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Review Article

AN ALTERNATE METHOD FOR NASAL MEDICINE DELIVERY IS IN-SITU GEL

Sumit Sinha Mahapatra*, Arif Mahammad, Sanjib Bahadur, Pragya Baghel

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Abstract

Nasal medication administration has been used for therapeutic and recreational purposes since the dawn of civilization. The importance of and interest in the systemic effects of medications taken orally has grown over the past few decades. Medications administered intra-nasally provide an intriguing option to the parenteral route, which can occasionally be uncomfortable. These might involve avoiding pre-systemic release in the digestive tract and eliminating the first-pass effect (GIT), necessitating the use of a tiny dose of a specific medicine. Lowering the dose will lessen the negative effects and, ultimately, lower the cost of the medication. The likelihood for intranasal medication delivery to overcome certain significant drawbacks is linked with the other stated routes making it the most exciting path for drug administration. This review covered how in situ gel became more popular than previous nasal administration forms

INTRODUCTION

The majority of commonly used medications have been given via oral and parenteral methods throughout the past few decades[1]. Even while the oral route is practical and affordable, there are occasionally inefficiencies such as limited drug solubility and the first pass effect (For drugs taken orally, the liver transports them to the systemic circulation, where they are metabolized), which may make it less bioavailable, as in the case of griseofulvin. The lower the bioavailability, the stronger the first-pass effect of the medicine (the rate and breadth of the drug reaching systemic circulation).[2]. Parenteral, transdermal, and transmucosal modes of drug delivery which concentrate on the mucosal linings of the vagina, nasal, rectal, and buccal cavities offer definite benefits over oral delivery. There may be a way to avoid the first-pass effect and bypass it, thus a little dose of a certain medicine is needed. A dose decrease will lessen the negative effects and ultimately lower the cost of the medication. While the parenteral route causes pain at the injection site, lowers patient consent, and is not suitable for long-term therapy, the topical route, though successfully used for the administration of some drugs, is limited in its use because of the poor passable of the skin to many drugs. Less popular delivery methods include transmucosal, vaginal, and rectal since they irritate patients and are less patient-compliant. In the buccal route, drugs with unpleasant tastes may present problems of acceptability [3]. The mucous membrane of the nose is the primary route for administration in the transmucosal path of drug delivery in order to achieve quicker and greater levels of medication absorption. An especially promising delivery method is transmucosal nasal administration. Transmucosal nasal administration has been a very promising route of delivery. Comparing the nasal route with the oral route, it has been demonstrated that several medicines attain greater systemic bioavailability. In the Ayurvedic systems of Indian medicines, the nasal path is a well-recognized form of treatment; it is referred to as NASYA KARMA [4]. The supply of nasal medication, which dates back thousands of years, has been given fresh life. It is a helpful delivery strategy for medications like proteins as well as peptides that are effective at low dosages and have no effect on oral bioavailability. One cause of the low level of protein and peptide absorption is when anything is inhaled by the nose, the mucosal surface quickly moves away from the absorption site thanks to the mucociliary evacuation process[5]. When delivered nasally it avoids the oral delivery method's hepatic first-pass elimination: It is comfortable and appropriate for self-medication. Pharmaceutical scientists and medical professionals have been paying more focus to the viability of drug delivery via the nostrils during the past few decades. Animals have served as models to test potential medications ranging in size from tiny metal ions to massive macromolecular proteins[6].

Nasal Drug Delivery System

Intranasal medication administration primarily provides a potentially viable option. It is appropriate for the systemic and local delivery of a variety of medicinal substances. As a result, the nasal fossa has been the subject of numerous studies regarding its viability as a site for the delivery of numerous medicinal drugs. It works well to treat both regional and systemic factors.

1. Local: Traditionally, nasal cavity administration has not been used to deliver medication for local disorders including rhinitis and nasal congestion. The distribution of medicinal substances, such as biopharmaceuticals, as well as topical nasal therapies, such as antihistamines and corticosteroids for rhinosinusitis and nasal decongestants for cold symptoms, are currently being recognized for this method. The intranasal route is typically the best choice for drug delivery in these situations since it provides quick symptom alleviation with few adverse effects.

*Department of Pharmaceutics, Himalayan Pharmacy Institute, Majhitar, East Sikkim, India 737136

For correspondence: sumitsinhamahapatra3@gmail.com

2. Systemic: Intranasal (IN) delivery, a prospective medication administration method for systemic absorption of analgesics, sedatives, hormones, vaccines, and cardiovascular medicines via the nasal mucosa, has received a lot more attention in recent years. in light of the nose passage's structure and physiology, which include its highly vascularized epithelium, ready access, extensive surface area, permeable endothelium membrane, high total blood flow, and suppression of first-pass metabolism, this is the case.[7].

Advantages of nasal drug delivery system[8,9]

1) There is no drug breakdown that is visible in the digestive system.
2) One should prevent hepatic first-pass metabolism.
3) The medicine can be absorbed quickly and start working right away.
4) The bioavailability of larger drug molecules can be improved by a chemical that promotes absorption.
5) Smaller medication molecules are well-bioavailable through the nose.
6) Nasal drug delivery is a way to get medications into the bloodstream that are not absorbed when taken orally.
7) Comparatively convenient route to parenteral medication for long-term treatment.

Nasal medication delivery method limitations[8,10]

1) The histopathological toxicity of the absorption enhancers utilised to improve nasal drug distribution system is not yet well demonstrated.
2) Compared to GIT, the absorption area is less.
3) Once delivered, a drug cannot be withdrawn.
4) Both the substance and components added to the dose form carry the risk of local side effects and irreversible damage to the cilia on the nasal mucosa.
5) When present in high concentrations, certain surfactants that are utilised as chemical enhancers can disintegrate or even dissolve membranes.

Physiology and anatomy of the nose

The nose, which acts as the primary entry to the respiratory tract, is where the body needs to receive air to breathe. The cavity inside the nose is divided by a cartilaginous wall called the nasal septum and it is 120-140 mm deep, extending from the nasal vestibule to the nasopharynx. The nose's overall capacity is between 16 and 19 ml, and its surface area is roughly 160 cm^2. The nose serves as a conduit for warm, humid air to enter the lungs. As it makes touch with the membrane covered in mucus by bringing the inspired air into contact with it, it functions as the principal organ for removing particles from the inspired air and also as the body's first line of defense against pathogens. Vestibular, turbinate, and olfactory areas are the nose's three primary structural components.[1].

- **Olfactory region**[11]**:** The largest and most vascularized component of the body, the respiratory region is primarily in charge of systemic drug absorption. The respiratory epithelium is constituted of four different types of cells. The proportions of the different cell types vary in different regions of the nasal cavity. Between 60 and 70 % of the cells in the lowest turbinate area are non-ciliated epithelium cells, while only about 15 to 20% of all cells there are ciliated.
- **Respiratory region:** The nasal respiratory region is the largest portion of the nasal cavity, also called conchae. For the distribution of drugs throughout the body, the respiratory system is most crucial. There are four different cell types that make up the respiratory epithelium: goblet cells, basal cells, non-ciliated, and ciliated columnar cells. The respiratory region contains three nasal turbinates: superior, middle, and inferior which project from the side walls of each nasal cavity. For systemic drug delivery, the nasal respiratory mucosa is considered the most important section.
- **Vestibular region**[12]**:** The nasal vestibule is a portion of the anterior nasal cavity that is located just inside the nostrils, which measures 0.6 cm, this nasal portion is covered by a stratified squamous and keratinized epithelium with sebaceous glands is responsible for filtering out the airborne particles. It is considered to be less important in the three regions concerning drug absorption.

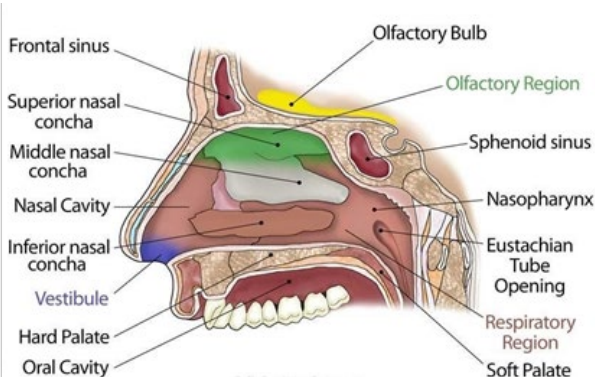

Figure 1: Nasal cavity

Narrative of nasal absorption technique

Drugs must first travel through mucus in the nasal cavity in order to be absorbed. This layer is easily penetrated by small unaltered particles, but larger charged particles have a harder time doing so. Mucin, which constitutes the bulk of the protein in mucus, has a propensity to stick to solutes and obstruct diffusion[13]. Environmental modifications such as pH, temperature, etc. may also cause structural alterations. Several mechanisms, including transcellular or straightforward membrane diffusion, paracellular transport between cells, and transcytosis, which utilises vesicle carriers in cellular transport, have been considered to explain how drugs can pass through mucus. Of these mechanisms, two are regarded as being particularly significant[14]. The two biggest barriers to drug absorption are possible metabolisms prior to reaching the overall blood flow and a short time of stay in the nasal cavity[15]. Despite the fact that several different absorption techniques have been created, only two are primarily used, including:

I. **First method**- It involves a sluggish, passive water transport channel, also often called the paracellular route. Intranasal retention and water-soluble material molecular weight are inversely correlated. The medicines, which have a molecular weight of more than 1000 Daltons have a low bioavailability.

II. **Second method**- It is additionally known as the transcellular process, which involves transport via a lipoidal pathway. It is in charge of transporting medications at a rate dependent on their lipophilicity. Additionally, drugs are transported across tight junctions or carrier-mediated mechanisms to override cell membranes actively [6].

Advancement in the nasal dosage forms

1. Droplets and Sprays for the nose

Among all distribution methods for formulations, One of the easiest and most useful treatments is nasal drops. The biggest drawback is the absence of accuracy in the dosage that is provided, and the chance of contamination while being used.

A chamber, a piston, and a working actuator make up the nasal spray apparatus. Nasal sprays produce exact doses (25–200µl) of each spray and are, in comparison to drops, more accurate. Droplet size, dosage accuracy, applied energy, aperture size, and design of a device are possibly impacted by formulation qualities like thixotropy, interfacial tension, and viscosity. The pump can also modify the size of the droplets, which can change how sprays are deposited in the nose[16].

2. Emulsions and nasal suspensions

Rarely are suspensions utilized or researched as nasal medication delivery methods. However, emulsions were proven to be more effective than suspensions in increasing the bioavailability of barely soluble drugs for oral medication administration, and nasal formulations exhibit the same tendency[17–19].

3. Nasal Micellar and Liposomal Preparation

When hydrophilic macromolecular drugs, including peptides and proteins, are administered by the nasal route, a number of adjuvants, which are typically needed to obtain therapeutic plasma levels, may impact drug absorption. The nasal paracellular pathway is possibly impacted by mixed micelles, in light of the proposed mechanism as opposed to the pure bile salts' function of solubilizing membranes. In this way, it was thought that the salts of bile would solubilize the fatty acids, increasing their availability in the nasal mucosa[20].

In vitro, penetrable tests on insulin and calcitonin revealed that liposomes have absorption-enhancing effects when used as nasal medication delivery devices. It was hypothesized that the boosting impact resulted from higher peptide retention in the nose. The most effective carrier impact for calcitonin was revealed by cationic liposomes, which also allowed the drug to enter them by adhering firmly to the mucosal membrane of the nose[21].

4. Intranasal Powders

Commonly, the medicinal component and excipients are just combined, and then the medication is spray-dried, freeze-dried, or another method to create a particle-like nasal dosage method. In order to deliver nasally peptides and protein, dry-powder formulations with bioadhesive polymers are available. In contrast, the preparation that had the maximum bioavailability also had the highest storage modulus or the properties that were the most similar to those of solids. For this reason, multiple administrations of the powdered formulations, the bioavailability of insulin was significantly reduced. The causes were not fully understood, however, it was hypothesized that the powders did not completely leave the nasal passages after each dose but instead created anatomical obstacles on the mucous membrane of the nose, preventing the medication from penetrating on consecutive administrations[16].

5. Nasal Microvesicles

It was first used in 1987 to use microscopic particles as an additional method of extending the timeframe for residence in the nasal cavity[22]. According to the theory, microspheres of DEAE-dextran (diethyl aminoethyl dextran), albumin, and starch absorbed water to produce a gel-like layer that gradually disappeared out of the nasal cavity. Sixty percent that was delivered dextran microspheres and fifty percent of the albumin and starch microspheres that were recently delivered remained in the location of depositing three hours after delivery. It was hypothesized that extending the contact duration would improve medication absorption. From 0.1% for the solution to 2.7% for the preparation with degradable starch microspheres, the amount of intranasal hGH bioavailability in sheep rose. Lysophosphatidylcholine, an aid to absorption, was further added to the growth hormone solution to further boost absorption, yielding a 14.4% relative bioavailability[23].

6. Nasal Gel

A gel is defined as a material that is soft, solid, or semi-solid-like that is made up of multiple elements, of which at least one contains a sizable volume of liquid. Elastic modulus G' and viscous modulus G are two dynamic mechanical variables that have applications to how gels behave in a semi-solid state [24]. The kind of polymer, its concentration, and the gel's physical condition all affect its rheological characteristics. They can be really difficult, brittle gels (such as gellan gum, pectin, and alginate) or fluid solutions (such as hypromellose, methylcellulose, xanthan gum, and chitosan). Utilizing bioadhesive materials in nasal formulations has shown promise because they can regulate the pace and scope of the pharmaceutical release, reducing the need for repeated dosing and increasing patient compliance[25]. Additionally, the extended contact time provided at the place of absorption can increase medication bioavailability by reducing mucociliary migration. Several ideas can explain the nasal cavity's system for preventing mucoadhesion, However, it is generally acknowledged that the system is built on two critical steps, the interaction and confirmation stages. Therefore, products made with bioadhesive polymers can spread throughout the nasal epithelium when they are injected into the nasal cavity. Due to the greater surface area in the mucus, polymer chains may spread. This causes entanglement because there is enough touch. After then, mucin molecules and polymer chains establish secondary chemical bonds[26].

In situ gelatin-forming polymeric compositions are drug delivery techniques that go through in situ gelation in order to create a gel after injection within the body. The medication must be made available from the gel over time and under controlled circumstances due to factors including pH adjustment, temperature control, and the requirement of ions. The use of fluid gels in place of gels is possible. These liquid gels

are simply organised liquids that have a gel-forming polymer. These are produced by putting pressure on the polymer remedy while it is gelating. The result is, gelled particles are suspended in a polymer solution without gel[27].

In-situ Gel

There have been numerous patents for in-situ gel forming systems' use in diverse biomedical applications, for example, medicine delivery. Earlier this decade, according to an investigation into their development[28]. The Latin phrase "in situ" implies "in its original place or in position." Prior to being delivered to the body, medication is present as a solution; nevertheless, once delivered, the medication undergoes in-situ gelation to create a gel[29]. These might be produced either by themselves or in addition to other stimuli, such as pH changes, temperature changes, and solvent exchange. The making of a novel medicinal molecule is a costly and time-consuming procedure nowadays. Therefore, by delivering "old" medications in a regulated, gradual-release way or by targeted distribution, the safety and efficacy ratio can be boosted. This leads to the creation of in-situ gelling nasal medication administration systems[30].

Advantages of in-situ nasal gel formulation[31]

- Therefore, the medication being taken less frequently and being in the nasal cavity for a longer period of time, the effects start to take effect quickly.
- Prevents enzymatic or acidic deterioration of the medication in the digestive system.
- Low dose is required.
- Fewer harmful systemic and regional consequences.
- A greater bioavailability of the medication.
- Additionally possible are direct entrance and systemic circulation.
- Lowers the possibility of an overdose from a CNS-active medication.
- A rise in patient adherence.

Limitation of In-situ Nasal Gel Formulation[11]

- Unknown medicine administration technique.
- Surface area is smaller than GIT, and only a small volume can be sprayed.
- Appropriate for strong drugs.
- Dosage loss due to mechanical and technical issues.
- Nasal mucosa ciliary damage that might be permanent.
- Nasal mucosal sensitivity.
- Nasal mucosal injury

The benefits of in-situ nasal gel versus conventional nasal formulations [3]

- Reduction of post-nasal drip into the throat, which lessens the issue of foul taste and the loss of medication from the nasal cavity.
- Decreased anterior medication leaking from the nasal passageway.
- Localization of the composition on the mucosa increases the likelihood that the medicine will be absorbed.
- Gels can use emollients or soothing ingredients that may not be appropriate for solutions, suspensions, or powder dosage forms, reducing the likelihood of irritation.
- Can be created for systemic and regional distribution, and a metered dose nasal actuator device has the ability to administer a precise dose.

CONCLUSION

A cutting-edge platform called nasal medication delivery offers a potential substitution for the injectable mode of administration. It has a potential that other medications designed for systemic treatment will soon enter the market in the composition of nasal preparations.

The creation of a medication with a way to deliver it is influenced by a variety of elements. Novel nasal medications are also anticipated to be commercialised in required to treat chronic disorders like diabetes, osteoporosis, and fertility treatment. Among the main obstacles to the progression of nasal products is the bioavailability of nasal medicinal products. In contrast, since the rising demand for nasal medicine products in the worldwide pharmaceutical market, pharmaceutical companies are investing a sizable sum of money in the process of nasal products. Therefore, we should focus on basic research to prevent adverse effects and enhance the effectiveness of nasal products.

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