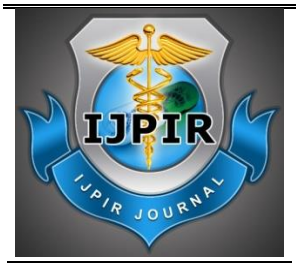
Review Article



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A review on intranasal drug delivery system

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ABSTRACT

In the present era, the nasal drug delivery system is considered as a viable and favorable way of drug delivery because it provides patient satisfaction, easy administration; bypass first pass metabolism, excellent access, low dose requirement, rapid absorption and optimal results. Therefore, many times nasal drug delivery is considered as an alternative to the parenteral route. Many drug delivery systems have been investigated for the delivery of drugs for the treatment of CNS disease (ie, Parkinson's disease, Alzheimer's disease) for nasal use of liquid, semiconductor, and solid formulations because it requires immediate and / or specific drug targeting in the brain. DNA vaccines are suitable for the delivery of biological products suitable for the delivery of proteins, peptides, hormones, DNA plasmids.

INTRODUCTION

Nasal drug delivery, which has been at the center of this review article, has received considerable attention in recent years, not only locally but also for systemic administration of the drug as a convenient and reliable route. The nasal cavity offers many specific benefits for systemic obstruction such as:

1. A big surface for drug abuse.
2. Facilities and good patient compliance.
3. Rapid recovery of therapeutic drug levels in blood.
4. High drug permeability, especially for lipophilic and drugs of low molecular weight.
5. Avoiding harsh environment and Gastrointestinal Conditions.
6. Bypassing the liver's first-pass metabolism.
7. Potential direct drug delivery to the brain the olfactory vein.
8. Direct contact site for lymphatic vaccines tissue.

In recent times, many drugs are used by the nasal passages, but there are many disadvantages such as poor contact of the formulation with nasal mucosa, rapid clearance, and dense formulation.

Nasal drug delivery that has been going on for thousands of years - life has been given a new lease. This is a useful delivery method for drugs that are active in low doses and show minimal oral bioavailability, such as proteins and peptides. One

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of the reasons for the low absorption of peptides and proteins through the nasal passages is the rapid movement away from the absorption site in the nasal cavity due to the mucous skin clearance mechanism. A wide range of pharmaceutical dosage forms, including solutions, gels, suspensions, emulsions, liposomes, and micro-particles, can be used to achieve systemic drug action. These dosage forms are designed to exploit the benefit of rapid onset of action when administered via most nasal passages. For example, morphine and ketamine can be delivered intra-nasally to achieve faster analgesic effects. In addition, vaccines can also be given using the nose as a possible route, such as for influenza.

Anatomy of the nasal cavity [5, 6, 7]

The nasal cavity extends from the external opening, to the nostrils, to the upper part of the throat (to the upper part of the throat), where it joins the rest of the respiratory system. It is separated below the center of the nasal septum, a piece of cartilage that shapes and separates the nose. Each nostril can be further divided into ceilings, floors and walls. The nasal cavity can be divided into vestibules, respiratory and olfactory segments.

Nasal vestibule

- This is the anterior part of the nasal cavity.
- Surface area is 0.6 cm2.
- The nasal part is protected by a squamous keratinized epithelium stratified with the stabias gland.
- Drug abuse is very difficult in this region, but it has a high resistance to toxic environment.

Atrium

- The area between the nasal vestibule and the respiratory tract is called the Atrium.
- In the foreground - is the stratified squamous - The pseudostratified columns in the rear are columns.

Respiratory area

- This is the largest part of the nasal cavity and is also known as Conchae.
- Humidity and temperature are its functions.
- Drug delivery in this region is very good.
- It consists of pseudo-pillar pillars, globate cells, basal cells, mucous and serous glands.
- Microvilli are important for increasing respiratory surface area.

Industrial Region

- It is located on the roof of the nasal cavity.
- It contains neuroepithelium -Neuropithelium is the cavity of the CNS that is directly affected by the external environment.
- It's pseudostraised.

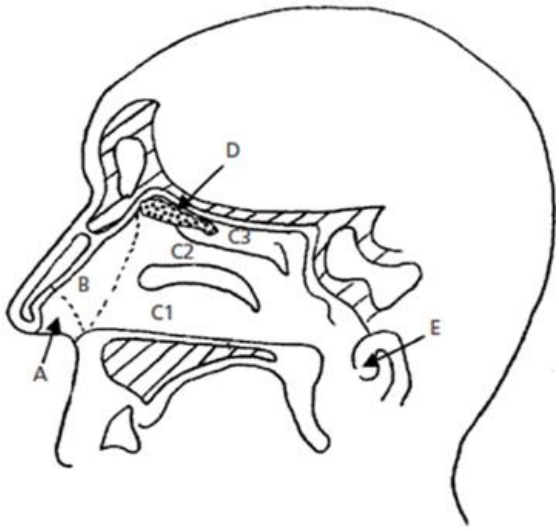

Figure 1. Sagittal section of the nasal cavity showing the nasal vestibule (A), atrium (B), respiratory area: inferior turbinate (C1), middle turbinate (C2) and the superior turbinate (C3), the olfactory region (D) and nasopharynx (E).

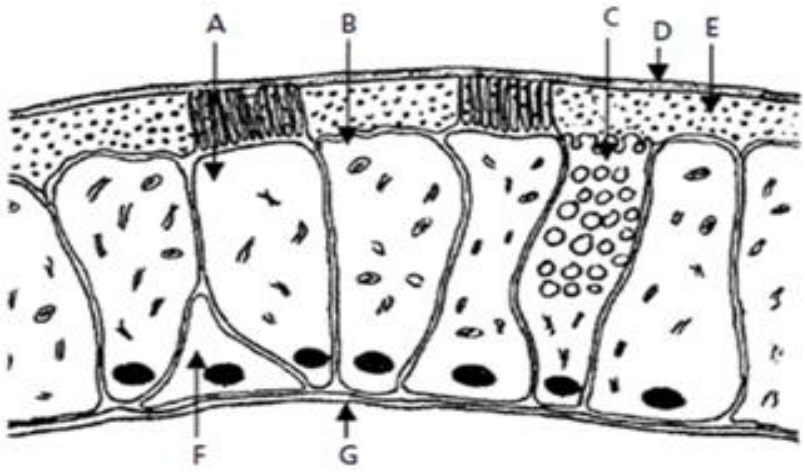

Figure 2. Cell types of the nasal epithelium with covering mucous layer showing ciliated cell (A), non-ciliated cell (B), goblet cells (C), mucous gel-layer (D), sol layer (E), basal cells (F) and basement membrane (G).

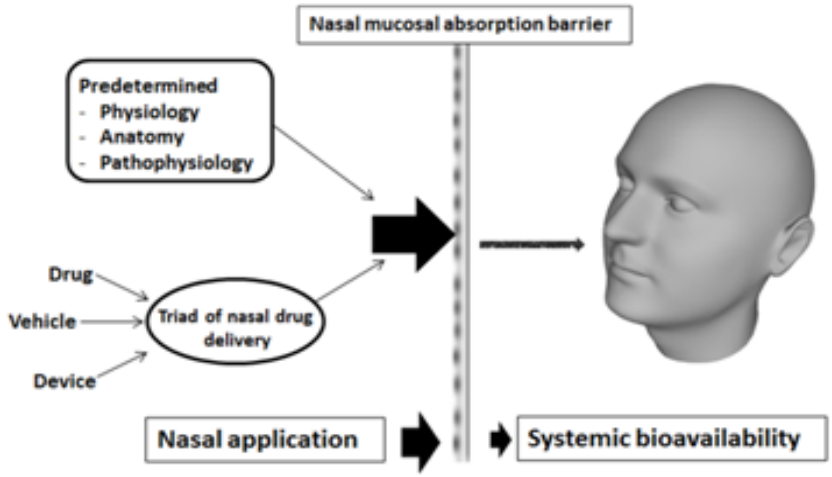

Figure 3. Consideration of formulation elements of nasal product development.

Factors affecting nasal drug absorption [8]

Drugs, nasal mucosa clearance and nasal absorption enhancers are the physical factors that affect drug absorption through nasal mucosa. The biggest limitation of nasal drug delivery is inadequate nasal drug abuse.

Many promising drug candidates cannot be exploited by the nasal passages because they are not absorbed enough to produce therapeutic effects. This motivated researchers to look for ways to improve drug abuse through the nasal passages.

Profile of an 'ideal' drug candidate for nasal delivery

An ideal nasal drug candidate should possess the following attributes [9, 10]

- Proper aqueous solubility to provide the desired dose in 25-150 ml of nasal administration formulation.
- Appropriate nasal absorption properties.
- No nasal irritation from the drug.
- A suitable clinical rationale for nasal dosage forms, e.g. rapid onset of action.
- Low dose. Generally, below 25 mg per dose.

- No toxic nasal metabolites.
- No offensive odours/aroma associated with the drug.
- Suitable stability characteristics.

Advantages of Nasal Drug Delivery System [11, 12, 13]

1. Drug degradation is absent in the gastrointestinal tract.
2. The first - pass metabolism of the liver is absent.
3. Rapid drug absorption and rapid onset of action can be achieved
4. The bioavailability of large drug molecules can be improved by absorption enhancers or other methods.
5. Nasal bioavailability is good for small drug molecules.
6. Oral absorption drugs can be given to systemic circulatory system by delivery of nasal drug
7. Studies done so far indicate that the nasal passages are an alternative route to mpared to parenteral drugs, especially for patients receiving long-term therapy.
8. Large nasal mucosa surface for dose absorption.
9. Rapid drug absorption by highly-vascular mucosa.
10. Fast start to action.
11. Administration is easy, not aggressive.
12. Avoid gastrointestinal tract and first-pass metabolism
13. Improved bioavailability
14. Low dose / reduced side effects
15. At least aftertaste
16. Improved facilities and compliance
17. Self-administration
18. New patent coverage for drug formulations is about to expire

Disadvantages

1. Histological toxicity of absorbent enhancers used in nasal drug delivery system has not yet been clearly established.
2. Patients are relatively uncomfortable when there is a potential for nasal irritation compared to the oral delivery system
3. The nasal cavity provides a smaller absorbing surface area compared to GIT

Drugs are used in nasal drug delivery system

Midazolam —sedation: [14-20] Midazolam is an easily administered drug with high bioavailability (BA), reasonable ability to cross the BBB, and pharmacodynamic effects. In a three-way crossover study of 12 healthy volunteers, similar doses of midazolam (3.4 mg) were evaluated with a respiratory-powered bi-directional-device prototype corresponding to standardized nasal spray and intravenous (IV) administration. Drug pharmacokinetics (PK) with both nasal delivery approaches were similar, as is not unexpected for a small molecule easily absorbed to the blood with a high BA of ≈70 %. Interestingly, the pharmacodynamic effects (onset and level of sedation) reported with Bi-Directional™ delivery were very similar to IV administration despite substantially lower maximum serum levels (Bi-Directional™ with median C_{max} = 3 Ng/ml vs. IV with median C_{max} = 5 ng/ml). In contrast, the onset was slower, and the degree of sedation was lower following traditional spray delivery despite similar PK values as Bi-Directional™ delivery. These findings suggest that the sedative effect following Bi-Directional™ nasal delivery may not merely be a result of absorption to the blood and subsequent passage into the brain across the BBB as occurs with a standard nasal spray. Alternative transport routes to the brain bypassing the BBB described in animal studies may contribute to the sedative effects. Absorption from the posterior part of the nose may offer a more direct route to brain arterial blood through the particular venous drainage pathway from the posterior parts of the nose called “counter-current transfer”. Moreover, direct transport to the brain for both small and large molecules may occur along ensheathed cells forming channels around the olfactory and trigeminal nerves. Contribution from such alternative transport routes would be consistent with a clinically important improvement in the pattern of deep nasal drug deposition with breath-powered Bi-Directional™ delivery.

Sumatriptan—migraine: [14, 20-25] Unlike midazolam, serotonin antagonist Sumatriptan has a bad BA when delivered orally (14%) and is only slightly higher when delivered as a nasal spray

(Pfizer single-dose device). It has been estimated that only about 10 % of the drug delivered by standard nasal spray (Imitrex) is absorbed rapidly across the nasal mucosa within the first 20 min with much of a dose undergoing delayed absorption from the GI tract with a T_{max} of 90 min. Hypothesizing that breath-actuated Bi-Directional™ powder delivery may produce clinically different results than previously reported for nasal spray delivery, investigators conducted a cross-over PK study in 12 migraineurs, comparing subcutaneous injection of 6 mg sumatriptan with 10 and 20 mg of intranasal sumatriptan powder. Bi-directionally delivered nasal sumatriptan powder was pharmacodynamically similar to injection, inducing a similar EEG profile and preventing migraine attacks in patients when delivered 15 min before glyceryl trinitrate challenge. PK curves showed the same bi-phasic absorption pattern as described for the distribution of sumatriptan nasal spray, but the initial nasal absorbance peak was approximately 5% of the total absorption over approximately 5 min. For marketed immitrex nasal spray, 10% fraction is absorbed in nasal proportion. These PK results are credited with the conclusion that clinically differentiated nasal deposition is performed by a breath-guided bi-directional ™ device compared to previously reported with previous nasal spray delivery. More precise studies are being conducted on direct nasal spray delivery, comparing direct sumatriptan delivery with inhaled-nasal spray, oral delivery and injection delivery, and results should be reported shortly (www.clinicaltrials.gov). In a randomized, double-blind, parallel group, placebo-controlled study, a single migraine attack was treated in-clinic with two doses of sumatriptan powder (7.5 or 15 mg delivered doses or placebo) administered intranasally by a novel Bi-Directional™ powder delivery device; fast onset of pain relief was observed for both doses . The pain relief rates were similar to historical data SC injection despite much lower systemic exposure. The results suggest that the enhanced deposition associated with the breath-powered Bi-Directional™ delivery of sumatriptan powder may contribute to greater initial nasal absorption and offer clinical benefits. However, based on comparisons with historical data on the PK and pharmacodynamics profiles of sumatriptan delivered through different routes, it has been speculated that the rate of systemic absorption of nasal sumatriptan may not alone explain differences in headache response suggesting the potential for an additional route to the site of action as discussed above. A Phase 3 study is currently in progress
(www.clinicaltrials.gov and www.optinose.com).

Fluticasone propionate — [chronic rhinosinusitis with nasal polyps: [13,26-32] Fluticasone is a topical steroid, available as a standard nasal spray for treatment of rhinitis but often used with limited benefit in the treatment of chronic rhinosinusitis (CRS) with and without nasal polyps. In a 3-month placebo controlled study in 109 patients with chronic rhinosinusitis (CRS) with nasal polyps, delivery of fluticasone (400 µg b.i.d.) with an OptiNose breath-powered Bi-Directional™ liquid drug delivery device was reported to be well tolerated and to produce a large magnitude of reduction in both symptoms and the overall polyp score. Particularly notable relative to expectations with standard nasal spray delivery, complete elimination of the polyps in close to 20 % of the subjects was reported after 3 months. The proportion of subjects with improvement in summed polyp score was significantly higher with OptiNose fluticasone propionate (Opt-FP) compared with placebo at 4, 8, and 12 weeks (22 % vs. 7 %, $p = 0.011$, 43 % vs. 7 %, $p < 0.001$, 57 % vs. 9 %, $p < 0.001$). Despite relatively lower baseline polyp scores after 12 weeks, the summed polyp score was significantly reduced from 2.8 to 1.8 in the active treatment group, whereas a minor increase in polyp score was seen in the placebo group (−0.98 vs. +0.23, $p < 0.001$). Peak nasal inspiratory flow (PNIF) increased progressively during Opt-FP treatment ($p < 0.001$). Combined symptom score, nasal blockage, discomfort, rhinitis symptoms, and sense of smell were all significantly improved. The highly significant progressive treatment effect of Opt-FP was observed regardless of baseline polyps score. Previous sinus surgery had no impact on the efficacy. Coupled with the complete removal of polyps in many patients with small polyps, this suggests that improved deposition to target sites achieved with the Bi-Directional™ delivery device

may translate into true clinical benefits and possibly reduced need for surgery. A Phase 3 study is currently in progress (www.clinicaltrials.gov and www.optinose.com).

The same drug–device combination product was also evaluated in a small placebo-controlled study ($N = 20$) in patients with post-surgical recalcitrant CRS without polyps, producing clinically significant improvements on both objective measures and subjective symptoms. Endoscopy score for edema showed a significant and progressive improvement [12 weeks (median scores): Opt-FP −4.0, PBO −1.0, $p = 0.015$]. PNIF increased significantly during Opt-FP treatment compared to placebo (4 weeks: $p = 0.006$; 8 weeks: $p = 0.03$). After 12 weeks, MRI scores in the Opt-FP group improved against baseline ($p = 0.039$), and a non-significant trend was seen vs. placebo. The nasal RSOM-31 subscale was significantly improved with Opt-FP treatment (4 weeks: $p = 0.009$, 8 weeks: $p = 0.016$, 12 weeks: NS). Sense of smell, nasal discomfort, and combined score were all significantly improved ($p < 0.05$). Notably, this is a condition marked by many recent negative placebo-controlled trials. This context, in addition to comparison with historical data in similar patient populations, again suggests that breath-powered bi-directional delivery is capable of producing superior deep nasal deposition in clinical practice (improved targeting of the middle meatus in this case) which can translate into improved clinical response.

Influenza vaccine: [33, 34] In a four-armed parallel group study, complete immunization with a virus-influenza liquid vaccine without sequestration, bi-directional ™ optinose device with breathing and nasal drops resulted in a better complete immune response than traditional nasal spray and oral. Unlike self-administration with an optinose device, the nasal drops were inserted in a controlled manner beyond the nasal valve by the assistant by inserting a nept tip. These results indicate that the two-directional ™ device is a viable delivery method capable of clinically wide and solid delivery of vaccines to nasal mucous mucosa, an area rich in dendritic cells, and a combination of lymphoid tissues, capable of delivering a variety of vaccines. To improve immune response in a non-parent delivery form.

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