# "ENHANCING NASAL DRUG DELIVERY THROUGH NIOSOMAL INNOVATIONS: A SYSTEMATIC REVIEW ON FORMULATION, STRATEGIES"

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***Abstract :***

The current analysis aims to elucidate the latest developments in nasal medication delivery technology. The non-invasive nature of the nasal pathway makes the nasal route of administration useful for a wide range of therapeutic uses. The nasal route is significant and preferred over other invasive approaches like intravenous, intracerebral, and transcranial for the systemic delivery of drugs and the treatment of central nervous system (CNS) diseases like depression, Alzheimer's disease (AD), and Parkinson's disease (PD) via the nose-to-brain pathway because it avoids the blood-brain barrier (BBB) and the hepatic first-pass effect. There are obstacles in the way of effectively delivering medication to the brain through the nasal route. Dosage constraints imposed by the nasal route are among the limitations. Limitations include the effect of mucociliary clearance and dosage limits to the nasal pathway. The effectiveness of the delivery mechanism used is a critical factor in the efficacy of nasal medication delivery. It has been confirmed that lipidic-based drug delivery systems have a positive effect on nasal delivery. Solid lipid nanoparticles, niosomes, and liposomes are a few of the well-researched lipidic carriers that have demonstrated promise for nasal medication administration. Enhanced stability, prolonged release patterns, and better drug solubility are just a few benefits of these lipid-based systems. Lipid bilayers, the building blocks of liposomes, are capable of encasing both hydrophilic and hydrophobic medications. Since niosomes are made of non-ionic surfactants, they are stable and biocompatible, which makes them appropriate drug delivery vehicles for the nose. Solid lipid nanoparticles, which are made of solid lipids, prevent pharmaceuticals against deterioration and offer controlled drug release. These lipidic-based drug delivery systems improve drug bioavailability and get around obstacles that prevent drugs from reaching the brain, hence addressing the problems related to nasal drug delivery. The possibility of lipidic-based nasal medication delivery systems to improve treatment results for CNS illnesses is highlighted by the current review in this field. As these technologies advance, they have the potential to completely transform the non-invasive nasal approach to treating neurological disorders. The purpose of this review is to examine nasal medication delivery methods, including their uses, formulations, benefits, absorption mechanisms, nasal anatomy, influencing factors, and current breakthroughs.

***Index Terms*** **- Nasal drug delivery, Noisome, Nanotechnology, Solid lipid nanoparticles.**

## I. INTRODUCTION

Compared to oral administration, intranasal therapy, a conventional treatment in the Indian medical system's Ayurvedic system, has garnered attention for its capacity to improve systemic bioavailability. With its natural benefits higher permeability, lack of pancreas and stomach enzymatic activity, neutral pH of nasal mucus, and reduced dilution by gastrointestinal contents, among others the nasal mucosa offers a quick and effective pathway for medication absorption. The nasal route's ease of use, accessibility, and permeable endothelium membrane facilitate quick absorption into the systemic circulation, preventing hepatic first-pass elimination.

One of the many benefits of intranasal medication delivery is that it can reduce dosages while still achieving therapeutic blood levels quickly, initiate pharmacological activity sooner, and have fewer side effects. The nasal cavity's low metabolic environment solves the drawbacks of the oral route while replicating the benefits of intravenous delivery. Lipophilic drugs absorb well from the nasal cavity, similar to intravenous administration, whereas hydrophilic drug absorption can be improved by absorption enhancers. This comprehensive review examines numerous techniques to nasal drug delivery and investigates various delivery systems, with a special emphasis on niosomal delivery systems. The prospective applications of these systems in nasal formulations are investigated, revealing light on their role in overcoming nasal medication delivery problems and enhancing overall efficacy [1-3].

**Merits of Nose to Brain Drug Delivery [4,5]**

i. There is no drug degradation.
ii. There is no hepatic first-pass metabolism.
iii. Quick medication absorption.
iv. Rapid commencement of effect.
v. Absorption can improve the bioavailability of bigger medication molecules.
vi. Increased nasal bioavailability for smaller medication molecules.
vii. Nasal drug delivery systems can transfer drugs that cannot be taken orally into the systemic circulation.
viii. Accessible route for long-term therapy when compared to parenteral route.

**Demerits [6]**

i. More uncomfortable for patients than oral administration systems due to the likelihood of nasal discomfort.
ii. Both the substance and the additives added to the dosage form provide a risk of local side effects and irreversible damage to the cilia on the nasal mucosa.
iii. In high concentrations, certain surfactants employed as chemical enhancers can destabilise and even dissolve membranes.
iv. Because of the wrong form of administration, there may be mechanical loss of the dose form into other regions of the respiratory system such as the lungs.

**Ideal drug condition for nasal delivery [7,8].**

i. Appropriate aqueous solubility to deliver the appropriate dose in a 25-150 µl volume of formulation provided per nostril.
ii. Appropriate nasal absorption characteristics.
iii. The medication caused no nasal irritation.
iv. An appropriate clinical justification for nasal dosage forms, such as quick onset of action.
v. There is no harmful nasal metabolite, and there are no objectionable odours or aromas linked with the medicine.
vi. Stability characteristics that are appropriate.

## II. Nasal Cavity Anatomy and Physiology

The nasal cavity is an important part of the respiratory system because it serves as the entry point for air entering the respiratory tract. The nasal septum divides it into two halves and extends posteriorly into the nasopharynx, with its anterior part, the nasal vestibule, accessible to the face through the nostrils [2]. The nasal depression is divided into three separate regions: the nasal vestibule, the olfactory region, and the respiratory region, with the surface area within the nose greatly enlarged by the presence of three turbinates: superior, median, and inferior, as illustrated in Fig. 1.

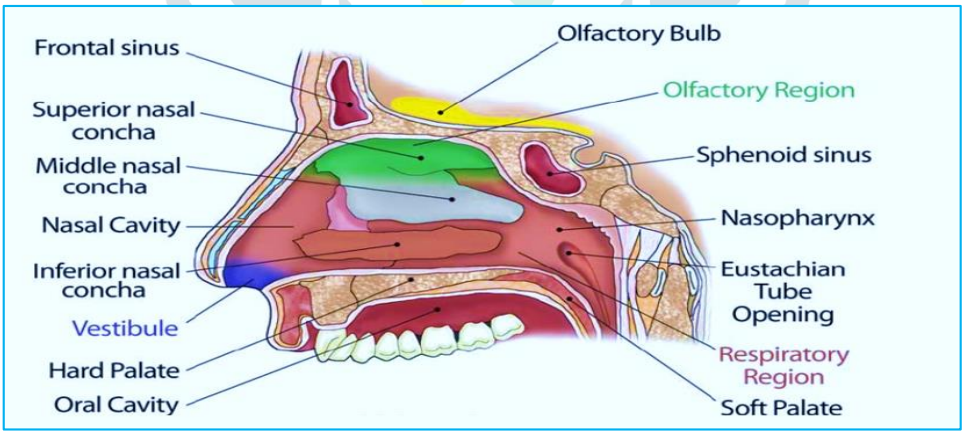


**Figure 1:** Anatomy and Physiology of Nasal Cavity

A mucous membrane lines the nasal cavity, which is divided into nonolfactory and olfactory epithelium. The skin-covered nasal vestibule with stratified squamous epithelial cells is found in the nonolfactory region, while the respiratory region has airway epithelium with many microvilli, which increases the surface area for drug absorption and transport. Goblet cells, which are found in the mucous membrane that covers the nasal turbinates and atrium, release mucus granules that contribute to the mucus layer. The mucus layer, which is composed of 95% water, 2% mucin, 1% salt, and 1% other proteins, provides immunological protection from inhaled pathogens [10, 11]. Mucus secretion serves several physiological purposes:

i. It protects the mucosa physically and enzymatically.
ii. Provides a high water-holding capacity.
iii. Exhibits surface electrical activity.
iv. Promotes efficient heat transfer.
v. Acts as an adherent, carrying particulate particles to the nasopharynx.

**III. The pathway involves administering drug to the brain via the nasal cavity.**

1. The Olfactory Pathway
2. Respiratory system
3. Systemic route

### 1. Olfactory Pathway

The olfactory route involves the direct transfer of olfactory signals from olfactory neurons to the brain. This pathway can be used for medication administration, allowing pharmaceuticals to enter the brain without going through systemic circulation, as shown in Fig. 2. The olfactory nerve acts as a route for this function, allowing direct transmission from the nasal cavity to the brain. The olfactory neurons, which reach from the nasal mucosa to the brain, promote medication administration via two pathways: intraneuronal and extra-neuronal.

Drugs travel through the intraneuronal route and reach numerous brain zones. The active components, however, take hours to days to reach the brain. The extra-neuronal system, on the other hand, provides for fast transport to the brain via perineural channels within minutes. Deeper parts of the brain, such as the cortex, cerebrum, and cerebellum, are innervated by the olfactory neural network. Drugs can enter the cerebrospinal fluid (CSF) and the olfactory bulb after intranasal administration, eventually reaching the brain via the CSF and interstitial fluid [12-14].

### 2. Respiratory Pathway

The respiratory system, which occupies a large percentage of the nasal cavity and contains numerous capillaries, provides an alternate route for medication delivery to the brain. Drugs administered to the respiratory region are absorbed into the bloodstream and circulated throughout the body. As seen in Fig.2, this establishes a circular channel for drug delivery to the brain via the blood-brain barrier (BBB). The trigeminal nerve, which is related to the brain stem and the olfactory bulb, plays an important role in pain and temperature feeling in the respiratory region.

While the respiratory region contains the majority of the trigeminal nerve, some trigeminal nerves can also be found in the olfactory region. As a result, medication administration to the trigeminal nerve in both regions provides a direct route from the nasal cavity to the brain. This dual connection increases the likelihood of medications reaching the brain efficiently via the trigeminal nerve [14-15].

### 3. Systemic Pathway

Drugs that do not stay in the nasal cavity but instead move through the airway or oesophagus follow the systemic route. As demonstrated in Fig.2, the indirect pathway involves absorption into the bloodstream and subsequent delivery to the brain via systemic circulation. Drugs supplied via this route, however, must overcome the obstacles posed by the BBB, resulting in smaller quantities reaching the brain when compared to direct nasal cavity distribution. The thickness of the BBB, as well as substantial drug metabolism or removal in the body, contribute to the possible constraints of systemic drug distribution [16].

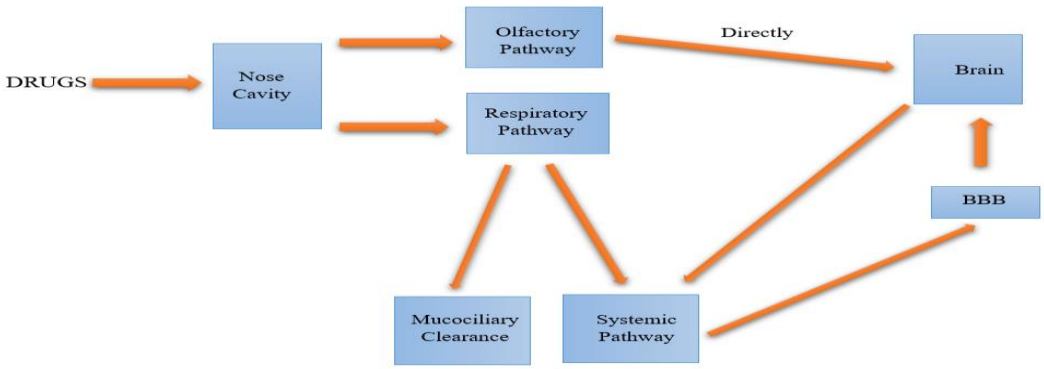


**Figure 2:** The pathway involves administering drug to the brain via the nasal cavity

## IV. Nasal Absorption Mechanism

The initial step in absorption is for drugs absorbed from the nasal cavity to pass through the mucus layer. Small, unmodified drugs move through this layer easily, but large, charged substances must be handled with care. Mucin is the main protein in mucus; it has a tendency to attach to solutes, preventing diffusion. Environmental changes (e.g., pH, temperature, etc.) can also cause structural changes in the mucus layer [17]. So far, several immersion techniques have been invented, but only two mechanisms have been widely used, as illustrated in Fig. 3.

**i. The first mechanism**

It uses an aqueous transport channel, also known as the paracellular route, however it is slow and inactive. Intranasal absorption and the molecular weight of water-soluble substances have an inverse log-log connection. Drugs with molecular weights fewer than 1000 Daltons have low bioavailability [18].

**ii. The second mechanism**

It is also known as the transcellular process and involves transport via a lipoidal pathway. It is in charge of transporting lipophilic medications with a high rate of dependence on their lipophilicity. Drugs can also cross cell membranes by active transport via carrier-mediated transport or via tight junction opening [18].

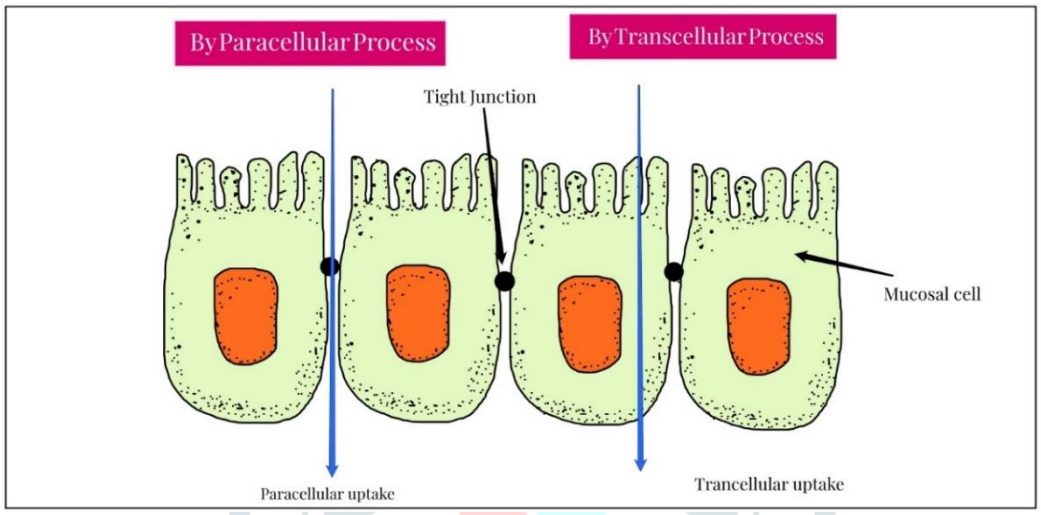


**Figure 3:** Mechanism of Nasal Absorption

## V. Factors affecting nasal drug absorption

### 1. Nasal Physiological factors

**i. Blood flow**

The nasal mucosa's robust blood supply and vast surface area make it an ideal target for drugs absorption. The rate of blood flow influences drug absorption, with higher blood flow allowing more drug to pass through the membrane and enter the general circulation. Vasoconstriction, on the other hand, can reduce nasal drug absorption by lowering blood flow [19]

**ii. Membrane Permeability**

The permeability of the nasal membrane is an important element in drugs absorption. Water-soluble drugs and drugs with high molecular weight, such as peptides and proteins, have low membrane permeability. Peptides and proteins are frequently absorbed in small amounts via endocytic transport mechanisms [20].

**iii. Mucociliary Clearance (MCC)**

MCC, also known as the mucociliary apparatus, is the bronchi's self-clearing system. Nasal mucus defends the respiratory tract by keeping foreign chemicals and bacteria out of the lungs. MCC has a substantial impact on nasal drug absorption by acting as a 'conveyor belt' in which cilia provide the driving force and mucus gathers and disposes of extraneous particles. MCC's efficacy is determined by parameters such as cilia length, density, beat frequency, mucus amount, and viscoelastic characteristics [4, 21].

**iv. Enzymatic Degradation**

The administration of drugs by the nose avoids the gastrointestinal and hepatic first-pass effects. However, due to the presence of numerous metabolic enzymes in the nasal cavity, drugs delivered intranasally may undergo enzymatic degradation. In nasal tissues, enzymes such as carboxyl esterase, aldehyde dehydrogenases, epoxide hydrolases, glutathione S-transferases, and cytochrome P450 isoenzymes can contribute to drug metabolism [22].

**v. Transport and Efflux Systems**

The nasal route for drug absorption into systemic circulation and the central nervous system (CNS) is of great interest. Efflux transporters, such as P-glycoprotein [P-gp], play an important function in limiting drug inflow via the nasal membrane. The apical portion of ciliated epithelial cells and submucosal arteries of the deadly olfactory region contain P-gp [23].

**2. Drug physicochemical properties**

Some medication parameters (molecular weight, lipophilicity, pKa, stability, and solubility) can influence nasal absorption [24].

**i. Molecular weight, lipophilicity, and pKa**

Lipophilic drugs such as propranolol, progesterone, and fentanyl are effectively absorbed through the nasal cavity, with pharmacokinetic profiles similar to those obtained following intravenous administration. Transcellular processes allow these drugs to pass the nasal membrane quickly and efficiently. This is applicable to lipophilic composites with molecular weights less than 1 kDa. Lipophilic drugs with molecular weights more than 1 kDa have dramatically reduced nasal absorption. Polar medicines, on the other hand, have a low rate and degree of nasal absorption that is mostly determined by molecular weight. Because the nasal membrane is lipophilic, drug absorption is expected to diminish with loss of lipophilicity; thus, polar drugs may not easily travel across nasal membranes. Because the drug does not dissolve smoothly in the aqueous environment of the nasal cavity when the lipophilicity is too high, drug penetration through the wall may be inhibited [24].

**ii. Stability**

Stability studies, which include biological, chemical, and physical elements, are critical in the creation of medication formulations. Nasally given drugs may have decreased natural stability due to enzymatic metabolism in the nasal cavity. To overcome this issue, prodrugs and enzyme inhibitors are frequently used to improve drugs stability [25].

**ii. Solubility**

Because molecularly dispersed drugs penetrate biomembranes, drug dissolution is required for absorption. As a result, drugs must dissolve in nasal cavity fluid before being absorbed. Inadequate water solubility might cause slower absorption and need greater doses, providing a problem. To solve this difficulty and ensure effective drug absorption in the nasal canal, various strategies, such as increasing solubility through formulation techniques, are used [26].

**3. Effect of drug formulation**

**i. pH**

The pKa of the drug and the pH at the absorption site are essential factors in drug absorption via the nasal route. Stability can thus be accomplished by carefully selecting the pH of a composition. To prevent sneezing, the pH of the formulation should be close to that of human nasal mucosa (5.0 6.5) [27].

**ii. Pharmaceutical formulation**

Although nasal drops are the simplest and most accessible nasal medicinal dosage form, the exact amount of medicine administered is difficult to quantify and frequently results in overdose. When using this dose form, you may have fast nasal drainage. Instead of powder sprays, suspension sprays are suggested since powder sprays might induce nasal mucosa discomfort. Nasal gel is currently being developed for precise drug delivery. This improves nasal absorption by increasing drug residence time and decreasing MCC [28].

**iii. Excipients used in pharmaceuticals**

Pharmaceutical excipients are chosen for their roles in nasal formulations. Solubilizers, buffer factors, antioxidants, preservatives, humectants, and gelling/viscosifying agents are the most commonly utilised excipients [26].

**vi. Viscosity**

Higher viscosity formulations spend more time in contact with the nasal mucosa, which can improve drugs absorption. Because of the prolonged contact duration, the drug can interact with the mucosal surface for a longer amount of time, enhancing the possibilities of absorption. High viscosity can also increase drug permeability, allowing medicines to enter the systemic circulation more easily. Higher viscosity increases residence time while decreasing medication absorption. This could be due to the drug lingering in the nasal cavity for an extended period of time but not being absorbed adequately [29].

**VI. Strategies for increasing nasal absorption**

Several techniques are utilised to improve medication bioavailability in the nasal mucosa, including

i. improving nasal residence time
ii. improving nasal absorption
iii. To change the physicochemical qualities of a medication by changing its structure.

Any one or a combination of the following procedures is used to improve formulation immersion and bioavailability. Several ways have been used to improve medication absorption through the nose, including:

**1. Nasal Enzymes Inhibitors**

Enzyme inhibitors, such as peptidase and protease inhibitors, are used to block medication metabolism in the nose, which is especially important for proteins and peptide compounds. Absorption enhancers, such as salts and fusidic acid derivatives, block enzymes, resulting in enhanced absorption and bioavailability [30].

**2. Permeation Enhancers [31]**

Permeation enhancers play an important role in enhancing active medication absorption via a variety of processes, including:

i. Reducing mucus viscosity or flexibility
ii. Inhibiting enzyme activity
iii. Reduce mucociliary clearance;
iv. Open tight junctions
v. Drug solubilization or stabilisation

**The following is the general condition of an ideal penetration enhancer.**

i. It should result in an effective increase in medication absorption.
ii. It should not cause lasting tissue damage or alteration.
iii. It must be nonirritant and harmless.
iv. It should be effective in modest quantities.
v. When absorption is required, the boosting effect should be used.

**3. Prodrug strategy**

The prodrug strategy is primarily intended for optimising favourable physicochemical features such as solubility, taste, odour, stability, and so on. A prodrug is often related to moiety; it is used to mask undesirable functional groups with another functional group. This prodrug method is significant for increasing nasal bioavailability, particularly for proteins and peptides to improve membrane permeability and enzymatic stability [32].

**4. Modification of the structure**

One of the most effective ways to improve nasal absorption is to change the structure of the drug without changing its pharmacological effectiveness. The chemical modification of drug molecules has traditionally been employed to affect the physicochemical features of a pharmaceutical comparable molecular size, molecular weight, Pka, and solubility are advantageous to promote drug nasal absorption [33].

**5. Particulate drug administration**

Particle design is becoming an increasingly significant aspect of absorption enhancement. Microspheres, Niosomes, and liposomes are all systems that can be employed to encapsulate active drugs as carriers. To maximize restorative effectiveness, the characteristics of these can be modified. Overall, this can lead to improved absorption effectiveness and stability, as well as lower toxin levels in the active component. Mucoadhesive systems can be developed to enhance retention time and allow continuous release [34].

**Table 1:** Strategies to enhance nasal bioavailability

| S.no. | Strategies | Examples [18] |
|---|---|---|
| 1 | Nasal enzyme inhibitors | Bestatin, boroleucine, fucidic acid, bile salt |
| 2 | Nasal permeation enhancers | Cyclodextrins, surfactant, saponins, fusidic acid, bile salt |
| 3 | Prodrug approaches | Cyclic prodrug, esters |
| 4 | Nasal mucoadhesive in nasal drug delivery | Carbopol, polycarbophil, cellulose derivations, lecithin, chitosan |
| 5 | Particulate drug delivery | Microsphere, niosomes, liposomes |

## VII. Formulations of nasal dosage forms

### i. Nasal Drops

Nasal drops are one of the most basic and easily accessible nasal administration techniques. The biggest downside of this approach is its lack of dosage precision, which means nasal drops may not be appropriate for prescription medications. Nasal Drops have been shown to deposit serum in the nostrils more effectively than nasal spray [9,35].

### ii. Nasal Spray

Metered dose pumps are used for precise dosing of nasal sprays in solution or suspension form. They are preferred over powder sprays because they do not cause mucosal irritation, resulting in effective and comfortable delivery [9,35].

### iii. Nasal Powders

If the result and suspension dose forms cannot be established, for example, because to a lack of medicament stability, this dosage form may be developed. The absence of preservatives and the formulation's greater stability are two advantages of the nasal powder dose form. However, the success of the powder formulation is based on the active medication's solubility, particle size, hydrodynamic qualities, and nasal irritancy. Another advantage of this technique is the ability to administer medication locally [9,35].

### iv. Nasal Gel

Nasal gels are becoming increasingly popular because to their reduced post-nasal drip, high consistency, and focused distribution to the mucosa for improved absorption. They also reduce the formulation's flavour impact, swallowing, and anterior leaking [36].

### v. Nasal Inserts

Nasal inserts, innovative bioadhesive solid dosage forms, administer systemic drugs via the nasal route for a longer period of time. They use nasal fluid to create a gel in the nasal cavity, which prevents foreign body perceptions [35].

**Table 2:** Formulation and Active Agent that has been employed in Nasal Drug Delivery

| S.no. | Formulation | Active Agent |
|---|---|---|
| 1 | In- situ Nasal Gel | Selegiline, Rivastigmine, prednisolone |
| 2 | Nasal Inserts | Chlorpromazine, Albuterol |
| 3 | Microspheres | Beta- Amyloid Fibril, Starch Microspheres, Dextran Gentamicin, Insulin, Desmopressin [9] |
| 4 | Microparticles | Serum albumin, Thiolated Chitosan Microparticles |
| 5 | Dry Powder | Zolmitriptan |
| 6 | Nasal Gel | Oxytocin, Metoclopramide Hydrochloride [9] |

## VIII. In-situ nasal gel application

The Latin term in situ means "in place." It is defined as a liquid formulation that, when administered, generates a solid or semisolid depot. When exposed to physiological conditions, in situ gel-forming systems enter a gel phase. In-situ gel is a novel dosage form for the nasal administration of a variety of drugs. It enters the nasal canal as a low viscosity fluid that gradually transforms into a gel. In situ gels were created using natural and synthetic polymers. These devices can provide very consistent sustained-release tube patterns [6,7].

### Merits of in situ gel

**i.** longer medication release.
**ii.** ii. Easy to manage.
**iii.** Less frequent administration.
**iv.** Reduced systemic side effects.
**v.** A smaller number of applications.

### In situ gel formulation

The following processes for synthesising in-situ gel are discussed:

### 1. Thermally triggered system

The in-situ gel is generated using a polymer that transitions from solution to gel by changing the physiological temperature of the body. When the temperature rises, the biomaterials employed to create in-situ gel undergo a transition from sol to gel, resulting in an in-situ gel [6].

### 2. pH activated systems

In-situ gel is also created by varying the pH of the gel based on physiological stimuli and then using pH-sensitive polymers. The swelling of hydrogel increases when the external pH increases if the polymer contains weakly acidic groups, but decreases if the polymer contains weakly basic groups [37].

### 3. Osmotically induced in situ gelling system

A change in ionic strength activates gelling of the implanted result in this system. The osmotic gradient across the changing conditions of the gel surface influences the gelation rate. In the presence of monovalent or divalent cations, the aqueous polymer forms a transparent gel. Gellan resin, hyaluronic acid, and alginates are polymers that promote gelation [38].

**Polymers utilised in in-situ gel**

i. Cellulose derivative
ii. Gellan gum
iii. Sodium alginate
iv. Pluronic F-127
v. Polyacrylate
vi. Chitosan and Carbopol

**Table 3:** Intranasal administration of bioactive agents via in situ gels.

| Sr.No. | Bioactive Agents | Formulation Composition | Neurological Disorder | Efficacy [39] |
|---|---|---|---|---|
| 1 | Levodopa | Pluronic F127, chitosan | Parkinson's syndrome | Delayed mucociliary clearance |
| 2 | Amantadine | Pluronic F127, carboxymethylcellulose | Parkinson's syndrome | No cellular toxin in human |
| 3 | Ropinirole | Chitosan, hydroxyl propyl methyl cellulose | Parkinson's syndrome | Enhanced brain uptake of drug in vivo |
| 4 | Sumatriptan | Gellan gum | Migraine | High drug concentration in plasma and brain tissues |

**IX. Nasal delivery methods based on lipidic technology** Various medication delivery technologies are being researched in order to optimise and improve nasal medicament intake. Lipidic-based nasal delivery systems, such as niosomes, liposomes, in-situ gel systems, cyclodextrins, microemulsions, and nanoemulsions, are among the most emerging drug delivery techniques used in the nasal route [40].

## X. Niosomes

Niosomes are microscopic lamellar structures generated in aqueous media by combining non-ionic surfactants such as alkyl or dialkyl polyglycerol ethers with cholesterol. The addition of cholesterol and a little amount of an anionic surfactant, such as diacetyl phosphate, often stabilises these vesicles. This combination of components aids in the formation of stable niosomes [41].

**Merits of niosomes [**41,42**]**

i. Effective at Lower Doses: Niosomes can achieve therapeutic effects with smaller drug doses, reducing the risk of side effects
ii. Stability: They are stable because of their hydrophilic nature and osmotically active properties, which can enhance the drug's stability.
iii. Enhanced Skin Penetration: Niosomes can improve the skin penetration of drugs, making them suitable for transdermal drug delivery.
iv. Patient Acceptance: The hydrophilic nature of niosomes makes them more acceptable to patients compared to oil-based systems.
v. Sustained Drug Release: Niosomes can act as depots, releasing drugs slowly over time, leading to prolonged therapeutic effects.

**Demerits of niosomes [**41,42**]**

i. Specialized Equipment: The production of niosomes may require specialized equipment, which can increase production costs and limit accessibility.
ii. High Production Cost: The manufacturing process can be expensive due to the need for specialized equipment and materials.
iii. Inefficient Drug Loading: Niosomes may not efficiently encapsulate certain drugs, leading to suboptimal drug-loading capacities.
iv. Fusion: Niosomes can fuse together, altering their structure and potentially affecting drug release.

## XI. Structure of Niosomes

Niosomes are lipid-based drug delivery vesicles. The vesicles of amphiphilic niosomes are non-ionic surface-active agents such as span -60, which is stabilised by the addition of cholesterol and a sufficient amount of anionic surfactant such as diacetyl phosphate, as illustrated in Fig. 4.

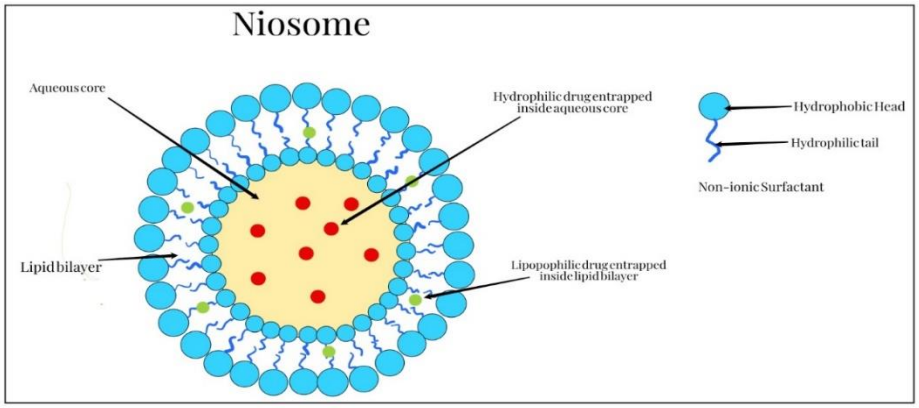


**Figure 4:** Structure of Noisome

**Composition of Niosomes** [43]

Some common components utilised in the manufacture of niosomes:

i. Cholesterol
ii. Surface-acting non-ionic agent

**i. Cholesterol:** Cholesterol is added to the porous membrane to increase its rigidity and stability, hence improving its structural integrity.

**ii. Non-ionic Surface-Active Agent:** Non-ionic surfactants are utilised to make the niosomes amphiphilic.

Eg. Spans (span20,40,60,80,85)
Tweens (tween 20,40,60,80)
Brijs (brij 30,35,52,58,72,76)

## XII. Methods used for the preparation of Niosomes

### 1. Ether Injection Technique

Niosomes can be made by gently adding a surfactant and cholesterol solution in diethyl ether to warm water at 60°C. The surfactant mixture in ether is injected into phosphate buffer 7.4 using 14-gauge needles (Fig. 5). Ether vaporisation causes the production of single-layered vesicles [44,45].

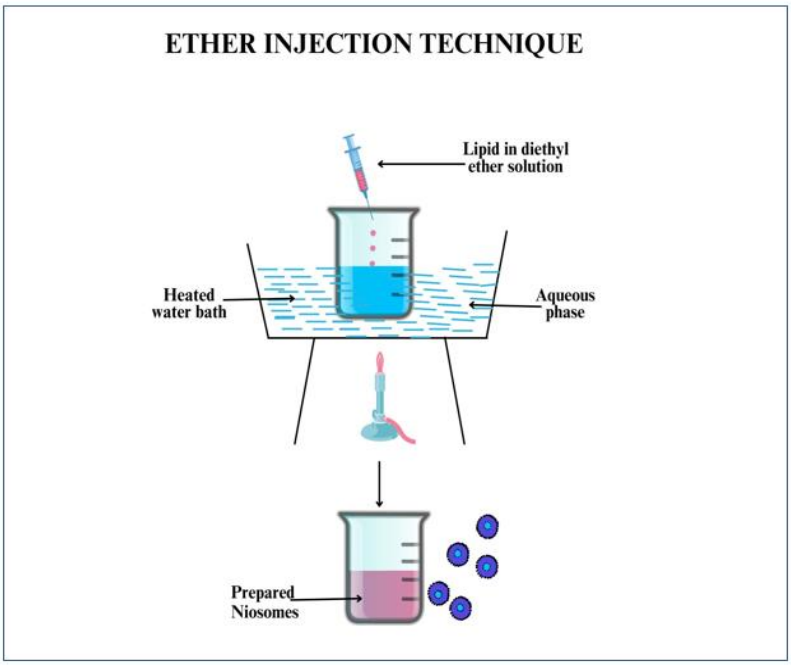


**Figure 5:** Ether Injection Technique

### 2. Thin Film Hydration Technique (Hand Shaking Method)

Surfactants, cholesterol, and additives are dissolved in an organic solvent in a round bottom flask using this process, and the solvent is evaporated using a rotating vacuum evaporator to form a thin layer on the flask's wall (Fig. 6). Adding an aqueous drug solution and hydrating

the dry film above the surfactant's transition temperature for a set period of time with steady shaking results in the development of multilamellar niosomes [45].

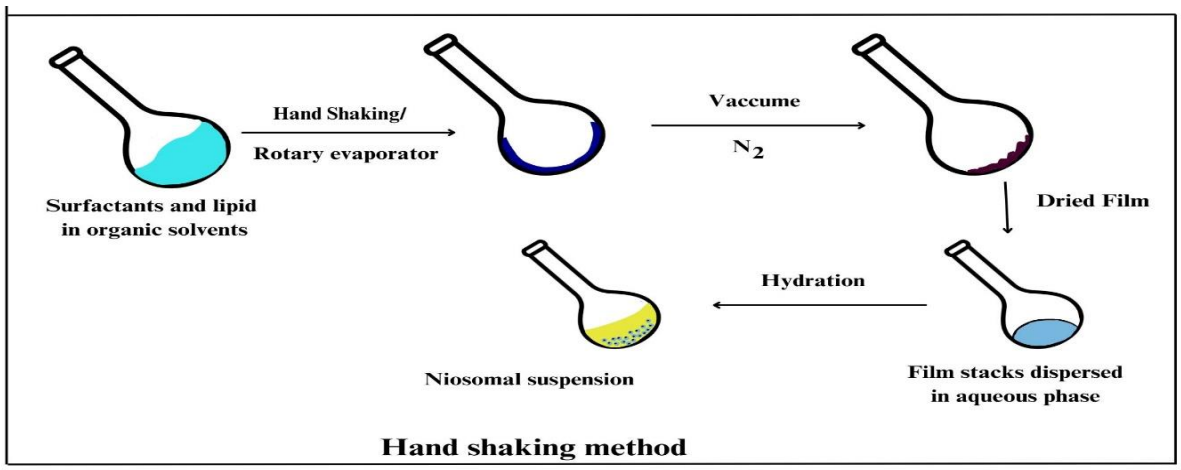


**Figure 6:** Hand Shaking Method

**3. Sonication Method**

To form niosomes, a drug solution is added to the buffer system and combined with a surfactant-cholesterol mixture in a 20 ml glass vial and sonicated at 60°C for 3 minutes using a titanium probe sonicator.

**4. Micro fluidization**

This method employs microfluidic technology to generate unilamellar vesicles with a predetermined size distribution that are more consistent and smaller in size [46].

**5. Reverse Phase Evaporation Method (REV)**

Niosomal components are dissolved in a solvent combination, then combined with the medication in an aqueous phase and sonicated to form an emulsion. After that, the organic solvent is evaporated, resulting in enormous unilamellar vesicles [47].

**6. The "Bubble" Technique**

Surfactants, additives, and buffers are combined in a three-necked glass flask. These components were distributed at 70 degrees Celsius and combined using a homogenizer before bubbling nitrogen gas was fed through a homogenised surfactant, resulting in enormous unilamellar vesicles [48].

**7. Heating Procedure**

Surfactants and cholesterol are hydrated in a buffer, heated to dissolve the cholesterol, and then surfactants and additives are added to the buffer to produce niosomes while stirring continuously [49].

**8. Multiple Membrane Extrusion Method**

A film composed of surfactant, cholesterol, and diacetyl phosphate is hydrated with a drug solution and provided through polycarbonate filters.

**9. Transmembrane pH Gradient (Inside Acidic) Drug Uptake Process**

After dissolving surfactant and cholesterol in chloroform, a film is created, which is subsequently hydrated with a citric acid solution and exposed to freeze-thaw cycles and sonication. When heated, the pH is regulated, and niosomes are created [50].

**10. Niosome Formation from Proniosomes**

This technique includes covering a water-soluble carrier with a surfactant to form "proniosomes." Niosomes are created by adding an aqueous phase at a temperature higher than the transition temperature of the surfactant [51].

**Table 4** Brief instance of some drugs incorporated into niosomes usage of unique methods

| Method of preparation | Drug incorporated |
|---|---|
| Ether injection method | Sodium stibogluconate<br>Doxorubicin |
| Hand shaking method | Methotrexate Doxorubicin |

## XIII. The significance of niosome-based nasal drug delivery systems [52-54].

**i. Improved Nose-to-Brain medication Delivery:** Niosomes have the potential to increase medication delivery to the brain by bypassing the blood-brain barrier (BBB), which frequently inhibits systemically delivered pharmaceuticals' access to the brain. This is specifically beneficial in the treatment of neurodegenerative diseases.

**ii. Versatile Drug Encapsulation:** Because of their distinctive vesicular structure, niosomes may encapsulate a wide spectrum of compounds, both hydrophilic and lipophilic. Because of their adaptability, they can efficiently transport a wide range of medicinal substances.

**iii. Customised features:** Niosomes can be created to have certain features, such as surface charge and size, that can be critical for optimising drug delivery and targeting specific tissues or cells.

**iv. Ease of Handling and Storage:** Because niosomes are relatively simple to create, handle, and store, they are a viable option for drug delivery systems.

**v. Reduced Systemic Side Effects:** Niosomes can lessen systemic side effects by improving drug stability and lowering the total dose needed for therapeutic benefits.

**vi. Olfactory and Trigeminal Pathways:** Niosomes can carry drug directly to the brain via olfactory neurons and facial trigeminal pathways in the nasal cavity, offering an efficient route for drug administration.

In conclusion, Niosomes represent a viable platform for nasal medication delivery, particularly in the context of neurodegenerative treatment. They are a crucial tool in the creation of successful and patient-friendly drug delivery systems due to their capacity to improve medication administration to the brain, diverse drug encapsulation, customised characteristics, and ease of use.

**Table 5** Examples of research work on niosomal–based nasal drug delivery systems

| **Bioactive Agents** | **Formulation Composition** | **Disorder** | **Aim** [54] |
|---|---|---|---|
| Sumatripine succinate | Span 60 Cholesterol Dicetyl Phosphate Sephadex, | Acute migraine | To increase bioavailability |
| Melatonin | Span 60 Sodium deoxycholate Dimethyl sulfoxide Cholesterol | Sleep disorder | To reduce side effects such as unconsciousness, GI disturbance, |
| Folic Acid | Span 60 Cholesterol | Prevention of depression in Alzheimer's disease | To provide a faster therapeutic effect (faster onset of action |
| Nefopam | Span 40 Cholesterol | Moderate and acute pain | To improve bioavailability |
| Buspirone | Span 40 Cholesterol | Anxiety | To improve bioavailability |
| Olanzapine | Cholesterol/ Span 60 (1:4) | Schizophrenia | To improve brain targeting |

## XIV. Evaluation

### 1. Determination of Particle Size

To measure the size of particles, use a particle size analyzer. To avoid multi-scattering, dilute the sample with double-distilled water. Calculate the particle size and polydispersity index from the sample.

### 2. Polydispersity Index [PDI] Measurement

Dynamic light scattering is used to calculate the PDI of niosomes. The particle size distribution narrowness is measured using PDI.

### 3. Zeta Potential

Use zeta potential to assess the stability of niosomal formulations. Utilise an electrophoretic cell with a voltage of 150 mV to measure the nanoparticles' charge.

### 4. pH determination

A niosomal formulation sample should be transferred to a volumetric flask and diluted with distilled water. Using a digital pH metre that has been previously calibrated with pH 4 and pH 7 buffers, find the pH of the resultant solution.

**5. Clarity**

One way to evaluate the formed solution's clarity is to visually check it against a black and white background. This assessment aids in ascertaining the degree of clarity or transparency of the solution [55].

**6. Viscosity**

Viscosity is an important attribute of the formulation and may be tested using various viscometers such as a Brookfield viscometer and a cone and plate viscometer. The viscosity of the solution or gel is measured using the Brookfield viscometer both before and after gelation. It offers details on the formulation's thickness and flow resistance [56].

**7. Gel-Strength**

The strength or consistency of the gel created by the formulation is measured by gel strength. Gel strength is measured with a rheometer. In a beaker, a certain volume of gel is created, and a probe is gradually inserted into the gel. As the probe is lowered farther into the gel, the variations in the weight on it are measured, giving information about the strength of the gel [57].

**8. Mucoadhesive Potency of Niosomal Formulation**

Incubate porcine mucin suspension with the niosomal formulation at 37°C. Centrifuge the samples and measure the free mucin in the supernatant to determine mucin binding efficiency.

**9. Determination of Drug Content**

Sample the gel from different locations and assay it for drug content. Dissolve a weighed quantity of gel in pH 6.8 phosphate buffer and subject it to spectrophotometric analysis to determine the drug content.

$$\%\ \boldsymbol{Drug\ content} = \frac{\boldsymbol{Actual\ drug\ content}}{\boldsymbol{Theoretical\ drug\ content}} \times \mathbf{100}$$

**10. Entrapment Efficiency**

Ultra-centrifuge the formulations at 4°C and collect the supernatant. Wash the pellets and measure the drug concentration in the supernatants to calculate the entrapment efficiency.

$$\boldsymbol{EE} = \frac{[\boldsymbol{Qt} - \boldsymbol{Qr}]}{\boldsymbol{Qt}} \times \mathbf{100}$$

**11. Nasal Mucosal Permeation Study**

Perform ex vivo nasal permeation study using goat nasal mucosa. Mount the mucosa in a Franz Diffusion cell with continuous stirring and collect samples at predetermined time intervals for analysis [58].

**12. In-vitro Drug Release study**

To investigate the in-vitro drug diffusion of niosomal formulations, use a dialysis membrane. To maintain sink conditions, withdraw aliquots at regular intervals and refill them with phosphate buffer.

**13. Differential Scanning Calorimetry (DSC)**

examine the temperature reactions of dried nasal gel compositions. Over a specific temperature range, use a ramp rate of 10°C/min.

**14. Fourier Transform Infrared Spectrometry (FTIR) Study**

Perform FTIR analysis to identify functional groups in niosomal nasal formulation. Scan the sample over a specific wavenumber range. This methodology provides a comprehensive approach to evaluating various parameters of niosomal formulations, ensuring the quality and effectiveness of the product.

## XV. CONCLUSIONS

When compared to parenteral administration, the nasal drug delivery system is a viable alternative method for giving drug with low bioavailability, having advantages such as improved patient acceptance and compliance. This method is especially useful in circumstances such as Parkinson's disease, Alzheimer's disease, and pain, where rapid and specific drug targeting to the brain is required, making it a suitable pathway for triggering an immune response against numerous disorders.

Niosomal-based drug delivery systems, which are distinguished by nanosized vesicular nanocarriers, provide significant benefits over existing lipid-based delivery systems. These nonionic surfactant vesicular carriers show promise in optimising drug release patterns, specific targeting of bodily tissues or cells, reducing systemic side effects and toxicity, and improving therapeutic efficacy and bio-distribution throughout the body. Niosomes play an important role in improving drug delivery via the nasal route, particularly through the olfactory region, by increasing

the solubility of weakly water-soluble drugs and allowing drug transmission through biological membranes, resulting in increased bioavailability.

## XVI. List of abbreviations

| Abbreviations | Full form |
|---|---|
| BBB | Blood-brain- barrier |
| CNS | Central nervous system |
| AD | Alzheimer's disorder |
| PD | Parkinson's disorder |
| GIT | Gastrointestinal track |
| CSF | cerebrospinal fluid |
| MCC | Mucociliary Clearance |
| Pgp | P-glycoprotein |
| REV | Reverse Phase Evaporation Method |
| PDI | Polydispersity Index |
| DSC | Differential Scanning Calorimetry |

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