Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 12 [5] April 2023 : 237-246

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

REVIEW ARTICLE **OPEN ACCESS**

Intranasal *In Situ* Gelling Systems - An Approach for Enhanced CNS Delivery of Drugs

Damagundam Srilakshmi[1], Jupally Pooja[2], Prasanthi.D*[3]
1,2,3 G. Pulla Reddy College of Pharmacy, Mehdipatnam, Hyderabad, Telangana 500028.
Corresponding author's Email: prasanthidhanu@gmail.com

ABSTRACT

The most preferred route for the administration of drugs is the oral route. However, dueto gastrointestinal degradation and extensive hepatic first-pass metabolism, this oral route is not ideal for the delivery of certain drugs. As an alternative, the nasal route can be chosen to deliver drugs. This route has been successfully used to deliver drugs to the central nervous system through the olfactory and trigeminal neurons bypassing the Blood Brain Barrier(BBB). The advantages of the nasal route are its non-invasiveness, self-medication, and patient compliance. However, the main limitation associated with this route is the rapid mucociliary clearance, which results in low absorption and hence poor bioavailability which can be avoided by using mucoadhesive in situ gelling systems. The in-situ gelling systems are solutions that are administered and get converted into gel due to various physiological stimuli like temperature/pH/ionic. The present review critically evaluates the importance of in situ gelling systems for the nose-to-brain delivery of drugs along with the polymers used in the formulation of in situ gel, approaches of in situ gelation, mechanism of gelation, and their evaluation.

KEYWORDS: *Nose-to-brain delivery, CNS targeting, Intranasal drug delivery, In-situ gelation, Stimuli-responsive polymers.*

Received 15.02.2023 Revised 15.03.2023 Accepted 26.04.2023

INTRODUCTION

The most preferred and convenient route for the administration of a drug whenever systemic effects are intended is the oral route. However, low oral bioavailability of certain actives due to extensive hepatic metabolism and gastrointestinal degradation evokes the search for new routes to deliver these drugs. The parenteral route, transdermal route, and transmucosal routes are versatile and allow the delivery of various drugs. One of the main advantages of parenteral and transmucosal routes of drug delivery are that they bypass the first-pass effect, can reduce the dose and improve the safety of the drugs and reduce the overall treatment cost. One of the main disadvantages of the parenteral route is that it can cause pain at the site of injection. This can be very inconvenient for patients to continue taking the medication for a long time. On the other hand, the transdermal route though successfully exploited for the delivery of certain drugs is not as effective as the oral route due to the poor permeability of the skin. The problem with choosing the rectal and vaginal routes is that they cause irritation. In the buccal route, the unpleasant taste of the drugs can cause a problem with acceptability. Thus, Intranasal drug delivery is considered a promising alternative to the oral route due to its potential to overcome various major limitations.[1]

Traditionally, drugs delivered by the nasal route were used for local treatment. In the past three decades, studies have shown that this route can also be used as an efficient and effective way to deliver drugs to the systemic route. The rich vasculature of the nasal passageway and the high drug permeation rate makes it an ideal route for the administration of proteins, peptides, various polar drugs with small molecular weight, and macromolecules like vaccines and DNA which are highly metabolized or incompletely absorbed. Intranasal drug delivery provides a concentration-time profile similar to that of intravenous administration. This allows for the quick onset of action of the drugs given by the nasal route.[1]

In addition, it is a non-invasive alternative to deliver a therapeutic substance directly to the CNS bypassing the blood-brain barrier (BBB) by utilizing pathways along olfactory and trigeminal nerves. [1,2]

Despite the advantages of intranasal delivery, some of the formulations remain unideal due to their low permeability and short residence time. One of the main reasons for this issue is the rapid mucociliary clearance(MCC), which can be reduced by increasing the viscosity and mucoadhesion of the formulation.These can increase the residence time of drugs at the nasal absorption site and facilitate the uptake of the drug. However, due to the high viscosity of the solution, it is difficult to accurately dose and administer the drug. As a consequence, the desire to overcome such new challenges stimulated the development of an intranasal in-situ gel-forming system.[2]

INSITU GEL -

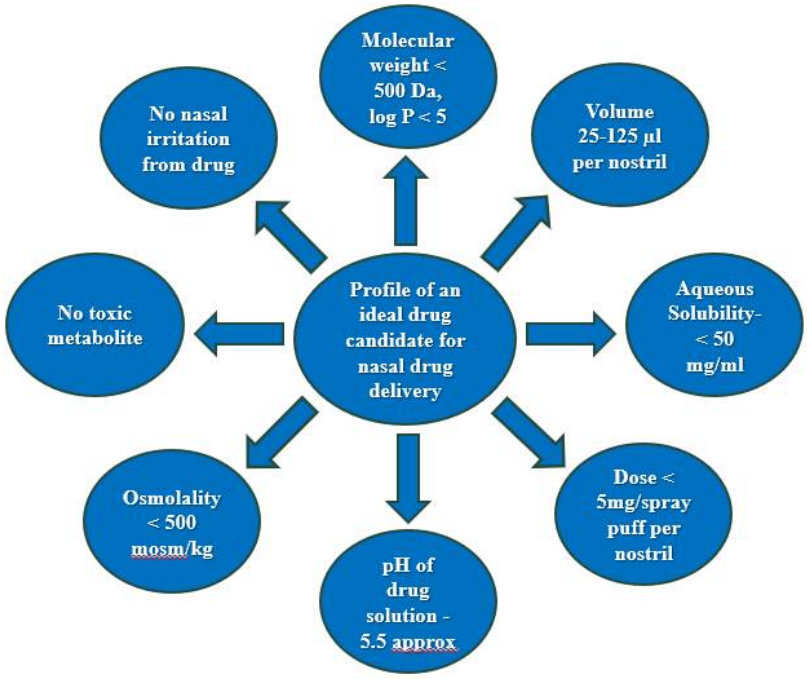
In-situ is a Latin word that means 'In its original place or in position'.[3]A gel is a state between liquid and solid, which is made up of physically cross-linked networks of long polymer molecules, with liquid molecules trapped within a three-dimensional polymeric network swollen by a solvent.These nasal In-situ gels are made from low-viscosity biocompatible materials which are in liquid form and upon contact with the nasal mucosa, the polymer undergoes conformation changes making a gel so that it is able to improve the interaction between the drugs and the nasal mucosa. They can also release the drugs slowly in the nasal cavity in reliable quantities making it more accurate.[4]

The process of gelation can be achieved through the crosslinking of the various components of the polymer chain. This can be done through the formation of non-covalent (physical) or covalent(chemical) bonds. There are various mechanismsthat can be utilized to develop in-situ gel systems like physiological stimuli (e.g., temperature modifications, pH-triggered systems),physical changes in biomaterials (e.g. Diffusion, osmosis, and swelling), and chemical reactions (e.g. UV radiation, enzymatic and ion activated systems).[4,5]

NASAL DRUG DELIVERY SYSTEM:

Intranasal delivery is a promising alternative to the traditional route of drug delivery. Numerous studies have shown that the nasal cavity can be utilized as a site of administration for local and systemic delivery of various therapeutic agents. It can be used in the treatment of local, systematic, and CNS sites.[4]

Figure 1: Profile of an ideal drug candidate suitable for the Nasal drug delivery system [1].



ANATOMY AND PHYSIOLOGY OF NOSE

In humans, the major functions of the nasal cavity are breathing and olfaction. It has a total volume of around 15 to 20 ml and a surface area of around 150cm. It is divided into two cavities by the nasal septum. The nasal passage epithelium is covered by a mucus membrane consisting of mucus.The pH of the nasal mucous ranges from 5.0 to 6.5 and it moves at a rate of 5 to 6 mm/min resulting in particle clearance (mucociliary clearance) within the nose every 20 min.[6]

Each part has three distinct regions namely,

1. **Respiratory region:** The respiratory region also called conchae, is the largest section of the nasal cavity. It is the area that is most important for systemic drug delivery. It is composed of four different

types of cells, namely the basal cells, non-ciliated cells, ciliated columnar cells, and goblet cells.Three nasal turbinates namely superior, middle, and inferior project from the lateral wall of each of the nasal cavity.

2. **Vestibular region:** The nasal vestibule is located just inside the nostrils and it has a surface area of around 0.6 cm. This region is covered by a stratified squamous and keratinized epithelium. The sebaceous glands present in this region are responsible for filtering out the airborne particles.

3. **Olfactory region:** The olfactory region is located on the roof of the nasal cavity and has a surface area of about 10 cm2. It extends a short way down the septum and lateral wall. It plays an important role in the transportation of drugs to the brain and cerebrospinal fluid.[4,6,7]

PATHWAYS:

The primary pathway for the transport of drug from the nasal cavity to the brain region is supposed to be the neuronal path via olfactory and trigeminal neurons and the secondary pathway utilize the CSF, lymphatic system and another is vascular absorption (through general circulation).

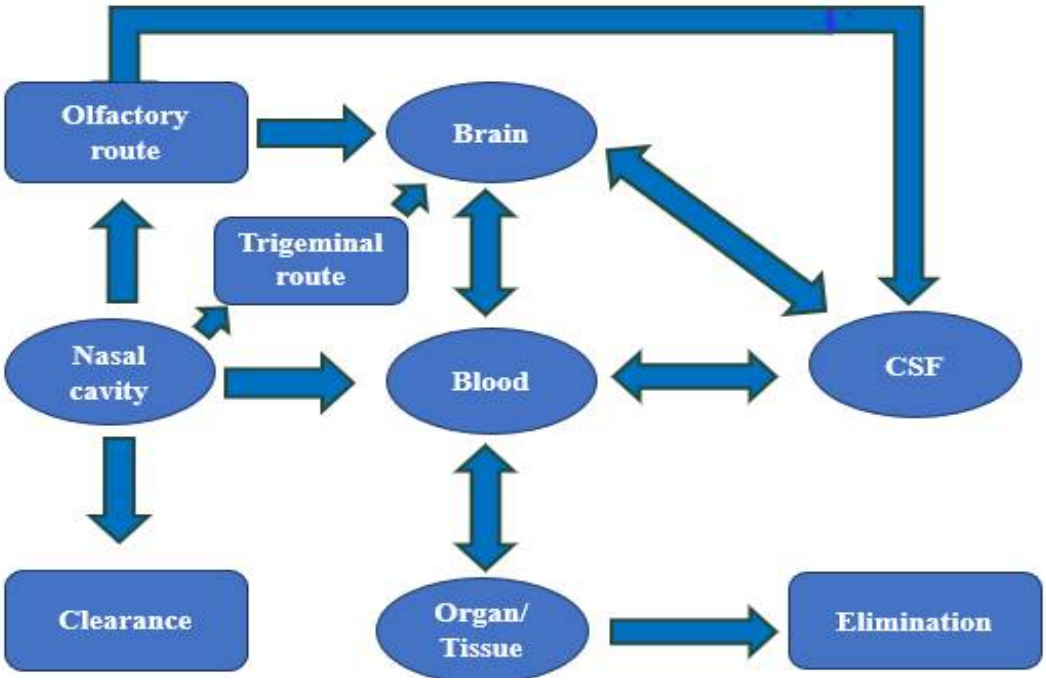
1. **Pathway utilizingolfactory and trigeminal neurons**: Passage through olfactory and trigeminal nerves is the primary and direct route of drug absorption from the nasal to the brain region. The first mechanism involves a transfer of the drug to primary neurons of the olfactory epithelium and then to the olfactory bulb by intracellular axonal transport with subsequent possible distribution into more distant brain tissues. The second mechanism depends on the permeation of the drug across the olfactory sustentacular epithelial cells followed by uptake into the CNS. The drug transport through olfactory neurons takes place by passive diffusion, endocytosis, or paracellular transport.

On the other hand, the trigeminal nerve forms a connection between the nasal cavity with the cerebrum and pons region of the brain and also to the frontal cortex and olfactory bulb to a smaller extent. Thus, by precisely understanding the mechanism of drug transport, one can predict the target site of the brain. But it is quite challenging to control transport through a single route only.

2. **Pathway utilizing the CSF** &**lymphatic system**: The drug absorption through the lymphatic system of the nasal cavity to the CSF of the subarachnoid space of CNS takes place by olfactory nerves present in the perineural space. In this pathway, the drug first enters the CSF and perivascular region which is further distributed to the rest of the brain. The drug transportation and distribution in the CSF are merely based on the properties like lipophilic behaviour, polarity, solubility, degree of ionization, and molecular weight.

3. **vascular absorption (through general circulation):** When the drug is instilled deeper into the nasal cavity, some amount of the drug also enters into the systemic circulation through the vasculature of the respiratory region and then reached the brain upon crossing the BBB (especially lipophilic drugs) as per the blood volume distribution.[7-10]

Figure 2: Different transport pathways for nose-to-brain drug delivery [7]



CHALLENGES/BARRIERS TO NASAL DRUG DELIVERY:

Some important characteristics of different barriers which affect nasal drug delivery are discussed below:

Poor permeation and low bioavailability of drugs: The nasal cavity is lined by a thin lining of mucous that has inherent lipophilicity. In addition, cellular transport is the primary mechanism of nose-to-brain drug delivery which allows the permeation of small lipophilic molecules only. Hence, the nasal route is more suitable for delivering smaller size, lipophilic moieties, while restricting the entry of polar drugs.

Mucociliary clearance and poor drug retention: Mucociliary clearance is a combined action of cilia and mucus of the nasal cavity which prevent the entry of foreign particles into the body. The clearance is between 15-20 min. The poor drug retention in the nasal cavity along with such rapid clearance confines drug absorption.

Enzymatic degradation: The exopeptidase and endopeptidase enzymes present in the epithelium and lumen of the nasal cavity cleaves the peptide/protein-based bio actives and minimizes their bioavailability.

Nasomucosal toxicity: Most of the drugs and excipients, specifically organic solvents and surfactants, exert some toxic effects, irritation or damage to the nasal mucosa. The formulations meant for the nose-to-brain delivery should be safe on the CNS to prevent toxic effects.[9]

ADVANTAGES:[4,5,7,11,12]

LIMITATION:[4,5,7,11,12]

Advantages and limitations are given in Figures 3 and 4 respectively.

APPROACHES OF IN SITU GELS:

There are three generally defined mechanisms that trigger the in situ gel formation of biomaterial:

A. Physiologically induced In-Situ Gelling System (e. g., Temperature and pH)

B. Physically induced In-Situ Gelling System (e. g., solvent exchange or diffusion, Osmosis and swelling)

C. Chemical induced In-Situ Gelling System (e. g., enzymatic, chemical, and photo-initiated polymerization)

A. Physiological induced In-Situ Gelling System

Based on physiological stimuli in situ gelling systems are classified into two types:

Temperature triggered systems:

Temperature-sensitive gelling systems are commonly used stimuli-responsive systems. They do not require any external heat except body temperature to cause gelation. These in-situ gelling systems are in the liquid state at 20˚-25˚C temperature and undergo gelation when coming in contact with body fluids at 35-37˚C. This is the easiest and most applicable strategy both in-vivo and in-vitro. Three main strategies are utilized in the design of these systems.

i. **Negative thermo-sensitive type**: e.g., poly-N-isopropyl acrylamide (PNIPAAm)

ii.**Positive thermo-sensitive type**: e.g., polyacrylic acid (PAA), or polyacrylamide, poly (acrylamide-co-butyl methacrylate).

iii. **Thermo-reversible type**; e. g. Pluronics (poloxamer), tetronics (poloxamines), cellulose derivatives (Methylcellulose, HPMC, Ethyl hydroxyl ethyl cellulose (EHEC) and poly (ethylene oxide)-b-poly(propylene oxide).

pH triggered systems:A pH-sensitive gelling system can be created by the use of various polymers that are capable of reacting to the changing environmental pH. These polymers have ionizable functional groups that can easily lose or accept protons in response to the changing environmental pH.These polymers can be triggered by the presence of certain ionizable groups called poly-electrolytes. These groups can either increase or decrease the external pH, which leads to swelling and formation of the in-situ gels. Some of the anionic groups that are commonly used in the production of pH-sensitive gelling systems include the following: PAA (Carbopol, carbomer), polyethylene glycol, pseudo latexes, Polymethacrylic acid and cellulose acetate phthalate (CAP).

B. Physically Induced In-Situ Gelling System

These in-situ gelling systems are based on the concept that when a material absorbs water from the surrounding environment, it swells and expands to desired space.

Diffusion or Solvent exchange: In this, solvent molecules diffuse into the surrounding tissue from the polymer solution. This process results in the solidification or precipitation of the polymer matrix. N-methyl pyrrolidone (NMP) is the commonly used polymer in this approach.

Swelling: When the water from the environment is absorbed by a certain material, it can swell and forms an in-situ gel. One of the substances that can be used in this process is myverol 18-99 (glycerol monooleate), which contains polar lipid that swells in water and forms a lyotropic liquid crystalline phase structure. It is bioadhesive and can be degraded in vivo.

Osmotically Induced In-Situ Gelling System: The osmotically induced gelling process is carried out by introducing a certain type of polymer that is sensitive to changes in ionic strength. It is considered that

the rate of gelation can vary depending on the osmotic gradient across the surface of the gel. The aqueous solution of polymer forms a clear gel in the presence of mono or divalent cations. The polymers like gellan gum and alginates show osmotically induced gelation.

C. Chemically Induced In-Situ Gelling System: Chemical reactions that result in in-situ gelation may involve precipitation of inorganic solids by following processes.

Ionic cross-linking: Ion-sensitive polymers like carrageenan, gellan gum, pectin, and sodium alginate undergoes a phase change to form gel in the presence of various ions like k+, Ca2+, Na+, and Mg+2.

Enzymatic cross-linking: In this process, the gel was formed by cross-linking with the enzymes that are present in the body fluids.This approach has advantages over chemical and photochemical methods like it performs effectively under physiologic conditions without the need for potentially harmful chemicals like monomers and initiators.

Photo-initiated polymerization: In this process, in-situ gels are formed by injecting monomers or reactive micromere solutions and the initiators into a tissue site, and the application of electromagnetic radiation. Usually, long UV (i.e., ketones) and visible (camphor-quinone and ethyl eosin) wavelength polymers areused.[4,5,13]

CLASSIFICATION OF IN SITU GEL POLYMERS

The polymers used for in situ gelling systems can be broadly classified into two types:

1. **Natural polymers** (E.g., Alginic acid, Gellan gum, Pectin, Chitosan, Carrageenan, Xanthan gum, and Guar gum, etc.)
2. **Synthetic or semi-synthetic polymers** (E.g., Hydroxy propyl methyl cellulose, Cellulose acetate phthalate, Methylcellulose, polyacrylic acid, poly (lactic-co-glycolic acid, and poloxamers).

1. **Natural polymers**

a) **Alginic acid or sodium alginate:**Alginic acid is a linear block copolymer that is hydrophilic in nature. Aqueous solutions of alginates form gels upon the addition of di (Ca^{+2}, Mg^{+2}) and trivalent metal ions. Its favourable biological properties include its mucoadhesion, biodegradability, and nontoxicity.

b) **Carrageenan:** Based on the number and position of sulphate group it is classified into three types:

i. **Iota carrageenan:** It is completely soluble in hot water and forms an elastic gel in the presence of calcium or potassium ions.
ii. **Kappa carrageenan:** It is also soluble in hot water and forms a 'gel' in the presence of potassium ions and shows similar properties to locust bean gum.
iii. **Lambda carrageenan:** It is completely soluble in cold water but does not induce gel formation. However, it forms highly viscous solutions.

c) **Chitosan:**Chitosan is a cationic, amino polysaccharide that can be formed by the alkaline deacetylation of chitin. It is a thermosensitive, biocompatible, and biodegradable copolymer that forms an in-situ gel by various stimuli such as temperature, pH, and ionic. Phosphate, oxalate, molybdate, and sulphate ions are responsible for the gelling of chitosan. Chitosan has been proven in enhancing the absorption of certain drugs by nasal delivery due to its high viscosity and bioadhesive properties.

d) **Gellan gum:**An anionic deacylated gellan gum like alginate, forms gel in the presence of mono or divalent metal cations. Gellan gum is a commonly used polymer in the preparation of in-situ gels. It is generally accepted for nasal delivery due to its rapid gelling properties upon contacting the nasal mucosa as potassium, calcium, and sodium in the nasal mucus are sufficient to stimulate the gelation process.

e) **Pectin:**Pectin is a cationic polysaccharide that is composed of methylated esters of α-(1, 4)-D galacturonic acid. It is applicable in water-soluble formulations only. Its gelation properties can be determined by the degree of esterification of the galacturonic acid. Low methoxyl(LM) pectin is ideal for the delivery of drugs to the nasal cavity as it is highly mucoadhesive and able to gel upon contact with the nasal mucosa without the addition of exogenous cations.

f) **Thiolated chitosan or Thiomers:** These are cationic, hydrophilic macromolecules, exhibiting much higher mucoadhesive properties compared to other polymers. It acts as a permeation enhancer. It interacts with mucus glycoproteins or cysteine-rich sub-domains by the simple oxidation process via crosslinking intra-and inter-disulphide bonds that lead to gel formation reaching the physiological environment.

g) **Xanthan gum:**Xanthan gum is a high-molecular weight polysaccharide that is soluble in both hot and cold water and exhibits good stability in acidic and alkali conditions.

2. Synthetic or semi-synthetic polymers

a) **Poloxamers:**These are commercially known as Pluronics. They undergo in situ gelation due to physiological temperature. The concentration of polymer and PEO to PPO ratio influence the gelation

temperature of the polymer. Among different grades, Pluronic F-127 is a commonly used in-situ gelling polymerthatcan be combined with other mucoadhesive polymers such as HPMC and Carbopol 934 to ensure a long residence time at the application site. Poloxamer also has been used to increase the rate of drug permeation across the mucosa. In addition, it can be used as a non-ionic surfactant to promote the absorption of drugs through the mucus by decreasing the elasticity and viscosity of the mucus.

b) Hydroxypropyl methylcellulose (HPMC) and **Methylcellulose(MC):**These are in-situ gelling cellulose derivatives that are biocompatible, thermoreversible, and mucoadhesive in nature. The aqueous solution of MC and HPMC undergoes a phase transition into gelling polymers at higher than the physiological temperature but this temperature can be lowered by making various physical and chemical changes in the polymers.

c) Carbopol: This cross-linked polyacrylic acid has a high molecular weight and exhibits good mucoadhesive properties compared with other cellulose derivatives. It stays in solution form at acidic pH but forms a low viscosity gel at alkaline pH.A large concentration of Carbopol is required to form stiff gels and it is not easily neutralized by the buffering action of nasal mucus. To improve the gelling properties and reduce the total polymer content, a suitable polymer should be added to the formulation.

d) Poly (lactic-co-glycolic acid) or PLGA: It is a synthetic, biocompatible, and biodegradable copolymer of polylactic acid (PLA) and polyglycolic acid (PGA). These are used in controlled drug delivery systems.

e) Poly (N-isopropyl acrylamide) or PNIPAAm: It is a temperature-sensitive phase transition polymer with a phase transition at 32-35°C which is closer to the human body temperature.[1,2,12-14]

METHODS OF PREPARATION

Generally, in-situ gelling systems are prepared by two methodsnamely:

1. Cold Method and **2**. **Hot Method**

1. **Cold method:**The cold method involves stirring a drug in a sufficient quantity of distilled water and keeping it in a refrigerator at 4°C overnight. Then the in-situ gelling polymer is slowly added to the solution with continuous stirring. The mixture is then stored in a cool refrigerator until it has a clear solution. Finally, the volume is adjusted. This method is usually used when chitosan, Carbopol, and poloxamer are used as gelling polymers.
2. **Hot Method:**When pectin or gellan gum is used as a gelling polymer, the hot method is usually used. During the process, at high temperatures, the chains of the gellan gum are slowly dissolved in water and assume a random-coil conformation with high segmental mobilityin the solution. This solution slowly undergoes gelation upon cooling in the presence of ions like K^+ or Ca^{2+}. Likewise, pectin also needs high temperatures for its demethoxylation, which helps in solubilizingthe pectin.[1,14]

EVALUATION PARAMETERS OF NASAL IN-SITU GELS

1. **Texture analysis:** Texture analysis is performed to determine the consistency, firmness, and cohesiveness of the gel formulation. It is used to measure the syringability of the gel so it can be easily administered in-vivo.[4]
2. **Measurement of Gelation Time:** 2 ml of formulation is taken in a test tube and kept in an oven at 37° C temperature. At specific time gelation of in-situ gel is examined.[4]
3. **Gel strength determination:** This test was performed using the modified Gel strength apparatus. Gel was placed in a 100 ml measuring cylinder. Gelation was induced by Simulated nasal fluid(SNF).The apparatus for measuring gel strengthwas then placed onto the gel. The gel strength was measured as the time (in seconds) required to move the apparatus (35g piston) 5 centimeters down through the gel.[4]
4. **In vitro drug release studies:** The drug release studies were performed on a plastic dialysis cell which is composed of a receptor and a donor compartment. The two compartments were separated using a membrane made up of cellulose. The formulation is then placed inside the donor compartment. The specific volume of the receptor solution can be removed at specific time intervals and replaced with fresh media. This receptor solution is analysed for the drug release by a specific analytical method.[4]
5. **Drug content determination:** The vials containing the formulation were shaken for 2–3 min manually and 100 µL of the preparation was transferred to 25 ml volumetric flasks and a sufficient quantity of the phosphate buffer pH 6.2 was added to made up the volume. The amount of drug was determined using UV–vis spectrophotometer..[4]
6. **Nasal Mucociliary Transport Time:** This test is used to know the residence time of in situ gel in the nasal cavity. The in situ gel formulations and physiological saline solutions both containing methylene blue (5 mg/mL) was prepared. Rats (n = 5) were anesthetized by sodium thiopental (7

mg/mL) intramuscular injection. Then 10 µL of each sample was infiltrated into the right nostril of the rat using a micropipette, respectively. By using wet cotton swabs the throats of the rats were wiped, and the appearance time of the blue dye was recorded. [4]

7. **Histopathological studies:** Histopathological studies were performed on the isolated nasal mucosa of sheep obtained from the local slaughterhouse. The tissue incubated in phosphate buffer (pH 6.2) was compared with tissue incubated in the diffusion chamber of Franz cell with in situ gel formulations. Tissue was fixed in 10% buffered formalin (pH 6.2), routinely processed, and embedded in paraffin after these paraffin sections were cut and stained with hematoxylin and eosin. The sections were examined by optical microscopy to examine the morphological changes to the tissue.[**4]**
8. **Ex vivo permeation study:** A piece of the fresh sheep nasal mucosa obtained from the local slaughterhouse was fitted as a flat sheet with the mucosal side facing the donor compartment in a two-chamber diffusion cell which is maintained at 37 ± 0.5°C. Phosphate buffer pH 7.4 was then added to the receptor compartment. After a preincubation time of 20 min, 2 mL formulations were placed on the mucosal surface in the donor compartment. Gelation was induced by simulated nasal fluid. At a predetermined time 0.5 ml samples were withdrawn from the receiver compartment and replaced the same volume with phosphate buffer pH 7.4 after each sampling. Samples so withdrawn were analysed. Permeability coefficient "p" which is given in cm/h was calculated by: [4]

$$\boldsymbol{P = \frac{dQ/dt}{C0\ A}}$$

Where,
p - dQ/dt is flux or permeability rate (mg/h),
C0 - Initial concentration of drug in the donor compartment and
A - Effective surface area of the nasal mucosa.

9. **pH of gel:**After preparing the insitu gel pH of the formulation is immediately checked using a calibrated digital pH meter. In the case of nasal preparations, the pH should between 5.5 to 6.5 pH to avoid irritation and improve patient tolerance and compatibility.[**5]**
10. **Gelling capacity:** By placing a drop of a freshly prepared formulation in a vial containing 2 ml of stimulated nasal fluid (SNF) and note down the time taken for the 'gel' formation and 'gel' to dissolve in 7.4 pH phosphate buffer. It is used for the determination of the suitable polymer concentrations or gelling agents to form in situ gelling systems.[**5]**
11. **Viscosity and rheology:** At room (i.e., 25 °C) and body temperatures (i.e., 37±0.5 °C)viscosity was measured using a Brookfield viscometer. Rheology was observed to know the thixotropic behaviour of the gel. Before and after the gelation process the in-situ gelpreparations should show pseudo-plastic and Newtonian flow. Before it should be 5-1000 m Pas ('sol') and after 50-50,000 m Pas ('gel'), respectively.[**5]**
12. **Appearance and Clarity:**The appearance of the gel should be transparent. The formulations were observed for colour, odour, and the presence of suspended particulate matter by the naked eye under the white and black background to inspect the clarity.[**5,13]**
13. **Sol-gel transition temperature:** In situ gelling systems are composed of thermoreversible polymers which are known to exhibit a phase transition at a temperature known as the sol-gel transition temperature. The formulation in solution form is kept in a sample tube at a specific temperature and then heated at a specified rate. The sol-gel transition temperatureis defined as the temperature at which the sol gets converted into a gel which is indicated by a lack of movement of the meniscus on tilting the tube.[**13]**
14. **In Vitro Mucoadhesive Strength:** The force that was required to remove the in-situ gel formulation from the two nasal mucosae was determined using a specialized chemical balance. On one side of the balance, one of the nasal mucosae was placed on top of the clear glass surface and tied with a rubber band while the other was placed to the bottom of left pan in an inverted position so that it faces the first mucosa. A 50mg of the in-situ gel formulation was then placed in between the two nasal mucosae and allowed to remain in contact with the two mucosae for a few minutes. On the right pan, weight was gradually increased until two mucosae get detached from each other. Mucoadhesive strength is expressed as force or stress detachment per cm square of the area of mucosa used. It is given by the equation: [**15]**

$$\boldsymbol{Detachment\ stress = \frac{m * g}{A}}$$

Where,
m- Weight in grams required to separate the two mucosae

g - Acceleration caused due to gravity
A - Exposed surface area of the mucosal tissue in cm^2

Table 1: In situ gelling systems

S.no	Drug	Category	Stimulus responsive agent	Triggering factor	Year	Ref
01	Doxylamine succinate and pyridoxine HCl	Gestational, nausea and vomiting	poloxamer407, poloxamer188, Carbopol 971P	Temperature	2022	**16**
02	Methotrexate	Anti-cancer	chitosan and Poloxamer 407	Temperature	2022	**17**
03	Granisetron	Anti-emetic	Poloxamer 407, Poloxamer 188 and Carbopol 971P	Temperature	2022	**18**
04	Darunavir	HIV infection	Poloxamer 407 and Carbopol 934P	Temperature	2022	**19**
05	Selegiline	Antidepressant	chitosan and ß-glycerophosphate	Temperature	2022	**20**
06	Mamentine HCl	Alzheimer's disease	Poloxamer-188 and Carbopol-934	Temperature	2021	**21**
07	Piribedil	Anti-Parkinson	Methyl Cellulose	Temperature	2021	**22**
08	Rufinamide	anti-epileptic	xyloglucan	Temperature	2021	**23**
09	Paroxetine	Antidepressant	Gellan gum and HPMC E15 LV	Ionic	2020	**24**
10	Sumatriptan succinate	Anti-migraine	Poloxamer 407 and HPMC K4 M	Temperature	2020	**25**
11	Duloxetine HCl	Antidepressant	F127, and Pluronic F68	Temperature	2020	**26**
12	lamotrigine	Anticonvulsant	sodium alginate, methyl cellulose and chitosan	pH	2019	**27**
13	Clonazepine	Anti-psychotic agent	Pluronic F-127 and F-68	Temperature	2019	**28**
14	Almotriptan maleate	Anti- migraine	Poloxamer 407	Temperature	2018	**29**
15	Buspirone HCL	anxiolytic agent	Carbopol 934P	pH	2018	**30**

Figure 3. Advantages of in-situ gelling systems.[4,5,7,11,12]

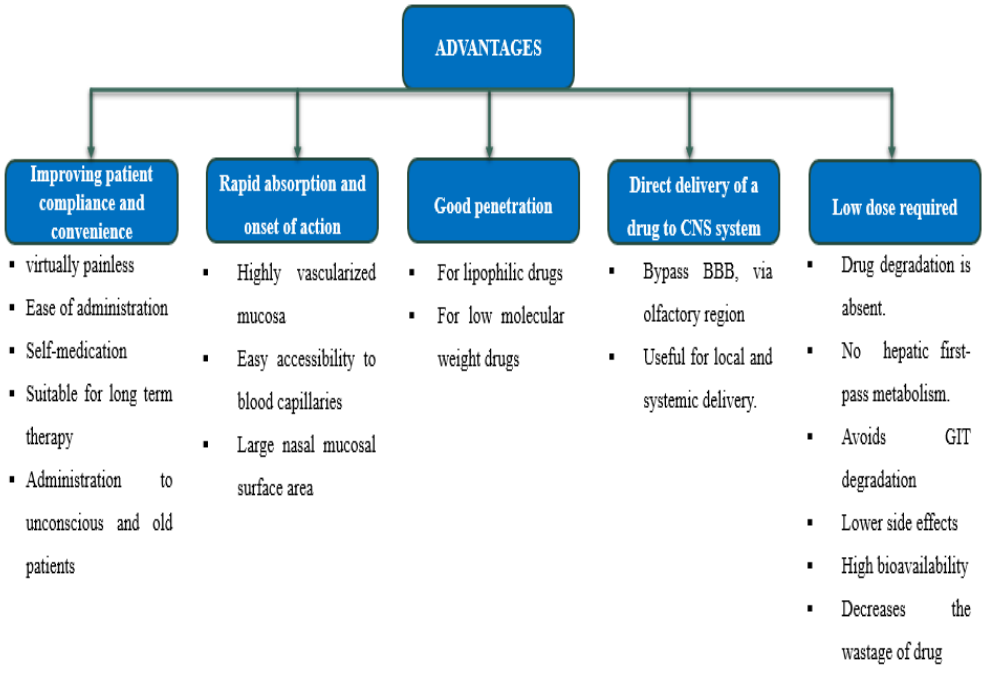
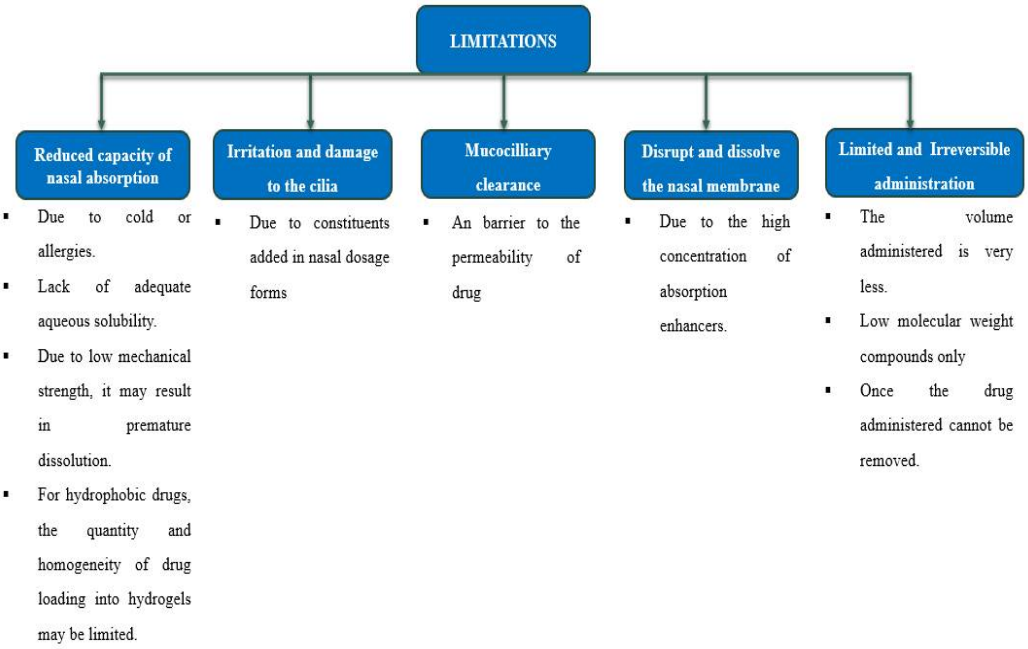


Figure 4. Limitations of in-situ gelling systems.[4,5,7,11,12}



CONCLUSION

Nasal drug delivery is a fast-emerging field as an alternative route for the administration of drugs and biomolecules that are susceptible to gastrointestinal degradation or produce undesirable effects when administered orally. Nasal route circumvents bioavailability issues and also offers the advantage of direct nose-to-brain delivery through various pathways. The success of any dosage form is directly linked to patient compliance which in situ gels can offer. In situ nasal gelling systems can be considered a `reliable and non-invasive alternative for nose-to-brain delivery that can overcome some disadvantages associated with conventional dosage forms.

REFERENCES

1. Mayuri Ban, M., Vijay Chakote, R.,GuneshDhembre, N., Jeevan Rajguru, R.,&Deepak Joshi, A.(2018). In-situ Gel For Nasal Drug Delivery.Int. J. Dev., 08(2):18763-18769.
2. Wang, X., Liu, G., Ma, J., Guo, S., Gao, L., Jia, Y., Li, X., & Zhang, Q. (2013) In Situ Gel-Forming System: An Attractive Alternative for Nasal Drug Deliver.Crit. Rev. Ther. Drug Carr., 30(5):411–434.
3. Devi,R D., Abhirami, M., Brindha, R., Gomathi, S.,&Vedhahari, B.N. (2013)In-situ gelling system – potential tool for improving therapeutic effects of drugs.Int. J. Pharm. Pharm. 5(3):27-30.
4. Sabale, A., Kulkarni, A., Sabale, A. (2020) Nasal In-Situ Gel: Novel Approach for Nasal Drug Delivery.**J. drug deliv. Ther.**10(2-s):183-197.
5. Padmasri, B.,Nagaraju, R., &Prasanth. D. (2020) A comprehensive review on in situ gels. Int. J. Appl. Pharm. 12(06):24-33.
6. Lochhead, J., &Thorne,RG. (2021) Intranasal delivery of biologics to the central nervous system. Adv. Drug Deliv. Rev.64(7):614-628.
7. Vijay singPardeshi,C S., &Belgamwar, V S.(2013). Direct nose to brain drug delivery via integrated nerve pathways bypassing the blood--brain barrier: an excellent platform for brain targeting. Expert Opin Drug Deliv. 10(7):957-972.
8. Tyler P. Crowe, Heather West Greenlee, M.,AnumanthaKanthasamy, G., Walter Hsu, H. (2018). Mechanism of intranasal drug delivery directly to the brain. Life Sci.195:44-52.
9. Agrawal, M., Saraf, S., Saraf S., Dubey S, K., Puri, A.,Gupta U., Kesharwani P., Ravichandiran, V., Kumar, P., Naidu, V.G.M., Murty U S.,Ajazuddin.,Alexander, A.(2020). Stimuli-responsive In situ gelling system for nose-to-brain drug delivery.**J Control Release**. 327(10):235-265.
10. Dhuria, S V., Hanson, L R., Frey, W H.(2010). Intranasal delivery to the central nervous system: mechanisms and experimental considerations. J. Pharm. Sci.99(4):1654-1673.
11. Arora, P., Sharma, S., & Garg, S. (2002) Permeability issues in nasal drug delivery. Drug Discov. Today.7(18):967-975.
12. konatham, M., Gorle, M T., Pathakala, N.,bakshi, V., mamidisetti,Y D., chinthakindi, P., & Jadi, R K.(2021) In situ gel polymers: a review. Int. J. Appl. Pharm. 13(1):86-90.
13. Hejal,PB., jivani, R., Jivani np., Patel ld., ami, M.,&krunal, S. (2012) Novel insitu polymeric drug delivery system: a review. J. drug deliv. ther. 2(5):136-145.
14. Singh, RMP., Kumar, A.,&Pathak, K. (2013) Mucoadhesive in situ nasal gelling drug delivery systems for modulated drug delivery, expert opinion on drug delivery. 10:115-130.

15. Asha Paul, K.M., Fathima, & Nair, S C. (2017) Intra Nasal InSitu Gelling System of Lamotrigine Using Ion Activated Mucoadhesive Polymer. 11:222-244.
16. Salem, F., Ali, A.,Hegazy, A M., Abdel-Rahman A., Heba M. S. &Aboud.(2022) Harnessing of Doxylamine Succinate/Pyridoxine Hydrochloride-Dual Laden Bilosomes as a Novel Combinatorial Nano paradigm for Intranasal Delivery: In Vitro Optimization and In Vivo Pharmacokinetic Appraisal. J. Pharm. Sci. 111(3):794-809.
17. Ourani-Pourdashti, S., Mirzaei, E.,Heidari, R., Ashrafi, H. &Azadi, A. (2022) Preparation and evaluation of niosomal chitosan-based in situ gel formulation for direct nose-to-brain methotrexate delivery.Int. J. Biol. Macromol.213:1115-1126.
18. Eissa, E.M.,Elkomy, M.H., Eid, H.M., Ali, A.A., Abourehab, M.A.S., Alsubaiyel, A.M., Naguib, I.A., Alsalahat, I., Hassan, A.H. Intranasal Delivery of Granisetron to the Brain via Nanostructured Cubosomes-Based In Situ Gel for Improved Management of Chemotherapy-Induced Emesis. Pharmaceutics.14:1374.
19. Nair, A.B., Chaudhary, S., Shah, H., Jacob, S., Mewada, V., Shinu, P., Aldhubiab, B., Sreeharsha, N., Venugopala, K.N., Attimarad, M. (2022) Intranasal Delivery of Darunavir-Loaded Mucoadhesive In Situ Gel: Experimental Design, In Vitro Evaluation, and Pharmacokinetic Studies. Gels.8:342.
20. Srivastava, S K., Prasad, M. & Jha. A K. (2022) Development and Evaluation of Thermo Triggered in situ Nasal Gel of Selegiline for Depressive Disorders: In vitro, in vivo and ex vivo Characterization.**Res J Pharm Technol**.15(4):1424.
21. MohapatraS., jain, S., &Shukla,K. (2021) Formulation development and evaluation of MamentineHclLoaded Thermosensitive in situ nanogel for nasal delivery. J. Adv. Sci. Res. 12(1):172-178.
22. Uppuluri, C T., Ravi, P R.,&Dalvi, A V. (2021) Design, optimization and pharmacokinetic evaluation of Piribedil loaded solid lipid nanoparticles dispersed in nasal *in situ* gelling system for effective management of Parkinson's disease**.**Int. J. Pharm.606:120881.
23. Dalvi A., Ravi PR.,&Uppuluri CT. (2021) Rufinamide-Loaded Chitosan Nanoparticles in Xyloglucan-Based ThermoresponsiveIn Situ Gel for Direct Nose to Brain Delivery. Front. Pharmacol. 12:691936.
24. Thakkar, H.,Vaghela, D., Patel, B P.(2021) Brain targeted intranasal in-situ gelling spray of paroxetine: Formulation, characterization and in-vivo evaluation,J Drug Deliv Sci Technol.62.
25. Mahapatra, AP k.,Dr.Saraswat, R., Dr.Mahapatra A K.,Patil, R Y.,Dr. panda, K C. (2020) Formulation and Evaluation of thermal induced intranasal in-situ gel of Sumatriptan Succinate, IOSR J. Pharm.10(2):16-26.
26. Elsenosy, F M., Abdelbary, G A.,Elshafeey, A H.,Elsayed, I., Fares, A R. (2020). Brain Targeting of Duloxetine HCL via Intranasal Delivery of Loaded Cubosomal Gel: In vitro Characterization, ex vivo Permeation, and in vivo Biodistribution Studies.Int J Nanomedicine.15:9517–9537.
27. Parashar, P., Diwaker, N., Kanoujia, J., Singh, M., Yadav,A.,Indu Singh, I.&Saraf, S A. (2020) In situ gel of lamotrigine for augmented brain delivery: development characterization and pharmacokinetic evaluation, J. Pharm. Investig. 50:95-105.
28. Ravikrishna V. &Krishnaveni J. (2019) Development and evaluation of clozapine intranasal mucoadhesive in situ gels for brain targeting.J. drug deliv. ther. 9(2-s):198-207.
29. Abdel Hamid Abou Youssef, N., Kassem, A., MohamedFarid, R., AhmedIsmail, F., Abd ElsameaEL-Massik, M., Ahmed Boraie, N. (2018)A novel nasal Almotriptan loaded solid lipid nanoparticles in mucoadhesive in situ gel formulation for brain targeting: Preparation, characterization and in vivo evaluation. Int. J. Pharm.548(1):609-624.
30. Mathure D., Madan, J R., Gujar, K N.,Tupsamundre, A., RanpiseH A., & Dua, K. (2018) Formulation and Evaluation of Niosomal in situ Nasal Gel of a Serotonin Receptor Agonist, Buspirone Hydrochloride for the Brain Delivery via Intranasal route.Pharm. Nanotechnol. 6:69-78.

CITATION OF THIS ARTICLE

D Srilakshmi, J Pooja, Prasanthi.D. Intranasal *In Situ* Gelling Systems - An Approach for Enhanced CNS Delivery of Drugs. Bull. Env.Pharmacol. Life Sci. Vol 12[5] April 2023: 237-246.