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# A COMPREHENSIVE REVIEW ON THERMOREVERSIBLE NASAL IN-SITU GEL DRUG DELIVERY SYSTEM

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**ABSTRACT:**

The desire for prolonged and controlled drug delivery has led to research into improving product effectiveness, reliability, and safety. The in-situ polymeric system is gaining attention for its potential for controlled release. It has been used to administer drugs both locally and systemically. It has gained popularity due to its strong vascularization, permeability, rapid start of action, low enzymatic degradation, and avoidance of hepatic first pass metabolism. This article aims to provide insight into various nasal absorption mechanisms and drug delivery methods and challenges.

**Keywords:** in situ gel, nasal delivery, nose to brain delivery, polaxomer

## INTRODUCTION

There are increasing variety of medicines are available for systemic and local administration through the nasal route, making it a significant drug delivery method. In-situ gel is a novel dosage form that has been applied in nasal drug delivery recently.[1] Nasal in-situ gels are instilled into the nasal cavity as a low viscosity solution as compared to liquid nasal formulation. A gel is produced by the polymer changing its structure upon coming into contact with the nasal mucosa. Such that it delivers the drug gradually and increases the amount of time the medicine is in touch with the nasal cavity's absorptive site. Gel is a state that exists between liquid and solid. It is made up of long polymer molecules that are physically cross-linked, trapping liquid molecules inside a three-dimensional network that has been swelled by a solvent. Before administration, in-situ gelling system is a liquid aqueous solution, under physiological circumstances it transforms into gel.[2]

Drug distribution using in situ gel can occur through different routes including oral, ophthalmic, vaginal, rectal, intravenous, and intraperitoneal. Crosslinking of the polymer chain, which can be achieved by either non-covalent (physical crosslinking) or covalent (chemical) bond creation results in gel formation. A variety of mechanisms can cause the formation of in-situ gels. These include mechanisms based on chemical reactions, temperature changes, and pH-triggered systems, as well as mechanisms based on physical changes in biomaterials, such as swelling and solvent exchange, and UV radiation, ionic crosslinking, and ion activated systems.[3] Migraine is neurological condition frequently characterized by recurring episodes that are followed by main symptoms such as headache, gastrointestinal, neurologic, and occasionally auditory problems. Numerous parameters, including the nasal cavity's capacity for drug volume (<0.2 mL), anterior leakage, and mucociliary clearance, enzymatic breakdown might influence the nasal drug delivery system. [4,5] It is possible to develop intranasal formulations to address the causes of limited bioavailability. The high vascular mucous membranes of nose facilitate the faster absorption of unmetabolized drug into the central nervous system.[6] In order to improve bioavailability, new research has recently been conducted on solid dispersion, liposomes, chitosan microparticles, polymeric lipid-core nanocapsules, and lipid vesicles. This present study focuses on the challenges that may face to develop in situ gel, mechanism of drug permeation and absorption, method of preparation and evaluation of in situ gel.

## MECHANISM OF ACTION:

The primary part of the respiratory system that serves as an entrance and passageway for breathed air is the nasal cavity.[7] The nasal septum helps separate it into two lateral portions. As part of the body's first line of defense, the mucous membrane that lines the inside of the nose cavity shields the respiratory system from pathogens, poisons, infections, and allergens. In addition to breathing, it is often referred to as the olfactory center.[8] Olfactory sensory neurons, which detect smell from inhaled air, are abundant in the posterior portion of the nasal cavity.[9] Depending on the physical structure and function of various regions, the nasal cavity is divided into three sections: the vestibular, respiratory, and olfactory regions. The vestibular area, often known as the nostril opening, is located in the nasal cavity's anteriormost part. The mucus layer and ciliated hairs responsible for mucociliary clearance surround it.[10] Following that, the region responsible for breathing functions is known as the respiratory region. It is responsible for breathing and covers a considerable amount of the nasal cavity (about 130 $cm^2$). The ciliated and non-ciliated epithelium, goblet cells, and basal cells make up the respiratory area. It is rich in blood capillaries and contains trigeminal (higher) and olfactory (lesser) neurons.[11] The next and most posterior portion is known as the olfactory region. It is located in the top section of the nasal cavity, beneath the cribriform plate, and is connected to the ethmoid bone of the skull. The olfactory layer is made up of basal, microvillar, supporting, and olfactory epithelium cells. It is densely packed with olfactory sensory neurons and, to a lesser extent, trigeminal neurons, which connect the nasal cavity to the brain's olfactory bulb.[12]

The olfactory neuroepithelium is an unique structure that links the CNS to the external environment directly. As a result, the olfactory route is being extensively researched in order to directly transport the drugs to the CNS while bypassing the BBB. The olfactory neurons only enable the transfer of smaller particles (200 nm) from the nasal cavity to the brain via a straight path (passive diffusion).[13,14] The precise mechanism of nose-to-brain medication targeting is unknown at this time; however, certain ideas or routes have been proposed by various scientists based on in vitro, in vivo, and clinical studies, which we will examine in the following text. The major route of drug transport from the nasal cavity to the brain area is thought to be the neuronal channel via olfactory and trigeminal neurons, while the secondary routes use CSF22, the lymphatic system, and vascular absorption (by general circulation).[15] The major and direct route of medication absorption from the nasal cavity to the brain area is via the olfactory and trigeminal nerves. The cribriform plate is crossed by the olfactory neuronal route, which connects the nasal cavity directly from the olfactory bulb of the brain. Passive diffusion (small lipophilic molecules) and endocytosis or paracellular transport (hydrophilic and big moieties) transfer drugs across olfactory neurons. [16,17] The trigeminal nerve, on the other hand, connects the nasal cavity to the cerebrum and pons region of the brain, as well as, to a lesser extent, to the frontal cortex and olfactory bulb. [16,10] Thus, by studying the specific process of drug transport, one may forecast the brain's target site. However, controlling transportation along a single route is difficult. Furthermore, the second route involves drug absorption via the lymphatic system and CSF, which connect the lymphatic system of the nasal cavity to the CSF of the CNS's subarachnoid space via olfactory nerves situated in the perineural space.[18,19] Various investigations revealed CSF-lymphatic drug transport as a minor route of nose-to-brain drug transfer, but no separate analysis has been undertaken. The medicine enters the CSF and perivascular area, where it is transported to the rest of the brain. Drug distribution and transport in the CSF are solely determined by drug molecule features such as lipophilic behavior, polarity, solubility, degree of ionization, and molecular weight.[20] Another transport mechanism is the vascular path, which is the secondary route of transport when it comes to nose-to-brain delivery. When the drug is administered deeper into the nasal cavity, part of it enters the systemic circulation via the vasculature of the respiratory area and subsequently reaches the brain via the blood volume distribution after crossing the BBB. As a result, the also receives peripheral exposure and may have an adverse effect on peripheral organs. Nonetheless, treatments' modest peripheral exposure mitigates the peripheral side.[21] **Figure 1** depicts a different transport mechanism for nose-to-brain medication delivery.

The nasal cavity's olfactory area is densely packed with olfactory (to a greater extent) and trigeminal (to a lesser extent) nerve terminals. When drugs come into contact with these nerve terminals in the posterior area of the nasal cavity, they begin to travel to the brain via the lamina propria via cellular transport pathways. Depending on the type of the drug molecule, the cellular transit involves both extracellular and intracellular transport. The drug moiety first enters the brain via the lamina propria area before crossing the cribriform plate via nerve channels generated by olfactory ensheathing cells. After entering the CSF, the drug is dispersed to the various areas of the brain by bulk flow after mixing with the interstitial fluid, and then throughout the entire CNS via perivascular transport.[16,10,22]

The essential method of nose-to-brain delivery, in particular, is cellular transport (drug transport through nerve cells), which is divided into two stages (i) intracellular/intraneural transport and (ii) extracellular transport. The drug entered the nerve cells (trigeminal and olfactory sensory neurons) from the nasal cavity (respiratory and olfactory epithelial cells, respectively) via endocytosis in intracellular transport and then moved to the brain and distributed to different regions based on nerve cell dissemination via transcellular and intracellular transport. Transcellular transport is appropriate for tiny lipophilic moieties, while intracellular transport is appropriate for hydrophilic molecules.[23] The intracellular transport route is slower than the extracellular path and takes around 24 hours to disperse to different regions of the CNS.[24] The extracellular route is preferred by diverse hydrophilic molecules and big bioactives such as different proteins, peptides, and so on. Although this process is faster than the previous one, full absorption from the nasal cavity requires time. As a result, improved drug retention is a critical parameter for nose-to-brain drug delivery.[25] A more detailed mechanism is outlined in our earlier review paper, which focuses on bioactive transport from nose to brain.[16]

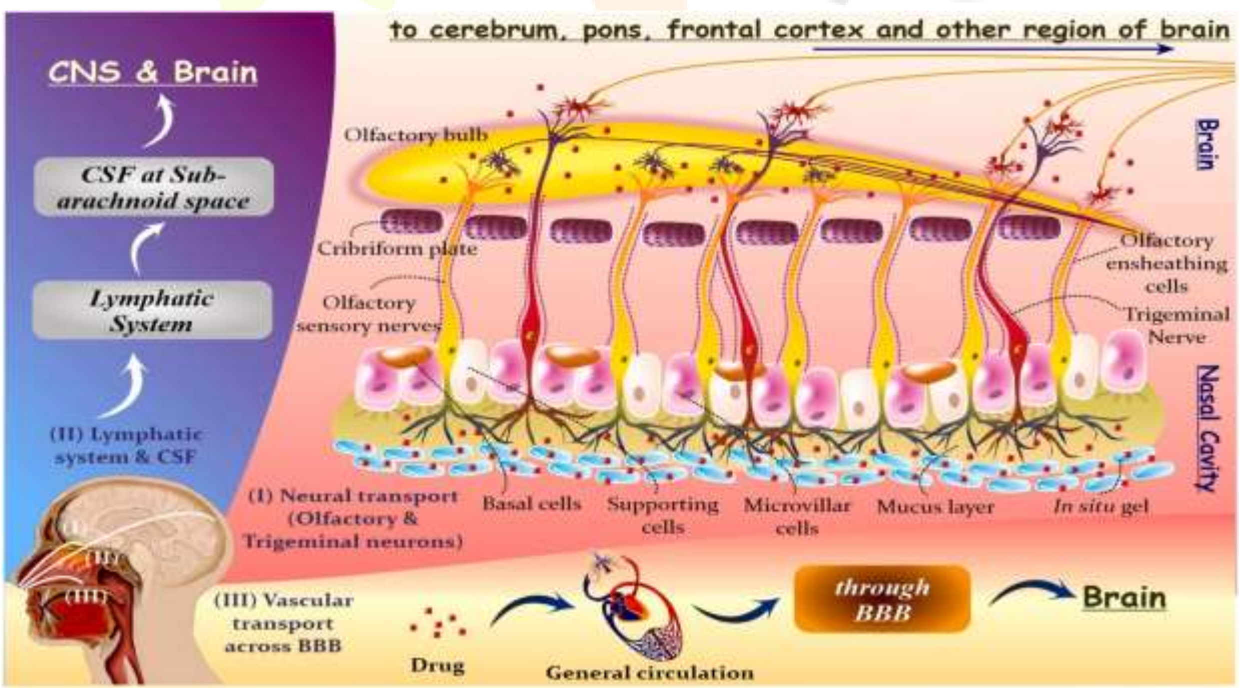


Figure. 1. Different mechanisms of nose-to-brain transport of therapeutics

**THERMOREVERSIBLE SYSTEM:**

The thermoreversible in situ gel is a technology that responds to temperature change and converts fluid into gel form at a defined temperature range. It is made up of thermosensitive polymers that undergo sol-gel transformation at temperatures ranging from 30ºCto 37°C. Aside from this temperature range, early or late gelation can occur, which means that a lower temperature results in sol form or a low viscosity liquid, while a higher temperature causes instant gelation of the outer layer with liquid imprisoned inside. Early gelation (sol form) complicates administration and handling, whereas late gelation may result in drug leakage.[27,28] The polymer that exhibits sol-gel transition at temperatures ranging from 30ºC to 37°C is thought to be appropriate for nasal in situ gel production because it prevents the transition at room temperature during storage and transportation and allows for quick sol-gel transition after administration in the body.[29]

Poloxamer is a key thermoresponsive polymer that is frequently utilized in the production of nasal in situ gel. P407 and P108 are two types of poloxamer that are often used for nasal preparation. Because of its qualities, the first is often chosen over the latter, while a combination of both P407 and P108 in varied ratios is sometimes utilized to achieve desired gelling behavior.[30,31] Furthermore, chitosan is an essential polymer in this category that is used in nasal formulations. In addition to thermoresponsive gelation, chitosan has outstanding bioadhesive properties and is utilized as a viscosity enhancer. The sol-gel transition and gel strength of chitosan-based formulations, however, were not determined to be suitable for nasal medication delivery. As a result, it is frequently utilized in conjunction with poloxamer to create a potential nasal in situ gel for neurotherapeutic brain delivery.[32]

Temperature-triggered sol-gel transformation involves the micellization of a thermoresponsive polymer or polymeric blend, such as P407, chitosan, or other polymeric mix, in response to a thermal stimulus. As the temperature rises, the polymer units arrange themselves into micellar packing, resulting in gel formation. The temperature change causes the polymer to desolve at first due to a conformational shift in the side chain. Furthermore, water molecule displacement results in micellar orientation.[28] **Figure 2** depicts the temperature-triggered sol-gel transition.

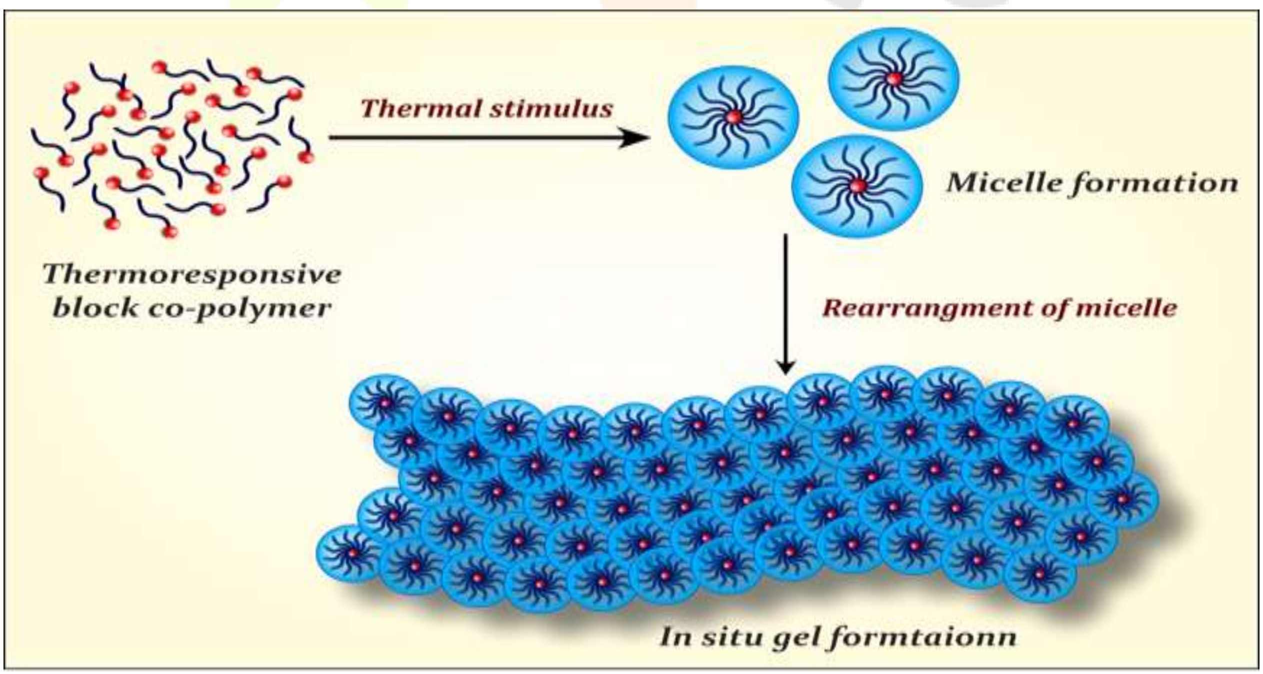


Figure 2. In situ gelation of thermosensitive polymers in response to temperature change

**CHALLENGES OF NOSE-TO-BRAIN DRUG DELIVERY:**

Nasal medication administration is made difficult by low bioavailability, muco-ciliary clearance, and enzymatic degradation. The following section discusses some essential characteristics of various barriers that primarily affect nasal medication delivery.

1. **Low bioavailability:**[31]
   - Polar drugs have a low bioavailability (approximately 10% for low molecular weight drugs and 1% for peptides like calcitonin and insulin).
   - Polar drugs have poor nasal absorption due to their high molecular weight.
   - Drugs can cross the epithelial cell membrane via transcellular and paracellular pathways.
   - Polar medicines with molecular weights less than 1000 Da will flow through the membrane via the latter methods.
   - Coadministration of absorption-enhancing medications improves nasal absorption of polar medicines.
   - Lipophilic polarity:
     i. LMW lipophilic -100% bioavailability
     ii. HMW amphipathic -10% bioavailability
     iii. Peptides<1%
   - Examples:
     i. Surfactants (Sodium lauryl sulfate, sodium dodecyl sulfate,)
     ii. Bile salts (Sodium glycocholate, sodium taurocholate, Sodium deoxycholate)
     iii. Fatty acids and their derivatives (linoleic acid)
2. **Muco-ciliary clearance:**[32]
   - It is a necessary factor that involves the joint activity of mucus and cilia in defending the respiratory tract against inhaled foreign particles.
   - Because of the high clearance over the nasal mucosa, it results in decreased drug transport.
   - It has also been demonstrated that the half-life for clearance for liquid and powder formulations that are not bioadhesive is in the range of 15-30 minutes.
   - Bioadhesive excipients are employed in formulations to counteract the fast mucociliary clearance.
   - The formulation's clearance can also be reduced by depositing it in the anterior and less ciliated region of the nasal cavity, resulting in better absorption.
3. **Enzymatic degradation:**[33]
   - When peptides and proteins move through the nasal mucosa, the molecule may be enzymatically degraded in the nasal cavity lumen or during passage through the epithelial barrier, limiting the drug's bioavailability.
   - Exopeptidases such as mono and diamino peptidases can break peptides at their N and C termini, while endopeptidases such as serine and cysteine can target interior peptide bonds, are found in these two sites. In order to overcome this barrier, enzyme inhibitors, cosolvents, and prodrugs may be used.

**FACTORS INFLUENCING NASAL DRUG ABSORPTION:**

- **Factors related to drug**
  i. **Molecular weight**[34]
     Fisher et al. concluded that the permeation of drugs less than 300 Da is not significantly influenced by the physicochemical properties of the drug (like molecular weight, size, formulation pH, and pKa of molecule). As molecular weight increases, nasal absorption of drug increases.
  ii. **Chemical form**[35]
     The chemical form of the drug is an important factor for absorption. Conversion of the drug into a salt or an ester form can change its absorption; for example, in situ absorption of carboxylic acid esters of L-tyrosine was significantly greater than that of unmodified L-Tyrosine.
  iii. **Polymorphism**[36]
     Polymorphism affects the rate of drug dissolution, solubility, and absorption through biological membranes.
  iv. **Solubility & dissolution rate**[37]
     Both are important factors in determining nasal absorption of drugs from powders and suspensions. In the nasal cavity, the deposited particles need to be dissolved prior to absorption. No absorption

takes place if particles remain in the nasal cavity. The mucosa in nasal cavity is insufficient for dissolution of drug particles, when compared to gastrointestinal fluid available in the case of oral drug delivery.

v. **Lipophilicity[38]**

On increasing lipophilicity, the permeation of the compound through the nasal mucosa increases because of high lipophilicity, though it has some hydrophilic character. Lipophilic compounds easily cross biological membranes through the transcellular route, since they are fit to partition into the lipid (bilayer) of the cell membrane and diffuse into and traverse the cell in the cell cytoplasm. Systemic bioavailability is decreased due to the hydrophilic nature of many drugs.

vi. **Partition coefficient and pKa[39]**

The pH partition theory states that non ionized species are absorbed well, when compared with ionized species, and hence it is the same in the case of nasal absorption as well.

- **Factors related to formulation**

i. **pH and mucosal irritation[40]**

In addition to the properties of the nasal surface, the pH of the formulation can affect a drug's permeation. Both the pH and pKa of drug are considered to rationalize systemic absorption. To avoid nasal irritation, the pH of the nasal formulation should be adjusted to 4.5–6.5. Avoiding irritation results in obtaining efficient drug permeation and prevents the growth of bacteria. Nasal secretions contain lysozyme, which, at acidic pH, destroys certain bacteria. Under alkaline conditions, lysozyme is inactivated and the nasal tissue is susceptible to microbial infection.

ii. **Osmolarity[41]**

Isotonic solutions are administered for shrinkage of the nasal epithelial mucosa, because of the effect of osmolarity on the absorption. This results in increased permeation of the compound because of structural changes. Isotonic solutions also known to inhibit or cease ciliary activity.

iii. **Viscosity[42]**

A higher viscosity of the formulation increases contact time between the drug and the nasal mucosa, thereby increasing permeation time. At the same time, highly viscous formulations interfere with the normal functions like ciliary beating or muco-ciliary clearance, and thus alter the permeability of drugs.

iv. **Buffer capacity[43]**

Nasal formulations are administered in small volumes ranging from 25 to 200 mL. Therefore, nasal secretions may alter the pH of the administrated dose, which can affect the concentration of nonionized drug available for absorption. Hence, an adequate formulation buffer capacity may be required to maintain the pH in situ.

v. **Drug concentration, dose, & dose volume[44]**

These are three interrelated parameters that impact the performance of the nasal delivery. • Therapeutic dose: upper limit 25 mg/dose
Higher the drug concentration, higher the permeation
Dose volume: 0.05–0.15 ml/dose

- **Physiological factors**

i. **Effect of deposition on absorption[45]**

Deposition of the formulation in the anterior portion of the nose provides a longer nasal residence time and better absorption, and this is an area of low permeability, whereas in the posterior portion of the nose, where the drug permeability is generally higher, the deposited drug is eliminated by muco-ciliary clearance and therefore has a shorter residence time.

ii. **Nasal blood flow[46]**

The nasal mucosal membrane is very rich in vasculature and plays an important role in thermal regulation and humidification of the inhaled air, and therefore the drug absorption will depend upon the vasoconstriction and vasodilatation of the blood vessels.

iii. **Effect of enzymatic activity[47]**

Many enzymes might affect the stability of drugs which are present on the nasal mucosa. For example, proteins and peptides are subjected to degradation by proteases and aminopeptidases at the mucosal membrane.

iv. **Effect of muco-ciliary clearance[48]**
The muco-ciliary clearance is inversely related to the residence time, and therefore inversely proportional to the absorption of drugs administered. It is important to maintain the nasal clearance mechanism to perform normal physiological functions like removal of dirt, allergens, and bacteria.

v. **Effect of pathological conditions[49]**
Intranasal pathologies such as infections, nasal surgery, cold, and allergic rhinitis may affect the nasal muco-ciliary transport process and/or capacity for nasal absorption. Nasal pathology also alters mucosal pH, and thus affects the absorption of drugs.

## EVALUATION PARAMETER[50]:

a) **Clarity:**
Abbe's refractometer is used to measure the refractive index of liquids. The clarity of sols, that is, formulations before gelling, can be determine in term of refractive index using Abbes refractometer. Calibrate the refractometer with water as reference standard. Adjust the refractometer scale is in such a way that the cross wire of the telescope is exactly on the boundary between the bright and dark regions. Compare the results with refractive index of water.

b) **pH:**
Calibrate the Digital pH meter by using pH buffer of 4 and 7. Take twenty milliliter of each formulation in beaker and dip glass electrode into the samples of formulations. Determine pH of the solution in triplicate.

c) **Drug content:**
Drug contents of formulation can be determined in triplicate by using double beam UV visible spectrophotometer. Take one milliliter of formulation in capacity of 10 ml volumetric flask, dilute with double distilled water and volume adjusted to 10 ml. again dilute one milliliter quantity from this solution with 10 ml of double distilled water. Finally, measure the absorbance of prepare solution at 226 nm by using UV visible spectrophotometer.

d) **Viscosity:**
Brookfield viscometer is use for viscosity measurement. performed the viscosity measurement using small volume adapter. Dip the temperature sensing probe in gel and record the temperature of gel.

e) **Mucoadhesive strength:**
It is the force required to detach the formulation from nasal mucosal tissue. The mucoadhesive force, the detachment stress of the formulation can be determined by using a modification of the mucoadhesive force measuring device. The modified balance technique using two-glass vials and sheep nasal mucosa can use. Cut a nasal mucosa from the olfactory region of sheep nasal cavity with thickness of 0.6 mm and surface area 2.5 to 3cm$^2$ and secure instantly with the mucosal side out onto each glass vial using a thread. Store the vials at 32-37$^{O}$C for 10 min. Attach one vial to one side of balance and place 0.5 ml of gel sample between the two mucosal membranes attach to the bottom of the vials. Measure the minimum weight of water require to break the mucosal adhesion.

$$\text{Mucoadhesive Strength}\ (\text{dynes/cm}^2) = \text{mg/A}$$

Where, m is weight required for detachment in g,

g is acceleration due to gravity (980 cm/s$^2$) and

A is surface area of mucosa exposed (cm$^2$)

f) **In vitro drug release:**

In vitro drug diffusion study of various formulations can be performed by using Franz diffusion cell. Use Dialysis membrane having molecular weight cut-off range of 12000–14000 kDa as diffusion membrane. Allow dialysis membrane to soak in phosphate buffer pH 6.4 for 24hr before experiment. Fill the diffusion cell with 21 ml phosphate buffer pH 6.4 and mount dialysis membrane on cell. Place the gel containing drug equivalent to 10 mg onto donor chamber. Maintain the temperature at 32–37$^{O}$C by circulating water bath. Withdrawn the samples of 1 ml at different time intervals and replace with same volume of fresh solution, filter and determine amount of drug by UV visible spectrophotometer at 226 nm.

**g) Dissolution kinetics:**

Various models like zero-order, first-order, Higuchi models, Korsemeyer and Peppasare are used to test kinetics of drug release.

## CONCLUSION:

This work aims to address the growing interest in intranasal mucosal administration, a non-invasive and needle-free way for reaching the brain through the blood-brain barrier and avoiding hepatic first-pass metabolism while delivering the medication to the brain. This approach allows for direct drug administration to the CNS via the olfactory pathway through the mucosa, resulting in improved patient compliance and comfort, lower exposure, and fewer adverse effects. It is predictable that intranasal formulations will reach their market potential. The nasal mucosa provides controlled-release medication delivery, but due to restrictions, the use of the intranasal route for drug administration is restricted. To overcome restrictions, the mucoadhesive polymeric system is utilized. The in-situ gelling device meets the first need for controlled drug delivery: ensuring patient comfort. In situ gels have further advantages.

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