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# IN SITU GELLING SYSTEM: FOR TREATMENT OF NEUROLOGICAL DISORDERS

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## ABSTRACT

Intranasal drug delivery can be visualized as the promising route for the administration of drugs as it has the potential to overcome some major limitations associated with other routes. It is one of the promising approach for the systemic delivery of drugs because concentration time profile of drugs achieved after nasal administration is often similar to that obtained after intravenous administration. Nasal administration has a drawback of poor retention time which is overcome by novel drug delivery i.e. In-situ gelling system. In-situ gelling system is a polymeric solution which can be administered in solution form, and it undergoes sol-gel phase transition into a viscoelastic gel upon exposure to physiological conditions (e.g. pH, temperature and ionic concentration). This system also has a great impact in the treatment of neurological disorders. Neurodegenerative diseases are becoming prevalent as the population ages. Preclinical reports from several researchers have proven that the delivery to the brain via the nose-to-brain route using in situ gels holds great promise. The 'in situ gel' system has become one of the best novel drug delivery systems by its special characteristic feature of 'Sol to Gel' transition. The treatment of neurological disorders require the delivery of therapeutics to the brain in appropriate amounts to elicit a pharmacological response. Nose-to-Brain delivery has emerged as a powerful strategy to overcome the BBB and deliver drugs to the brain. The present review highlights anatomy of nose, nose to brain delivery and its advances in the treatment of neurological disorders.

**KEYWORDS:** In-situ gelling system, Nose-to-brain delivery, Neurological disorders.

## INTRODUCTION

Nasal mucosa has been considered as a potential administration route to achieve faster and higher level of drug absorption.[1] For many years drugs have been administered nasally for topical actions. Topical administration includes mainly the treatment of congestion, sinusitis, and related allergic conditions. In recent years, the increasing investigations of the nasal route has focused, especially on nasal application for systemic drug delivery.[2] Nasal mucociliary clearance is one of the most important limiting factors for nasal drug delivery. It severely limits the retention time for drug absorption. However, mucoadhesive preparations had been developed to increase the contact time between the dosage form and mucosal layers of nasal cavities.in situ gelling system is the recently developed mucoadhesive system.[3–5] 'In situ' is a Latin word which means 'in position'.[6] certain polymeric systems used for delivering the drugs in nasal cavity, these polymers undergoes sol-gel transition, once administered.[7] Gelation happens through cross linking of the polymer chain, which can attained through covalent bond formation i.e. chemical cross linking or non-covalent bond formation i.e. physical cross linking.[8]There are many triggering mechanisms in in situ gel formation some of them are pH change, temperature modification and solvent exchange.[9] It is one of the system employed in the treatment of neurological disorders.

Neurological diseases affect millions of people worldwide. WHO (World Health Organization) estimated that 47.5 million people globally are suffering from dementia, and over 7.7 million new cases are reported every year.[10] Brain disorders like Alzheimer, Parkinson's disease, infections like meningitis remain the world's leading cause of disability, and account for more hospitalizations than almost all other diseases combined.[11,12] Some approaches in the treatment of neurological disorders involve the direct delivery of the drug via injection into the brain, cerebrospinal fluid or intranasal delivery. Some of these techniques are unsafe, invasive, local, and short lasting.[13] The blood-brain barrier also acts as a barrier that inhibits the delivery of

some therapeutic agents to the central nervous system and inhibit drugs from passing through the endothelial capillaries to the brain. In order to overcome the limitations, gel-based drug delivery systems that can be administered via nose-to-brain routes have been developed.[14] The nasal route provides direct access to the brain along the olfactory and trigeminal nerve pathway. This feature has opened up for brain delivery of many drugs.[15,16]

**Anatomy And Physiology Of Nose**

The nasal cavity is divided into two halves separated from one another by a wall of cartilage called as the septum and extends posterior to the nasopharynx. The anterior part of the nasal cavity i.e. the nasal vestibule, opens to the face through the nostril.(fig.no.1) The nasal cavity has a total volume of about 16-19ml and surface area of about 180cm$^2$.[17] The three main regions in nasal cavity are nasal vestibule, olfactory region and respiratory region. It is covered with a mucous membrane which can be divided into two areas, non-olfactory and olfactory epithelium.[18] Vestibular region is anterior part of nasal cavity and its Surface area is 0.6 cm. It is covered by a stratified squamous keratinized epithelial with sebaceous gland. Olfactory region is about 10cm$^2$ in surface area, and it plays a vital role in transportation of drugs to the brain and CSF. The respiratory epithelium is composed of four types of cells namely non-ciliated, ciliated columnar cells, basal cells and goblet cells. These cells facilitate active transport processes such as exchange of water and ions between cells.[19] The nasal mucous membrane derives a sensory supply from the fifth cranial nerve and has both parasympathetic and sympathetic autonomic nervous system fibers. The neuroepithelium for olfaction is derived from the first cranial nerve. The control of the arterial and venous supply to the mucous membrane of the nose by the autonomic nervous system.[20] Olfactory sensory neurons are bipolar neurons at the surface of the epithelium in which dendrites present in the interior space of the nasal cavity. They transmit sensory signals to the brain.[21] In the olfactory epithelium, the nerve cells project into the olfactory bulb of the brain providing a connection between the brain, and the external environment, and this connection is useful for the transportation of drugs.[22]

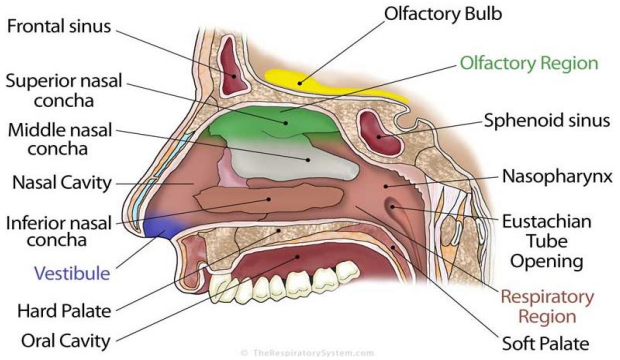


**Fig. 1: Anatomy of nose.**

**Mechanism of Nasal Absorption**

**Paracellular transport:** It is an aqueous route of transport. This route is slow, passive and Mainly responsible for the transport of hydrophilic drugs. There is an inverse correlation between intranasal absorption and the molecular weight of water-soluble compounds. Poor bioavailability was observed for a drug with a molecular weight greater than 1000 Dalton's.

**Transcellular transport:** It involves transport through a lipoidal membrane and is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity.[17] Drug can also cross cell membranes by active transport via carrier-mediated system or transport through the opening of tight junctions. For examples, chitosan, a natural bio polymer, opens tight junctions between epithelial cells to facilitate drug transport.[18]

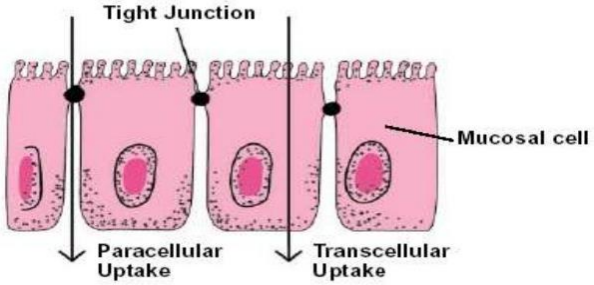


**Fig. 2: Absorption routes.**

**Nose to Brain Drug Delivery**

The nasal route has emerged as a useful target for drug delivery to the brain.[23] Drug transport from the nasal cavity to the brain takes place via the following three mechanisms i.e. olfactory nerve pathway(major pathway), trigeminal nerve pathway, lymphatic, and vascular pathway(minor pathway).[24] The respiratory region is highly vascularized with blood vessels, and also consists of trigeminal sensory neurons. When drug is deposited on the respiratory epithelium the blood vessels present in the respiratory region facilitates the drug absorption to the systemic circulation.[25] However, rather than entering into the entire systemic circulation sometimes the drug may retain into the venous supply of nose which can quickly transfer to the arteries of brain, and CNS. This process is known as the counter-current transfer.[26] Drug deposited on the olfactory epithelia are transported to the central nervous system through paracellular or transcellular route via olfactory epithelial cells. Another route for the transportation of drug from the nose to the brain is via the trigeminal nerves.[27] The trigeminal neurons are responsible for drug transport from the nasal cavity to the pons and cerebrum of the brain and also delivers the drug in a lesser extent to the olfactory and frontal brain.[25] Once the drug enters the brain, it is rapidly distributed throughout the CNS via perivascular spaces. This phenomenon is known as perivascular transport.[28]

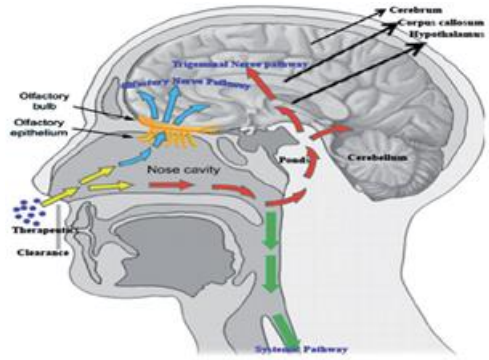


**Fig. 3: Transport mechanism from nose to brain.**

**Principle of In-Situ Gel**

The new concept of formation of a gel in situ was suggested first time in early 1980s. Formulation of in situ gel systems involves the use of gelling agent which can form a stable suspension system to contain the dispersed drug, and other excipients.[29] The sol-gel transition depends on one or a combination of different stimuli, like pH change, temperature modulation, solvent exchange, and the presence of specific ions or molecules. Drug delivery systems having such properties can be widely used for sustained delivery of the bio active molecules.[30] In situ gels can be engineered to facilitate drug targeting, especially through mucus membranes, for non-invasive drug administration.[31]

**Approaches**

**Temperature triggered system-**

In this system, gelling of solution is triggered by alteration in temperature, thus sustaining the drug release. The use biomaterial whose transition from sol-gel is triggered by increase in temperature is an attractive way to approach in situ formation.[32] For example- hydrogels are liquid at room temperature and undergoes gelation when in contact with body fluids (35˚-37℃). Some examples of polymers which show temperature induced gelation are pluronics, methyl cellulose, ethyl cellulose.[33,34]

- **pH triggered system**

In this system, gelation of the solution is triggered by change in ph. At pH 4.4 the formulation is free-form solution which undergoes coagulation when the pH is raised by the body fluid to pH 7.4.[33,35] Polymers included in these class contain an acidic or a basic group that either accept or donate protons when exposed to different environmental pH, Hence these are called pH sensitive polymers.[36] In case of weakly acidic groups (anionic), increase in swelling of polymers induced with increase in external pH, whereas polymers containing basic (cationic) groups exhibit decreased swelling. Polymers which show pH sensitive gelation are cellulose acetate phthalate (CAP), polymethacrylic acid (PMMA), polyethylene glycol (PEG), etc.[37]

- **Ion activated system**

This system is mainly observed in ocular drug delivery. Here, gelling of the solution is induced by the change in ionic strength. It is assumed that the osmotic gradient across the surface of the gel determines the rate of gelation.[38] Polymers that exhibit osmotically induced gelation include gellan gum, hyaluronic acid, alginates, etc. Certain ion sensitive polysaccharides such as carrageenan, pectin, sodium alginate undergo phase transition in presence of various ions such as k+, Ca2+, Na+.[39]

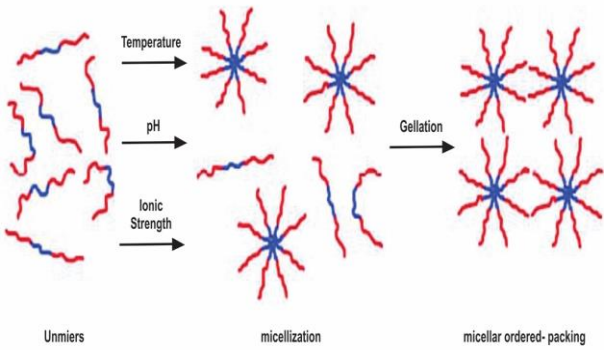


**Fig. 4: Mechanism of sol-gel transition by different stimuli.**

**Polymers Used In Preparation of In-Situ Gelling System**

**Thermo-responsive polymers**

These are the smart polymers which are sensitive to temperature and change their structural features in response to temperature change.[40] The most widely used thermo-responsive polymers are: Poloxamers , cellulose derivatives (HPMC, Ethyl cellulose), xyloglucan.[41,42]

- Poloxamer- poloxamer is commercially known as Pluronic, Poloxamer are water soluble, ABA-type triblock copolymer consisting of polyethylene oxide and polypropylene oxide units. This units are responsible for the solubility and hydrophilicity.[43,44] At low temperature, it forms small micellar subunit in solution and on increase in temperature it results in increased viscosity which leads to swelling to form large micellar cross linked network.[45]
- Guar gum- Guar gum is a naturally occurring gum which is also called as guaran.[46] Guar gum is insoluble in hydrocarbons, esters, alcohols, and ketones but soluble in water.[47] It has the capability of forming high viscous solution in low concentrations, the galactose side chains that are attached to mannose backbone interact with water molecules which are present in the solution leads to the formation of inter molecular chain which causes entanglement of gaur gum molecules causing the formation of gel.[48]

**Ph responsive polymers**

pH-sensitive polymers are polyelectrolytes that have in their structure acid (carboxylic or sulfonic) or basic groups (ammonium salts) that can accept or release protons in response to pH changes in the surrounding environment.[49]

Carbomer- It is high molecular weight, cross linked polyacrylic acid derivative. When dispersed in water, The carboxylic groups accept protons at low pH values and release protons at high pH values. Thus, when the pH increases, the polymer swells owing to the electrostatic repulsion of the negatively charged groups, delivering the drug molecules to the environment.[50]

**Ion activated polymers**

These polymers can undergo phase transition in the presence of different electrolytes, especially $Na^{+}$, $Ca^{2+}$ and Mg cations, are particularly initiate gelation of the polymer.[51]

- Pectin- Pectins are polysaccharides, in which the polymer contains mainly, α-(1-4)-D galacturonic acid residues.[52] Gelling property of pectin depends upon the molecular size and degree of esterification. The presence of hydrogen bonds between free carboxyl groups causes gel formation.[53] In the presence of free calcium ions, Low methoxy pectin readily forms gels in aqueous solution, which cross link the galacturonic acid chains. Although the gelation of pectin will occur in the presence of $H^{+}$ ions.[54]
- Alginic acid- Alginic acid is a linear block co-polymer polysaccharide consisting of β-D-mannuronic acid and α-L-guluronic acid residues.[55] Dilute aqueous solutions of alginates form firm gels on addition of Di- and trivalent metal ions by a cooperative process involving consecutive glucoronic residues in the α-L- guluronic acid blocks of the alginate chain.[56]
- Gellan gum- Gellan gum is an anionic hetero polysaccharide, secreted by microbe Sphingomonas elodea.[57] The mechanism of gelation involves the formation of double-helical junction followed by aggregation of the double helical segments to form a three-dimensional network by complexation with cations and hydrogen bonding with water.[58,59]

**In-Situ Gelling System For The Treatment Of Neurological Disorders**

**Parkinson's disease**

Parkinson's is a neurodegenerative disorder of the central nervous system.[60] symptoms of Parkinson's disease is characterized by the loss of pigmented melanin-containing neurons in the midbrain. The loss of these neurons results in neurodegeneration of dopaminergic neurons in the substantia nigra region of mid brain.[61] The symptoms are shaking, rigidity, slowness of movement and rigid muscular movements and difficulty in chewing and swallowing. Hence, nasal drug delivery is a promising alternative for the administration of drugs to Parkinsonian patients.[60] In nasal drug delivery system, the olfactory epithelium has a dense network of olfactory neuronal projection through which the drugs in contact with the epithelium are directly transported into the brain.[62,63] Intranasal delivery would be effective only when the drug is in contact with nasal epithelium for a sufficient period to diffuse into the olfactory projections. Hence, in situ gel is promising approach for nasal drug delivery which prevents clearance of drug by mucus and ciliary movement.[64] The treatment of Parkinson's disease is classified as a symptomatic and neuroprotective therapy. The drugs that are used to treat the disease are dopamine precursors, dopamine agonists, monoamine oxidase B inhibitors and anticholinergics.[65,66] Selegiline hydrochloride (SL), a monoamine oxidase B (MAO-B) inhibitor, holds a very important place in the treatment of Parkinson's disease.[67,68] Lungare et al. developed in situ thermo-responsive gels by the cold method using Pluronic F12 as a thermo-reversible polymer and carboxymethylcellulose as a mucoadhesive polymer. It was loaded with amantadine (anti-Parkinsonian drug). A concentration of 16% of Pluronic F127 was found to be suitable for the sol-to-gel transition of the formulation at nasal temperatures. These systems are potential therapeutics for the treatment of Parkinson disease.[69]

**Alzheimer's disease**

In Alzheimer's disease neurons of some brain areas, especially neocortex and limbic system (includes hippocampus, amygdala and their associated cortices), gradually deteriorate.[70,71] Mainly the brain nerve cells are destroyed, resulting in dementia. It is characterized by neurofibrillary tangles, insoluble beta amyloid plaques and loss of neurons.[72] For better therapy of Alzheimer's disease, intranasal delivery can be utilized as key to bypass presystemic metabolism of drug.[73] The United States Food and Drug Administration (FDA) has approved some drugs for the management of Alzheimer's disease, which include donepezil, galantamine, rivastigmine, memantine and the combination of donepezil with memantine. They act by maintaining the levels of acetylcholine, which then compensates for the loss of the functioning brain cells.[74] Abouhussein et al. investigated brain delivery of rivastigmine tartrate via thermosensitive in situ gel intranasally. It was developed from pluronic F127, HPMC (hydroxypropyl methylcellulose), chitosan, Carbopol 934 and Na CMC (sodium carboxymethyl cellulose). In vivo pharmacokinetic and bio-distribution studies using the radio labelling approach revealed that 84% intranasal permeation with a good distribution to the brain (0.54% ID/g) when compared to intravenous administration.[75]

**Migraine**

The treatment of brain disorders is the greatest challenge due to presence of protective barriers like blood brain barrier and blood cerebrospinal fluid barrier.[67,68]

Migraine is a brain disorder characterized by recurrent attacks of headache widely variable in intensity, frequency and duration. Attacks are commonly unilateral and are usually associated with anorexia, nausea, and vomiting.[69] There is substantial evidence that diencephalic and brain stem nuclei are involved in the modulation of trigeminovascular activation.[70,71] The activation of these pathways leads to meningeal vasodilation, neurogenic inflammation, central sensitization, and is eventually perceived as head pain.[72,73] Rizatriptan benzoate belongs to class of triptans which are used in therapy of migraine. Rizatriptan benzoate binds with high affinity to human cloned 5-HT1B and 5-HT1D receptors.[74,75] Zolmitriptan is a synthetic tryptamine derivative recently approved for use in acute migraine and related vascular headaches. They provide immediate analgesia in migraine and cluster headache.[76] Tripants recently employed in in-situ nasal delivery.

## CONCLUSION

Nasal drug delivery system is a promising alternative route for administration of the several systemically acting drugs, Hence can be employed in treatment of neurological diseases. The treatment of neurological diseases is challenging because of the number of factors associated and the progressive nature of the disease. This delivery system is beneficial in conditions like Parkinson's disease, Alzheimer's disease because it targets drugs to the brain. In situ gels offer the primary requirement of a successful controlled release product via the nasal route that is increasing patient compliance. The various preclinical studies have demonstrated the efficacy of in situ gels as a potential therapeutic platform for the intranasal administration of therapeutics for the treatment of neurological disease.

### Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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