Management of Neurological diseases with inclusion of *In situ* gels for delivery from nose to brain: A review

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ABSTRACT

In the recent times, *in situ* based gel drug delivery systems that can transport therapies to the appropriate region, circumvent the blood-brain barrier, lower peripheral toxicity, and regulate drug release kinetics have been established. The bioavailability of several medications used to treat neurological illnesses is poor. The use of *in situ* gels for medication delivery to brain through nose-to-brain pathway has shown considerable assurance in preclinical studies from a number of pharmaceutical scientists. However, in the development of these gels, safety concerns including the toxicity of nasal mucosa, drug delivery to specific brain regions, and dose estimation are aspects that must be taken into consideration. The in situ-based gels employed for therapeutic drug administration from the nose to brain, as well as preclinical studies and difficulties, will be mainly given emphasis in this review.

Keywords: *In situ* gels, brain tumour, Alzheimer's disease, neurological illnesses, nose-to-brain delivery.

1. INTRODUCTION

Neurological diseases affect the peripheral and central nervous system. These include the peripheral nerves, spinal cord, brain, cranial nerves, nerve roots, neuromuscular junction, muscles, etc.[1]. Parkinson's disease, epilepsy, multiple sclerosis, Alzheimer's disease, cerebrovascular illnesses, brain tumours, etc. are a few examples of neurological disorders [1]. Millions of individuals worldwide are affected by neurological illnesses. According to estimates from the World Health Organization (WHO), dementia affects 47.5 million people worldwide, and 7.7 million new cases are discovered each year [1]. Alzheimer's disease, which accounts for 70% of cases, is the most prevalent type of dementia. Neurological disorders can be caused by a number of variables, including genetics, physical trauma, infections, ageing, lifestyle, nutrition, and environmental factors [2–7]. The delivery of medicines topically, orally, and intravenously, as well as the utilisation of device-based therapies including deep brain stimulation, surgeries, and rehabilitation, are all used to treat neurological illnesses [8]. Some methods involve administering the medication directly into the brain through an injection, cerebrospinal fluid, or intranasal administration. Some of these methods are risky, intrusive, localised, and transient [9, 10].The repair of the central nervous system, which entails the regeneration of the injured neural tissue, is another method for treating neurological illnesses. Neurodegeneration, however, makes this strategy difficult [11]. Additionally, the blood-brain barrier functions as a barrier that prevents some therapeutic medicines from reaching the brain's endothelial capillaries and from reaching the central nervous system [9]. Inclusion of gel based drug delivery devices that can be used in nose-to-brain routes have been created to get around the aforementioned restrictions.
This method avoids the BBB, improves drug absorption, and has fewer systemic side effects (blood-brain barrier). This method, however, has drawbacks, including the inability to determine the precise dosage of medication to be administered and naso-mucosal irritation brought on by preservatives, additives, and some components added to formulation, that can result in epithelial cell loss, mucosal layer shrinkage, and ciliary layer loss [12]. The absorption of drugs can also be hampered by illnesses like allergies, flu, and other conditions [12]. This review will concentrate on preclinical studies, difficulties, and gel-based drug delivery systems that are utilised to administer treatments via the nose to brain route.

2. NASAL ANATOMY

The nose is a key organ that filters airborne pollutants and acts as an immune system. The olfactory nerves, which are in touch with inhaled air, produce the sense of smell, which is strongly related to taste perception [13]. Nasal bone and cartilage make up the nose's external opening. The nasal cavity extends from the throat to the external entrance of the nose [14]. The nasal septum, which divides the nasal cavity into the left and right sides, makes up the internal portion of the nose [13]. The olfactory epithelium, a tissue found on the nasal cavity's roof that contains sensory cells, is important for the sense of smell. It protrudes from its surface and is covered in mucus that the epithelium's goblet cells release. Bipolar olfactory sensory neurons are located at the epithelium's surface, with their dendrites pointing toward the nasal cavity's inner space. They deliver sensory information to the brain [14]. The largest paranasal sinuses are located to the left and right of the nasal cavity and are called the maxillary sinuses. They have a

little opening that connects them to the nasal canal and allows air to move back and forth between them [14]. The vestibular, turbinate, and olfactory areas of the nasal cavity are separated [14]. The vestibular area is located on the front of the nose. It is a very small area of the nasal cavity and contains vibrissae that aid in removing airborne particles larger than 10 m [15]. The primary site for the orderly absorption of medicines is the turbinate area.
administered intravenously. It is lined by a cell-filled pseudostratified columnar epithelium.
such as basal, mucus-secreting, ciliated, and non-ciliated cells [15]. The non-motile microvilli that cover both ciliated and non-ciliated cells serve to increase surface area and make up the area where absorption of drug takes place [15]. The nerve cells in the olfactory epithelium project into the olfactory bulb of the brain, which helps in establishing an association between brain and external environment, which is functional in drug transportation. Mucus coats the epithelium cells and traps foreign particles. Water, mucin, protein, and salts are all present in mucus. Albumin, lactoferrin, immunoglobulin, and lysozyme are among the proteins found in it [15].

2.1 Drug Delivery Mechanism from Nose to Brain:

When compared to oral drug administration, the mucous membrane has emerged as an efficient target tissue for drug delivery because of its easy accessibility, elevated blood flow, huge surface area, highly permeable endothelial membrane, and capacity to prevent hepatic first pass metabolism [16-18]. However, the exact pathophysiology of drug delivery for nose-to-brain delivery are unknown. The transport of bioactive agents from the nasal cavity to the brain has been attributed to pathways involving the cerebrospinal fluid, vasculature, and lymphatic system. One channel may predominate, nevertheless, depending on the characteristics of the medicines and delivery system [19]. The brain and nasal cavity are connected by the olfactory and trigeminal nerve system. These nerve systems are parts of the brain that are accessible from the outside which can be used to bypass the BBB for direct medication delivery from the nose to the brain [20]. The drug delivery system can be further divided into three groups: I the transcellular pathway, which uses passive diffusion, fluid phase endocytosis, or receptor-mediated endocytosis; (ii) the paracellular pathway, which uses tight junctions between olfactory neurons and sustentacular cells of the olfactory epithelium; and (iii) the olfactory nerve pathway, which uses endocytotic or pinocytotic mechanisms for drug uptake [20].

2.2 The Anatomical Components of Nose-to-Brain Transport:

Nose to brain transmission involves a few anatomical structures. The respiratory mucosa's cilia move the nasal mucus, which has a pH between 5.5 and 6.5. The volume of mucus in the nasal mucosal surface may have an impact on how well a medicine is absorbed [21]. Drugs given intravenously must first overcome this barrier before entering cells either paracellularly or transcellularly [22]. The drug that is delivered travels through the epithelial cells, which can be joined together by a variety of junctions including tight junctions, desmosomes, adhered junctions, and neuromuscular junctions [22,23]. The paracellular transport is influenced by the junctions' unmodified state. Some treatments have the ability to widen these connections, which speeds up delivery from the nose to the brain [22]. It is significant to note that the volume of the medicines affects the drug delivery method. It has been found that therapeutics bigger than 20 nm are delivered transcellularly. Caveolae-mediated endocytosis occurs for therapeutics smaller than 200 nm, whereas clathrin-mediated endocytosis occurs for those between 200 and 1000 nm.

The bioactive substances are delivered to the olfactory receptor neuron and then undergo intraneuronal transfer to the olfactory bulb due to the slower transcellular drug transport [22,24].

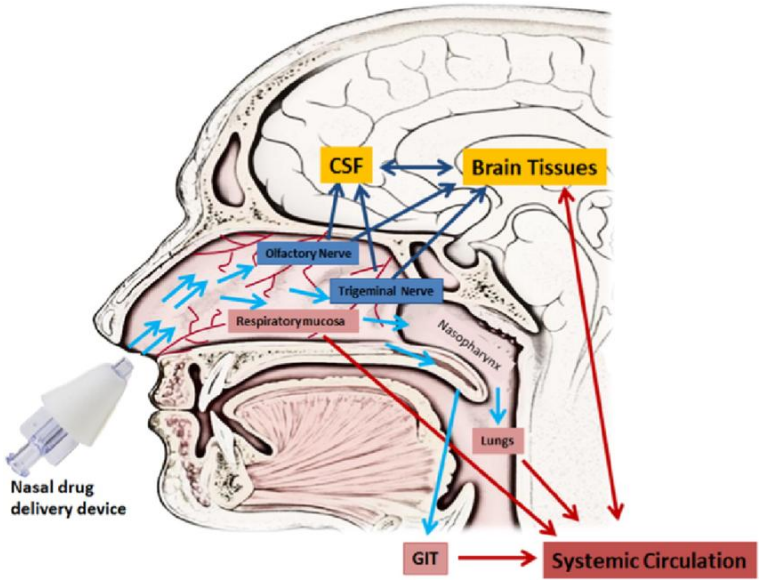

Figure No 1: Nose to brain drug transfer anatomical structures

Intranasal drug administration bypasses the BBB by entering the systemic circulation through this microvasculature. Small and lipophilic medications fall within this category. The perivascular pathway allows drugs to pass through channels between the blood vessels' outermost layer and the surrounding tissue's basement membrane [22,25]. This channel promotes fast drug distribution in the CNS because it is mediated by bulk flow, diffusion, and arterial of pulsation [25].

3. Neurological Disorders and Treatment Challenges

The blood-brain barrier, their association with numerous genes, the correlation of disease-associated genetics, adverse drug reactions with minimum impact on progression of the disease, and poorly understood mechanisms and biomarkers for neurological diseases make treating the majority of neurological diseases difficult [26-28]. Dementia is a symptom of Alzheimer's disease, a neurological condition in which the brain's nerve cells are damaged. In the basal forebrain amygdala, cortex, and hippocampal region of the brain, intracellular neurofibrillary tangles, insoluble -amyloid (A) peptides/senile plaques, and the death of various neurons are its defining features. Low oxygen availability, which causes cellular damage, head injuries, lack of vitamin D, excessive copper and homocysteine levels, which cause damage to the neurons, and vitamin D deficiency are risk factors for Alzheimer's disease [29-32]. Five medications, including donepezil, galantamine, rivastigmine, memantine, and the combination of donepezil and memantine, have received FDA approval for the treatment of Alzheimer's disease. The cholinesterase inhibitors donepezil, galantamine, and rivastigmine are used to treat memory, language, and other problems. They function by preserving acetylcholine levels, which then

offset the loss of active brain cells [33]. Donepezil and memantine are used together to manage mild to severe disease stages. These medications have some negative effects[33]. The central nervous system is affected by the autoimmune disease multiple sclerosis, which causes demyelination, axonal destruction, and the loss of neurological activities [34]. Common childhood diseases, inadequate sun exposure (vitamin D deficiency), smoking, and hereditary factors are thought to be causes of the disorder [34]. According to reports, intricate inflammatory processes are what cause the loss of axons [34,35]. Multiple Sclerosis is already incurable. To prevent immune system damage that leads to the disease's clinical manifestations and to create neuroprotection mechanisms that will make the CNS resistant to the immune response's harmful consequences are the two main approaches that have been suggested as viable treatments for the disorder [36]. Beta interferons, fingolimod, glatiramer acetate, teriflunomide, dimethyl fumarate, mitoxantrone, natalizumab, and other medications are used. These medications have serious adverse effects that make it difficult for patients to take them as prescribed, including injection site discomfort, symptoms similar to the flu, tightness in the chest, palpitations, and dyspnea, heart failure, leukaemia, etc [34,37]. Schizophrenia, epilepsy, Parkinson syndrome, brain tumours, etc. are examples of additional neurological illnesses. Delusions, hallucinations, abnormal conduct, etc. are all characteristics of schizophrenia, a long-term mental health illness [38]. Neurotransmitters, such as glutamate, dopamine, and serotonin, can either be in excess or insufficient, which is what triggers this disease. The disease is also influenced by other hereditary and environmental variables. Antipsychotic medications are used to treat the illness, but they include side effects such diabetes mellitus, weight gain, and hyperlipidemia that raise the risk of cardiovascular death [38,39].

Recurrent seizures brought on by excessive electrical discharges in a cluster of brain cells characterise the non-contagious, persistent brain condition known as epilepsy [40]. Aplastic anaemia, hepatitis, allergic rashes, and other side effects are caused by several medications used to treat epilepsy. Pharmacoresistance, which is caused by disease-related, genetically based, and drug-related causes, is the main drawback of some patients' access to the medications used to treat epilepsy. Antiepileptic medicines fail to inhibit excitatory sodium or calcium currents in the brains of pharmacoresistant patients due to changes in the pharmacological targets of antiepileptic therapies caused by the disease-related mechanism. Drug efflux transporters cause genetic changes that result in inadequate seizure control, and the drug-related process is what causes antiepileptic medications to be less effective [41,42].

Lewy bodies with accumulations of the protein alpha-synuclein and the absence of melanin-pigmented neurons in the midbrain are two features of Parkinson's condition [43]. Dopamine deficit in the striatum is a sign of neurodegeneration of dopaminergic neurons in the substantia nigra, which is revealed by the loss of pigmented melanin-containing neurons in the midbrain [43]. Parkinson's disease treatments is categorised as symptomatic and neuroprotective. There isn't currently a validated neuroprotective therapy for the illness. Deep brain stimulation (DBS) brain surgery is used in severe Parkinson's syndrome patients when medicine is no longer

effective to treat the motor symptoms [44-45]. A brain tumour, which can be either cancerous or non-cancerous, is defined as an abnormal development of tissue in the brain or central spine that impairs brain function [46]. Based on where the cells originated, tumours are categorised. When they start as brain cells and do not expand to other tissues, they are categorised as benign; aggressive brain tumours that invade the surrounding brain tissue by rapidly growing and spreading into adjacent regions; primary tumours that originate in brain cells and can spread to the spine or other regions of the brain; brain tumours that have spread metastatically from another region of the body [46]. Viral infection, toxins, ionising radiation, and genetic manipulation are potential causes of this disease [47]. A tumour which exists in brain can be challenging to cure. Temozolomide, lomustine, bevacizumab, carmustine wafer, and other similar classes of medications are some of those which are used to treat brain cancer.

4. Drug Delivery through Nose for the Management of Neurological Disorders like Epilepsy, Parkinson's Disease, and Alzheimer's Disease

For the treatment of neurological illnesses, gel-based drug delivery devices that can be utilised to provide medications intranasally have been created. These systems have the therapeutic potential for the treatment of neurological disorders since they are biocompatible and biodegradable, can deliver medications to the brain, and can get beyond the blood-brain barrier. The effectiveness of these systems is influenced by their design, polymer content, pore size distribution, and rate of degradation.

Hydrogels:

Hydrogels are cross-linked, hydrophilic matrices of water-soluble polymers that have a high water-retentive capacity. They can be created in many different physical forms, including slabs, films, in situ hydrogels, nanogels, microparticles, and nanoparticles, among others [48-49]. They display pores with dimensions that can be regulated by the density of crosslinking and are easily changed with certain functional groups. Because of their substantial water content and physiochemical characteristics that resemble the natural extracellular matrix, hydrogels are very biocompatible. They respond readily to environmental signals like temperature, pH, and magnetic field. They are made using several techniques, and the technique used to make them affects the pore size, rate of degeneration, mechanical strength, and release of drug mechanism. They have been created for nose-to-brain transport because owing to their special physicochemical characteristics.

In Situ Gels:

Systems known as *in situ*-based gels display the sol-to-gel transition at the point of administration into the body. When delivered, they are liquid, but when exposed to certain environmental stimuli, such as changes in temperature, pH, ions, magnetic fields, or biological environments, they go through a sol-to-gel transition [48-50]. They have beneficial characteristics that make them useful for drug delivery, such as being highly compatible with a variety of medications, including soluble, insoluble, low, and high molecular weight

medications; being less invasive and able to be used to achieve high drug concentrations at the desired site of action with reduced systemic side effects; biocompatibility; being biodegradable; and exhibiting sustained drug release over an extended period, thereby improving patient compliance [51].

Anti-Parkinson Drug Delivery employing *In Situ*-Based Gels:

Levodopa, an anti-Parkinson medication, is used to treat Parkinson's disease, but its effectiveness is constrained by its poor bioavailability, which is shown by a low brain absorption. Its poor bioavailability is a result of the medication's inconsistent gastrointestinal digestion before it binds to the L-amino acid carrier, which actively delivers the medication through the duodenum and into the circulation [52-55]. Levodopa-loaded chitosan nanoparticles were integrated by Sharma et al. into a thermo-reversible gel made from Pluronic F-127 using the sodium TPP ionic gelation process (1 mg/mL) (Poloxamer 407) [56]. Following the characterization of the formulations, in vitro drug release experiments showed that the formulation complied with the Hixson-Crowell model. By expanding the interconnections between epithelial cells and slowing mucociliary clearance, the inclusion of polycations improved the absorption of drug of the formulation on nasal mucosa. Additionally, *in vivo* investigations using Swiss albino rat models demonstrated that intranasal delivery of the chitosan nanoparticles increased the drug's brain uptake when compared to the gel formulation, indicating that the gel's viscosity decreased the drug's brain uptake [56]. Using carboxymethylcellulose as a mucoadhesive polymer and Pluronic F127 (Poloxamer 407) as a thermoreversible polymer, Lungare et al. created in situ thermoresponsive-based gels using the cold methodology [57]. It included a significant amount of the anti-Parkinsonian medication amantadine. The temperature of gelation raised with increasing bioadhesive polymer, and decreased with increasing amantadine. At normal nasal temperatures, a Pluronic F127 concentration of 16% was determined to be appropriate for the formulation's sol-to-gel transition. Potential medicines for the management of Parkinson disease include these systems [57]. The Fickian mechanism, which is a transport process in which the polymer settling time is greater than the solvent dispersion time, followed by an irregular drug release mechanism, or a mixture of diffusion and erosion controlled drug release, after storage of the formulation at 4 C for eight weeks, demonstrated the stability of the formulation. The human nasal epithelial cells were not significantly harmed up to 4 mg/mL and up to 1 mM. In vitro, the percentage of drug release from the formulation ranged between 43 and 44% [57-58]. For the intranasal transport of ropinirole to the brain, Khan et al. reported a mucoadhesive in situ gel formulation made from chitosan and hydroxyl propyl methyl cellulose [59]. When compared to intravenous administration, intranasal administration of 99mTc (Technetium 99m)-ropinirole-loaded gel AUC (area under the curve) (0-480 min) increased albino rats' in vivo brain absorption of ropinirole by 8.5 times [59]. Ravi et al. developed a thermosensitive gel for intranasal administration of Rasagiline Mesylate, a drug that helps in management of Parkinson's disease [60]. The mucoadhesive polymers carbopol 934 P and chitosan were combined in a 1:1 ratio with poloxamer 407 and poloxamer 188 to create the gels. The formulation's intranasal delivery showed a better drug bioavailability of six times greater than the oral solution, according to in vivo testing on New Zealand white rabbits. With the use of Pluronic F-127 and hydroxy methyl propyl cellulose, Rao et al. created thermoreversible nasal gels that they loaded with the anti-Parkinson medication ropinirole, which has a poor oral bioavailability [61]. When compared to the free medication, which was characterised by cellular damage, the gel showed a protective effect, according to a histological investigation of sheep nasal mucosa. The nasal

delivery technique has the potential to be used as a delivery mechanism for anti-Parkinsonian medications because the brain absorption of the medication was five times more after nasal administration than after intravenous treatment. The olfactory nerves were used for medication transport from the formulation to the brain [61].

In Situ Gels for Anti-Migraine Drug Delivery:

The medication sumatriptan succinate is used to treat migraines. It has a low retention period with in nasal cavity and a low olfactory route delivery to the brain, which contribute to its poor bioavailability. Sumatriptan has a relatively limited ability to pass the blood-brain barrier. Deacetylated gellan gum served as the gelling ingredient in the in situ gel that Galgatte et al. created in a simulated nasal fluid [62]. With the increase in temperature, the gel's strength improved.

While the rate of medication release was declined as gellan gum concentration was increased, the inverse was true of its concentration. A Fickian release model was used to predict how the medication would get released from the gel, which demonstrated an erosion diffusion mechanism. Employing sheep olfactory nasal mucosa with a diameter of 0.6 mm, ex vivo permeability was investigated. 93% of the medication was released during a 300-minute period, according to its penetration. After the formulation was administered, there was no evidence of cell necrosis in the mucosa's microscopic structure. Nasal in situ gel had a higher concentration of sumatriptan in the plasma and brain tissues than oral aqueous solution achieved. When compared to oral administration, in vivo investigations revealed that the formulation supplied via the nasal route had a greater AUC in the brain and plasma. When the formulation was given intranasally, the AUC of sumatriptan in brain tissues was 1.44 times greater than the AUC in plasma. The findings showed that olfactory pathways were responsible for drug molecules' passage via the nasal mucosa and into the brain [62].

Delivery of an Anti-Alzheimer's drug with employment of *In Situ* Hydrogels:

Selected medications of Alzheimer disease have been placed onto in situ gels, which has improved the drug's brain uptake in vivo. Tao et al. created an in situ gel based on gellan gum that was loaded with huperzine A. The method of precipitation was used to make the gel [63]. Huperzine AUC (0->6 h) value in plasma obtained after nasal delivery was 0.94 compared to intravenous administration, according to an uptake by the rat brain tissues following intranasal administration. In comparison to intravenous and intragastric injection, the AUC (0->6 h) of cerebrospinal fluid following nasal delivery was 1.3 and 2. The distributions of huperzine A in the rat brain tissues, particularly in the cerebrum and hippocampus, were dramatically boosted by the in situ gel [63]. For effective brain targeting, Chen et al. placed curcumin onto thermosensitive hydrogel. The gels were created using poloxamer 188 and pluronic F127 [64]. In the rat nasal cavity at body temperature, the gels demonstrated a shortened gelation time, prolonged mucociliary transport time, and prolonged curcumin retention. When the dialysis membrane method and membraneless methods were used, the curcumin release mechanism from the gel was controlled through diffusion and dissolution, respectively. After the formulation was applied, the nasal mucosal consistency was intact for 14 days. When compared to the drug's drug-targeting efficiencies following intravenous administration of the curcumin solution, the formulation's drug-targeting efficiencies in the cerebrum, cerebellum, hippocampus, and

olfactory bulb were 1.82, 2.05, 2.07, and 1.51 times, respectively. The gel significantly improved drug absorption and distribution in the cerebellum and hippocampus of rat brain tissue [64]. In order to administer geniposide, Wang et al. created a thermoreversible in situ nasal gel using the cold technique using poloxamers (P407, P188) and hydroxypropyl methylcellulose [65]. The discovery demonstrated the formulations' potential for treating neurological conditions. For the delivery of rivastigmine hydrogen tartrate in poly(lactic-co-glycolic acid) nanoparticles, Salatin et al. created an in situ gel using poloxamer 407 [66]. When compared to the free drug, a high drug penetration through the sheep nasal mucosa was found. Because the drug was embedded in nanoparticles, the permeability was increased, the formulation was stable, and the drug release was prolonged. Abouhussein et al. also explored rivastigmine tartrate brain delivery via mucoadhesive thermosensitive in situ gel intranasally [67]. In situ mucoadhesive pluronic F127, HPMC (hydroxypropyl methylcellulose), chitosan, carbopol 934, and NaCMC were used to create a gel (sodium carboxymethyl cellulose). When compared to intravenous administration, in vivo pharmacokinetic and biodistribution studies in normal albino mice using the radiolabeling approach revealed 84% intranasal permeation with good distribution to the brain (0.54% ID/g). These results indicated that intranasal drug administration diminished drug systemic distribution to various organs, allowing for better targeted therapy to the brain and, as a result, managed to overcome side effects [67].

Antidepressant drug delivery with the inclusion of *In Situ* Gels:

Doxepin is an antidepressant medication. Naik and Nair described thermoreversible gels made from chitosan and glycerophosphate or poly(ethylene) glycol for intranasal administration of doxepin to the brain. A good rise in activity count and a reduction in immobility time were seen during *in vivo* investigations on Swiss albino mice, which suggested that the drug had good antidepressant effect [68]. The nasal mucosal tissues were severely damaged by the drug solution, and this damage was shown as glandular hyperplasia and severe epithelial hyperplasia. However, the injection of the gel formulation caused very minor adverse effects, such as modest gland swelling, and there was no sign of the mucosal epithelium sluffing that was seen in mice that received the drug solution. Doxepin's release profile from the gel matrix had an impact on how quickly it permeated the gel. When compared to the formulation made from chitosan and glycerophosphate, the medicine from the formulations made from poly(ethylene) glycol, glycerophosphate, and chitosan permeated at a lesser rate [68]. Fatouh et al was involved in preparation of *in situ* gel that contained agomelatine, an antidepressant drug [69]. When compared to the drug release from the drug solution and solid lipid nanoparticles, which were 89% and 35%, respectively, the drug release from the gel formulations ranged from 8.9 to 21%. Ion-sensitive in situ nasal gel that is loaded with fluoxetine hydrochloride for transport to the brain was described by Pathan et al. The gel was created using HPMC and gellan gum (hydroxypropyl methylcellulose) [70]. Ex/in vivo permeation experiments showed that raising the concentration of HPMC from 0.1 to 0.2% and raising the amount of gellan gum from 0.2-0.6% lowered the drug release rate. All formulations had drug penetration rates ranging from 75% to 94% over a 240-minute timeframe. The nasal mucosa exposed with the formulation preserved the integrity of the epithelial cell, suggesting the formulations' non-toxic nature. The application of the formulation shortened the total period of immobility and enhanced climbing and swimming behaviour, according to an in vivo research [70]. Using mucoadhesive thermo-reversible gel, Kaur et al. explored the distribution of tramadol hydrochloride to the brain [71]. Ionic gelation was used to create the gels from chitosan nanoparticles, which were then mixed

with Pluronic and HPMC to create a mucoadhesive thermo-reversible gel. By incorporating antioxidant-like actions, significantly improved locomotor activity, and body weight of the rat model in vivo, the formulation effectively reduced forced swim-induced depression. The nanoparticles improved medicine delivery to the brain even further [71]. Nortriptyline hydrochloride-loaded thermoreversible gel was designed by Pathan and More for intranasal use [72]. The viscosity and mucoadhesive strength improved together with the poloxamer 188 and HPMC concentration, whereas the gelation temperature and drug % permeation diminished. A 98% drug release via sheep nasal mucosa was detected in the formulation with 3.6% poloxamer and 0.04% HPMC. The formulation remained consistent over a three-month period, and the observations suggested that the formulation has therapeutic promise for the treatment of depression [72]. Intranasal injection of venlafaxine-loaded alginate nanoparticles for the treatment of depressive disorders was developed by Haque et al [73]. When compared to the depressed group, adult Wistar rats in pharmacodynamic testing of the formulation for the antidepressant efficacy in vivo demonstrated superior swimming and climbing as well as diminished immobility (p 0.01). Due to variables like longer absorption time, decreased nasal mucus secretion, increased penetration across nasal mucosa, and regulation of P-gp efflux transporters located on BBB, the formulation boosted the drug concentration in the brain [73]. The potential of the formulation for nose-to-brain transport was proved by the brain/blood ratios of the formulation delivered intranasally, drug solution administered intravenously, and drug solution administered intranasally at 30 min, which were 0.11, 0.03, and 0.07, respectively.

Anti-Schizophrenia Drug Delivery with the incorporation of *in Situ* Gels:

Sherje et al. generated in situ gels for the schizophrenia treatment using carbopol 934 and hydroxypropyl methyl cellulose loaded with paliperidone [74]. The drug was slowly released and with good mucoadhesion from the formulation. The structure of nasal mucosa was unaltered following treatment with formulation. The formulation showed a significant rate of drug penetration through sheep nasal mucosa, demonstrating HP-CD (2-Hydroxypropyl)-cyclodextrin's function as an activator of nasal absorption [74].

5. Future Prospects and Challenges

The complexity of the genes involved, the persistent nature of the disease, and the lack of understanding of the underlying mechanisms and biomarkers make treating neurological diseases difficult. Because of the precedent variables, symptomatic and neuroprotective therapies are employed to treat these disorders. The majority of the medications used to treat these illnesses have serious adverse effects, and they are only effective at certain stages of the illness. Some researchers have investigated some of these medications in vivo when loaded with nanoparticles onto in situ gels and given intranasally in attempt to mitigate the severe side effects related with some of these drugs and to enhance the brain uptake. Drug transport to the brain is a difficult and complicated subject that calls for the collaboration of researchers from a variety of disciplines, including biomedicine, physics, and materials science. Designing therapies that may effectively target the appropriate group of damaged neurons without harming healthy neurons is the most challenging work [75]. Decreased levels of pinocytosis and tight junctions, which are crucial for retaining homeostasis in the central nervous system, are also correlated with low permeability of

the BBB, which is permeable to lipophilic molecules with a molecular weight of less than 600 Dalton [76,77]. Intranasal medications, however, can pass through the BBB. The nose-to-brain route for therapeutic drug delivery has benefits including quick start, non-invasiveness, high patient compliance, and reduced risk of systemic adverse effects and renal clearance. The precise factors governing medication transport via the nasal to brain route are not yet fully known. As a promising therapeutic platform for the intranasal administration of bioactive substances for the treatment of neurological disorders, the numerous preclinical investigations have shown the effectiveness of in situ gels. However, difficulties with intranasal medication delivery include mucociliary clearance, limited membrane permeability, and enzymatic destruction of the therapeutic agent in the nasal cavity. The mentioned problems are resolved by including absorption accelerators and mucoadhesive excipients in the composition, which also improves the formulations' effectiveness in vivo. Drug delivery performance to brain tissue employing innovative targeting moieties in vivo has enhanced because of the creation of in situ gels used in combination with bioactive compounds and nanoparticles [78]. The majority of the planned gels have only passed preclinical investigations; clinical trials for these produced gels are required. Because of factors like the obvious variations between animal and human anatomy, it is necessary to exercise caution when transferring animal data to people. More research is required to fully comprehend the mechanism of drug distribution to the brain in neurological illnesses following intranasal administration. In order to improve the drug's bioavailability, new excipients must be developed. There are few extensive toxicodynamic studies of the excipients, nanoparticles, and polymers needed for making the gels. According to research results so far in this, it appears to be possible that medications for the treatment of neurological illnesses in the form of nasal in situ gel formulations will enter the clinical stage in the near future.

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