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Drug Delivery System Through Nasal Route: A Review

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ABSTRACT
The nasal drug delivery system (NDDS) has been employed as an alternative route for the systemic accessibility of medications that are only administered intravenously. This is because of the porous endothelium membrane, huge surface area, high total blood flow, lack of first-pass metabolism, and ease of access. In recent years, there has been a great deal of interest in nasal administration of medications, including different chemical, peptide, and protein pharmaceuticals, for systemic therapy. Following intranasal delivery, drugs are rapidly discharged from the nasal cavity, resulting in rapid systemic drug absorption. Several ways for enhancing the residence period of drug formulations in the nasal cavity, resulting in better nasal medication absorption, are reviewed here.

Keywords: *NDDS, Drug administration, systemic Administration.*

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INTRODUCTION
Nasal drug delivery has a long history that begins with previous topical administrations of medications meant for local effects. Nasal therapy, also known as "Nasya karma," is a recognised method of care in the Indian medical system of Ayurveda [1]. The nasal route was first introduced as a viable systemic delivery alternative to other traditional drug delivery routes in the early 1980s [2]. With a porous endothelium membrane and a highly vascularized epithelium, the nasal route is simple to use, practical, and trustworthy. This allows for a quick absorption of substances into the systemic circulation without going through the hepatic first pass elimination. Intranasal drug delivery also permits dose reduction, speedy achievement of therapeutic blood levels, earlier commencement of pharmacological activity, and reduced adverse effects [3,4]. The low metabolic environment of the nose offers the potential to get around the oral route's drawbacks and match the advantages of intravenous administration. Furthermore, nasal delivery reduces the lag time associated with oral drug administration and provides non-invasiveness, self-administration, patient comfort, and patient compliance, which are barriers in intravenous drug therapy. [5] It was stated that lipophilic medications are typically well absorbed from the nasal cavity, with pharmacokinetic profiles that are frequently the same as those obtained after an intravenous administration and a bioavailability that is close to 100%. On the other hand, [1] absorption enhancers can improve the absorption of hydrophilic medicines. [2] Drugs are administered through the nasal passage, ranging in size from tiny compounds to huge macromolecules, including peptide/protein therapies, hormones, and vaccinations [6]. The nasal delivery method appears to be an effective strategy to get over the blood-brain barrier (BBB) barriers and enable direct drug delivery of central nervous system (CNS) active substances during their BioPhase. The administration of vaccines has also been given consideration [7–8]. Some peptides that have been successfully supplied via the nasal route include buserelin, desmopressin, calcitonin, insulin, luteinizing hormone-releasing hormone, growth hormone, and adreno-corticotrophic hormone. Other drugs that have been shown to have significant systemic effects include steroids (corticosteroids, estradiol, progesterone, testosterone, and so forth) [9,10], antihypertensives (nifedipine, nitro-glycerine, propranolol, hydralazine, and so forth), analgesics (buprenorphine), antibiotics, and antivirals [11]. Numerous technologies, including nasal spray, nasal pumps, gels, microemulsions, suspensions, powders, and thermoreversible mucoadhesive gels, have been investigated for nasal drug delivery [12]. Over the past few decades, pharmaceutical scientists and physicians have paid more and more attention to the viability of medication delivery through the nose.

POSSIBILITIES FOR THE DELIVERY OF MEDICATIONS THROUGH THE NASAL CAVITY

The nose is a potential medication delivery organ due to its accessibility and surface area. The development of pharmaceutical products is a crucial task that is directly related to their therapeutic goals.

The factors to consider while developing a product depend on whether it is meant for:

a) Local delivery.
b) Systemic delivery.
c) Repeated or isolated administration.

LOCAL DELIVERY

When compared to the oral route of administration, nasal delivery is the logical choice for local (or topical) treatment because there is less risk of systemic side effects. As a result, relatively low doses are effective when administered via the nasal route with less risk of systemic toxic effects. Decongestants for cold-related nose symptoms and antihistamines and corticosteroids for allergic rhinitis are two prominent treatment types of medications administered [13,14].

SYSTEMIC DELIVERY

Compared to oral and intravascular modes of administration, the intranasal delivery of medications is a useful method for increasing the systemic availability of pharmaceuticals. Compared to oral and parenteral delivery, it offered faster and longer drug absorption. Analgesics (exmorphine), cardiovascular medications like propranolol and carvedilol, hormones like levonorgestrel, progesterone, and insulin, anti-inflammatory medications like indomethacin and ketorolac, and antiviral medications like acyclovir are among the therapeutic classes of medications administered. For the treatment of migraines and cluster headaches, examples of products on the market include zolmitriptan and sumatriptan [13,15,16,17,1819].

REPEATED OR ISOLATED ADMINISTRATION

Nasal mucosa is the initial site of contact with inhaled antigens during inhalation, hence its use for immunisation, particularly against respiratory illnesses, has undergone substantial research. Because nasal vaccination can raise systemic levels of both nasal secretory immunoglobulin A and specific immunoglobulin G, it is a promising alternative to the traditional parenteral route. Intranasal vaccines against influenza A and B virus, proteosoma influenza, adenovirus-vectored influenza, native Group B meningococcal infection, attenuated respiratory syncytial virus, and parainfluenza 3 virus are some examples of those with human efficacy [13,20,21,22,23].

DELIVERY TO THE CENTRAL NERVOUS SYSTEM (CNS) THROUGH THE NASAL ROUTE

The intranasal method has shown promise for delivering medications to the brain. Olfactory neuroepithelium may be involved in the nasal transport of medicines to the central nervous system. Alzheimer's disease, brain tumours, epilepsy, pain, and sleep disturbances have all been treated using medications delivered into the CNS via the nasal route [24,25,26,27].

ANATOMY AND PHYSIOLOGY OF THE NASAL CAVITY

The nasal vestibule, which is the most anterior portion of the nasal cavity, opens to the face through the nostril. The nasal cavity is separated into two halves by the nasal septum and continues posterior to the nasopharynx. nose vestibule, olfactory area, and respiratory region are the three main regions that make up the nose cavity. The nasal cavity's lateral walls, which have a folded shape, can extend the surface area by around 150 cm2, giving the nose a remarkably large surface area for its relatively small volume. The superior, median, and inferior turbinate’s make up this folded structure [28]. The small channels in the primary nasal airway, which are typically 1-3 mm wide, help the nose perform its essential activities.

The mucous membrane that covers the nasal cavity can be divided into two regions: the non-olfactory region, which includes the nasal vestibule, is covered with skin-like stratified squamous epithelium cells, and the respiratory region, which has a typical airways epithelium covered with numerous microvilli, creating a large surface area that is open to drug absorption and transport [29]. In this manner, the mucus layer is pushed through the nasal cavity from the front to the back. The mucus membrane that covers the nasal turbinate and atrium contains goblet cells, which release mucus as granules that thicken in the nasal fluid to add to the mucus layer.

The mucus secretion is mostly made up of water, 2% mucin, 1% salts, 1% additional proteins like al-bumin, immunoglobulin S, lysozyme, and lactoferrin, and b 1% lipids. Immune defence against viruses and bacteria that are breathed is provided by the mucus sequestration. Additionally, it carries out a variety of physiological functions.

(1) It covers the mucosa and defends it enzymatically and physically.
(2) The mucus has ability to hold water.
(3) Surface electrical activity is present.
(4) It allows for effective heat transfer.

(5) It serves as an adhesive and transports particle in the direction of the nasopharynx [30,31].

ADVANTAGES OF NASAL DRUG DELIVERY SYSTEM

- Rapid medication absorption occurs through highly vascularized mucosa.
- Large nasal mucosal surface area is available for dosage absorption.
- The action starts up quickly.
- Non-intrusive and simple to administer.
- Avoid the BBB.
- Drug degradation that has been seen in the GIT is avoided.
- There is no hepatic first pass metabolism.
- Small drug molecules have a good nasal bioavailability.
- By using absorption enhancers, the bioavailability of big medication molecules can be improved.
- The nasal route can be successfully used to provide medication candidates that are inappropriate for the oral route.
- A substitute for parenteral administration, particularly for proteins and peptides.
- Convenient path for patients receiving long-term treatment.
- Increased biological availability.
- The modest dose reduces side effects.
- Patient comfort and compliance are increased.
- One could self-administrate.
- There is a lesser danger of overdose with direct transfer into the CNS and systemic circulation.
- Has no complicated formulation requirements [32].

LIMITATION

- The delivery volume in the nasal cavity is capped at 25–200 L.
- Due to the mass cut-off of 1 kDa, high molecular weight substances cannot be administered by this method.
- Negatively impacted by pathological circumstances.
- On this route, significant interspecies heterogeneity is seen.
- Common defence mechanisms like ciliary beating and mucociliary clearance have an impact on a substance's permeability.
- Nasal mucosa irritation caused by medications like budesonide and azilactine.
- Presently underdeveloped models and little understanding of mechanisms.
- It has not yet been proven that absorption enhancers can cause systemic toxicity.
- Less expansive absorption surface when compared to GIT.
- Potential for nose discomfort, making it less convenient than taking it orally.
- Enzymatic barrier preventing drug penetration. [33]

PROFILE OF THE 'PERFECT' MEDICATION CANDIDATE FOR NASAL DELIVERY

- The following qualities should be present in a candidate for a nasal drug:
- Sufficient aqueous solubility to deliver the required dose in a 25–150 ml formulation administration volume per nostril.
- Proper qualities for nasal absorption.
- The drug did not cause nasal irritation.
- A suitable clinical justification, such as a quick beginning of action, for nasal dose forms.
- Small dosage. Usually, each dose is less than 25 mg.
- No hazardous nasal metabolites exist.
- The medicine doesn't have any unpleasant aromas or odours.
- Proper stability properties. [34]

MECHANISM OF ABSORPTION

The transit through the mucus is the key step in a drug's absorption from the nasal cavity. Large particles may encounter some challenges, but small particles can easily pass through the mucus layer [35]. Mucin, a protein found in mucus, has the potential to attach to solutes and interfere with the diffusion process.

The mucus layer may undergo structural alterations because of environmental or physiological changes [36]. There are various methods for medication absorption through the mucosa once it has passed through the mucus. These include transcellular or straightforward membrane diffusion, paracellular transport including cell-to-cell migration, and transcytosis by vesicle carriers. There have been several mechanisms put forth, although paracellular and transcellular pathways predominate [37].

Slow and passive paracellular transport is the norm. Intranasal absorption and the molecular weight of water-soluble substances are inversely correlated. For medicines with a molecular weight greater than 1000 Daltons, poor bioavailability was found [36].

The second mechanism, sometimes referred to as the transcellular process, includes transport via a lipoidal pathway and is responsible for the movement of medicines that are lipophilic and exhibit rate dependence. Drugs can also enter cells through the opening of tight junctions or by active transport methods that use carriers [37].
Potential metabolism prior to entering the systemic circulation and insufficient nasal cavity residence time are barriers to medication absorption.

INCREASING DRUG UPTAKE

Many medications with a high-water solubility have low transepithelial permeability and may have limited bioavailability. penetration enhancers are commonly used to improve their penetration and bioavailability [38]. In theory, permeation enhancers cause reversible changes to the epithelial barrier's structural integrity. It is generally acknowledged that these materials alter the permeability of the epithelial cell layer by altering the phospholipid bilayer, even though the precise mechanism of drug absorption/permeation augmentation is not well understood [39]. Many types of absorption/permeation enhancers are given along with potential modes of action.

NASAL DRUG DELIVERY SYSTEM

NASAL DROPS

Nasal drops are among the most user-friendly and straightforward nasal administration systems ever created. Due to the lack of dose precision in this technique, nasal drops may not be appropriate for prescription medications. According to reports, nasal drops more effectively deposit human serum in the nostrils than nasal spray does.[40]

NASAL SPRAY

Nasal sprays can be made from formulas that are either solutions or suspensions. A nasal spray can deliver an accurate amount since metered dose actuators and pumps are readily available. Sprays of powder are favoured over these because powder irritates the mucous membranes.[40]

Nasal Powders

If solution and suspension dosage forms cannot be developed, for example because the medicine is not stable enough, this dosage form may be created. The lack of a preservative and the formulation's greater stability are benefits of the nasal powder dose form. However, the solubility, particle size, aerodynamic properties, and nasal irritancy of the active ingredient and/or excipients determine whether the powder formulation is appropriate. An additional benefit of this approach is the local application of drugs.[40]

NASAL GEL:

The nasal gel has gained popularity due to its ability to reduce post-nasal drip, high viscosity, taste impact due to decreased swallowing, anterior formulation leakage, irritation reduction using soothing/emollient excipients, and targeted delivery to mucosa for improved absorption.[41]

NASAL INSERTS

For prolonged systemic medication distribution through the nasal route, nasal inserts are innovative, bio adhesive solid dosage forms. The idea behind the dosage form is to remove nasal mucus after delivery and create a gel in the nasal cavity to prevent the sensation of a foreign body.[40]

NASAL EMULSIONS AND SUSPENSIONS

Rarely are suspensions used or researched as nasal drug delivery systems. Analogous to marketed aqueous ophthalmic suspensions of the soft corticosteroid, loteprednol etabonate (e.g., Alrex®, Bausch and Lomb Pharmaceuticals), a nasal aqueous suspension of same drug containing microcrystalline sodium carboxymethylcellulose for stabilisation and retention in the nasal cavity was patented by Senju Pharmaceuticals Inc., Osaka, Japan [42] and was intended for the local treatment of allergic rhinitis. Moreover, Ando et al. (1998) [43] investigated the use of a nasal suspension for the administration of insulin. Here, pharmacological bioavailabilities of 6.7% and 11.3% were attained using steryl glycoside and sterol mixes (1%) produced from soybeans as absorption enhancers. However, emulsions were found to be more effective than suspensions in increasing the bioavailability of poorly soluble drugs for oral drug delivery, according to several authors [44,45]. This trend is also seen with nasal formulations. The solubilization of the medication and the lipophilic absorption enhancers in the mix have been credited with improving absorption. Other low solubility chemicals, such as diazepam [46] and testosterone [47], have also been produced in emulsions to boost the drug's solubility.

Targeted the brain through the nose using a nano-suspension [48]. For particles between 1 and 500 nm, formulation as a nanosuspension enhanced blood-brain barrier (BBB) bypass. Additionally, researchers have recently reported using nasal nano-emulsion administration for brain targeting [49,50,51].

PRESSURIZED MDIs

With the help of a patient inhaling a brief burst of aerosolized medication, a metered-dose inhaler (MDI) delivers a precise dosage of medication to the lungs. It is the most widely utilised delivery method for the treatment of respiratory illnesses like asthma, chronic obstructive pulmonary disease (COPD), and others. Metered dosage inhalers are most frequently used to treat asthma and COPD with bronchodilators, corticosteroids, or a combination of the two. Mast cell stabilisers, such as cromoglicate or nedocromil, are additional, less frequently prescribed drugs that can also be given by MDI.The benefits of MDIs include their portability and small size, availability throughout a broad dosage range per actuation, dose constancy, dose accuracy, protection of the contents, and speedy readiness for use.[52]

The patient presses down on the top of the inhaler canister while supporting the lower part of the actuator with their thumb. The active component must be suspended or dissolved in the propellant, which also provides the force needed to create the aerosol cloud. In MDIs, propellants typically account for more than 99% of the dose that is delivered.A single metered dose of the formulation, containing the drug either dissolved or suspended in the propellant, is released upon activation of the device. The volatile propellant is broken up into droplets, which are then rapidly evaporated, creating an aerosol of micrometre-sized drug particles that are then inhaled (Finlay, 2001).[53]

INFLUENCES ON NASAL DRUG ABSORPTION

THE DRUG'S PHYSICOCHEMICAL CHARACTERISTICS

Numerous physicochemical factors, such as the drug's partition coefficient, pKa, molecular weight, perfusion rate, perfusate volume, solution pH, and drug concentration, may affect the rate and extent of drug absorption.[54]

MUCOCILIARY CLEARING

The mucus layer transports the particles that are trapped there, thereby clearing the nasal cavity. The term "mucociliary clearance" refers to the combined activity of the mucus layer and cilia. This is a crucial, general physiological defence mechanism of the respiratory system that guards against harmful breathed substances. [55] According to reports, the average mucociliary transit time in humans is 12 to 15 minutes. [56]

VISCOSITY

Higher viscosity formulations have longer contact times, hence ups the absorption. High viscosity simultaneously increased a drug's penetration. This has been noticed during the nasal delivery of metoprolol, acyclovir, and insulin. According to Zaki et al., as viscosity rose, medication absorption decreased while residence time increased. [57,58,59]

PH

When a medicine is absorbed by the nose, its pKa and the pH of the absorption site are crucial factors. Therefore, stability can be achieved by carefully choosing the formulation's pH. To stop sneeze, the formulation's pH should be close to that of the human nasal mucosa (5.0–6.5). [60, 61]

DRUG FORM

The simplest and most practical nasal pharmaceutical dosage form is nasal drops, however it's difficult to gauge how much medication is administered, which frequently leads to overdose. Moreover, using this dosage form may cause rapid nasal drainage. Solution and suspension sprays are preferable over powder sprays because the former may irritate the nasal mucosa. These days, nasal gel has been created for precise drug administration. By extending the drug's residence time and decreasing MCC, this raises nasal absorption. [62-64]

EXCIPIENTS IN PHARMACEUTICALS

Pharmaceutical excipients are chosen for nasal formulations in accordance with their activities. Solubilizers, buffer components, antioxidants, preservatives, humectants, and gelling/viscosifying agents are the most frequently utilised excipients. [62,63]

REGULATION-RELATED FACTORS

Long-term drug development processes finish with regulatory approval of a candidate for marketing, but regulatory considerations should be understood from the start. Any new drug product must consider safety, effectiveness, and quality requirements to receive approval in the USA. The FDA will receive this data as part of a new drug application (NDA). However, as it was previously described for several examples like inhaled insulin (Exbuera®), oral inhaled and/or nasal drug products (OINDP) are currently the most frequently discussed for repurposing an already approved product.

Since the US Food and Drug Administration (FDA) has specific safety, efficacy, and quality requirements for respiratory delivery, those are the main topics of this section. Additionally, biologics are not specifically mentioned because the same considerations that apply to small-molecule drug products also apply to biologicals.

A novel drug product can be approved by the FDA through one of three regulatory processes: 505(b)(1), 505(b)(2) for NDAs, or 505(j) abridged NDAs (ANDAs). Repurposed medications may be eligible for the regulatory procedure 505(b)(2) if they are administered by a novel method, such as pulmonary delivery. Since some safety and efficacy data from previously approved medications could be used, this could be advantageous [65-67].

Preclinical research and systemic safety can be justified by evidence from earlier studies of licenced medications, but further preclinical and clinical studies are still needed to gather more data [68,69].

CONCLUSION

Nasal drug delivery is a promising alternative to traditional drug delivery methods. The nasal cavity provides a large surface area and high permeability for drug absorption, making it an attractive route for delivering a variety of therapeutic agents. In recent years, significant progress has been made in the development of nasal drug delivery systems, including nasal sprays, drops, powders, and gels. These systems have demonstrated potential in delivering drugs for various indications, including pain management, allergies, and central nervous system disorders. Additionally, nasal drug delivery has shown advantages such as rapid onset of action, avoidance of first-pass metabolism, and reduced systemic toxicity. While there are still challenges to overcome, such as variability in drug absorption and patient adherence, ongoing research and development in this field offer promising prospects for improving drug therapy outcomes. Overall, the nasal drug delivery system has the potential to revolutionize the way we deliver drugs and improve the lives of patients worldwide.

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