additionally, nose-to-brain medication delivery uses cellular transport as its main mechanism, which only permits tiny lipophilic molecules to pass through [62]. Thus, the nasal route limits the penetration of polar medicines while being more suited for smaller, lipophilic moieties. Studies have shown that polar medications with smaller molecular sizes have a bioavailability of about 10%, compared to peptide drugs like insulin, calcitonin, etc., which have a bioavailability of only 1% [63].

- **Nasomucosal Toxicity**

A crucial factor to take into account when developing a nasal formulation is the potential for nasal mucosal toxicity or irritation. When a drug or drug carrier system is injected into the nasal cavity, it immediately makes touch with the intact mucosal membrane.

It is possible to increase the APIs retention time in the nose area and, as a result, the therapeutic effectiveness of the bioactive ingredient. Additionally, it lengthens the time that the medicine or dosage form is in touch with the nasal mucosa (containing various polymers and other excipients) [64].

DEVELOPED TECHNIQUE FOR ENHANCEMENT OF NASAL DRUG DELIVERY

Investigators proposed a few techniques to enhance drug retention via nasal mucosa by analyzing the necessary traits for designing effective (nasal drug delivery devices) NDDD and the causes of the failure of such systems. These techniques include:-

- Formation and Development, of precise and efficient IN medication delivery systems
- Forming inhibitors of enzymes with metabolism
- Development of efficient APIs absorption enhancers
- Forming formulations based on microparticles, nanoparticles
- Development of efficient pro-drug
- Forming formulations of mucociliary clearing inhibitors that adhere to the nasal mucosa for a prolonged period of time with mucoadhesive polymers

It is generally ideal to combine all or part of the methods for creating a nasal drug delivery system, and this has been done [65]. Effective nasal delivery systems have been designed and tested in a variety of configurations [66-69].

APPLICATIONS

- **Delivery of Macromolecules to CNS**

Intranasal administration of such macromolecular substances offers a good platform for direct transport to the CNS in the context of today's sophisticated proteins, peptides, and vaccine research. Large or big compound sizes and liable to enzymatic breakdown are the main causes of such substances' limited bioavailability.

Due to its physicochemical unreliability and exposure to hepatogastrointestinal first-pass metabolism elimination, proteins, and peptides are usually supplied parenterally. In this context, intranasal administration appears to be a viable choice [70].

- **Delivery of DNA Plasmids to CNS**

In addition to other immunization methods, the nasal route stands out for its simplicity of administration and ability to trigger strong immune reactions, precise in the respiratory system. Adjuvants and administering methods are nevertheless necessary to boost immune reply after nasal immunization [71].

Vajdy and O'Hagan reviewed the use of poly lactide-co-glycolide microparticles as adjuvants and administered vehicles for proteins and (DNA) vaccines for nasal immunization [72].

Additionally, it is noted that following IN injection of (DNA) plasmids, the concentration of plasmid in the brain was (3.9–4.8) times enhanced than the conc. of plasmid in the lungs and spleen. Additionally, it has been discovered that plasmid (DNA) entered the brain not more than 15 minutes after IN delivery [73].

This suggests that nasal delivery may be a viable method for delivering potential genes to the brain with minimal adverse effects on other organs.

- **Delivery Of Small Compounds To (CNS)**

Numerous tiny compounds are being demonstrated to be carried straight from the nasal void to the brain and to (CSF). The CNS transport of small compounds after intranasal administration depends on factors including size and lipophilicity.

Rats were given intranasal doses of 7.4 mol dopamine (153 Da) and 7.4 mol NGF (26,500 Da), and the concentrations of the brain's olfactory bulb measured 30 minutes later showed that the brain received five times more low molecular weight dopamine [74].

- **Delivery Of Stem Cells**

The method of administering the cells affects the security and effectiveness of unit-based therapy to treat neurological illnesses. Stem units have the capability for self-healing and cell differentiation [75].

For a wide range of human neurological disorders, including stroke, cerebral palsy disorder, traumatic wound, immune system-mediated disorder, multiple sclerosis, psychiatric disease, epilepsy, and neurodegenerative disorder like (PD) and (AD), cell replacement or gene transfer to the diseased or bruise brain has served as a foundation.

The use of stem cell technologies to study and treat brain disorders has grown more and more popular over the past 20 years. By replacing injured or dead neurons or by producing neurotrophic factors to nourish host neurons, stem cells can treat neurological diseases [75, 76].

DRUG COMPOUNDS AND TRANSPORTERS ARE DELIVERED BY DIRECT NOSE-TO-BRAIN TRANSPORT ROUTE

Pharmaceutical industry prospects for multi-particulates, including (micro and nano) dimensional drug delivery Systems, are outstanding and varied. The superior results from such transporters namely enhanced therapeutic potency with decreased dose frequentness, have attracted scientists from numerous disciplines. There have been reports of intranasal delivery of a range of medicinal drugs packaged in different carrier systems.

Table 1 lists the chemical compounds, proteins, peptides, hormones, or biological such as stem cells, that are carried directly from the (CNS) nose to the brain along with their corresponding drug carrier systems.

Table 1: Drug Compounds And Transporters Are Being Delivered By The Direct Nose-To-Brain Drug Transport Route

Sr. No.	APIs	Transporters	Difficulty	Result	Ref.
1	Venlafaxine	Polymeric nanoparticles (NPs)	The poor onset of action and bioavailability	The rapid onset of action, increased brain update	[77]
2	MSCs	Solution	Neuronal degeneration	Neuronal regeneration	[78]
3	Ropinirole	*In-situ* gel	poor oral bioavailability, and uptake across (BBB)	increased brain uptake and therapeutic efficiency	[79]
4	Zolmitriptan	Polymeric micelles	poor onset and oral bioavailability	increased onset and distribution in brain tissues and bioavailability	[80]
5	Estradiol	Polymeric nanoparticle	Nasal mucociliary clearance, low permeability	Enhanced retention, high brain uptake	[81]

PATENTS ON NASAL DRUG DELIVERY DEVICES (DDD)

Some of the patent applications on (IN) intranasal administration for (CNS) drug delivery have been filed and passed in the past 10 years. A patent file was awarded to Impel Neuropharma Industry, with the title of “Nasal drug delivery device” for nose-to-brain administration of drugs [82]. The same invention has also been granted a US patent and a Chinese patent. The "Brain-Targeted Nasal Drug Delivery Device and Body Position Fixator Thereof" Tongli biomedical patent was published by the World Intellectual Property Organization (WIPO). Chinese researchers used a specific made body posture fixator to maintain the user's body in the proper posture so that nasally administered APIs could reach the olfactory region. The fixator nourishes the user in the aforementioned bodily posture, and the APIs were delivered via an applicator whose form matched the user's nasal cavity to target and reach the brain. For direct (CNS) nose-to-brain targeting, an applicator-delivered drug is targeted to the olfactory region of the nasal cavity at the exact time with the aid of a fixator and smart controlling element.

FUTURE PROSPECTIVE

Diverse research teams have focused their efforts over the last few decades on creating new drug delivery strategies that get around the BBB. This is a result of the substantial difficulties faced by academics, businesspeople, and researchers who are trying to develop appropriate treatment plans for the rising prevalence of brain illnesses in the aged population. Numerous drug delivery methods, including polymeric microparticles, nanoparticles, polymeric micelles, liposomes, nanoemulsions, etc., are possible transport for drug administration through the (BBB) for the treatment of (CNS) diseases, as demonstrated by the current review. The majority of the powerful (CNS)-acting medications are water-hating in nature, which makes it tough for them to cross the (BBB), thus there are still a number of obstacles to overcome. One of the promising solutions to this emerging issue is to modify the surface of drug delivery vehicles. The use of this painless way of DD presents a capable alternative to intrude methods and could be burst, in the near future, for the development of novel DDS given the system’s advantage of nasal DDS (patient convenience and threat ratio). Without a doubt, the

pharmaceutical business would benefit greatly from this direct nose-to-brain APIs delivery method, which would undoubtedly result in the introduction of many new commercial goods to the pharmaceutical market in the coming future.

CONCLUSION

A successful DDS is one that provides pharmaceutical firms with commercial applications for mass production. Due to the BBB's restrictions, CNS medication administration is complicated. The Straight nose-to-brain DD device is one possible tactic for overcoming the BBB's challenges. Bypassing the (BBB) to reach the (CNS), intranasal administration minimizes drug systemic exposure and hence minimizes systemic side effects. Due to its non-invasive nature, it is a desirable method of drug delivery. By using this method, a large variety of neurotherapeutic compounds, including tiny chemical particles, peptides, hormones, proteins, and biological-like stem cells, can be administered, leading to new knowledge regarding the treatment and prevention of many neurological illnesses. However, it is unclear if the API is delivered from the carrier system in the nasal cavity and then transferred to the (CNS), or whether the transport system is transported into the (CNS) via the olfactory or trigeminal nerve route, where the APIs are released. Therefore, further fundamental study is needed to ascertain the potential therapeutic carrier transport pathway to the (CNS) and their subsequent destiny within the biological system. Same, for the field to advance, delivery of surface-engineered carrier systems through a passive or active targeting approach would be ideal.

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