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REVIEW ARTICLE

# NASAL DRUG DELIVERY: SUCCESS THROUGH INTEGRATED DEVICE DEVELOPMENT

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## ABSTRACT

Transmucosal nasal delivery is a promising drug delivery option where common drug administrations (e.g., intravenous, intramuscular, or oral) are inapplicable. Recently, it has been shown that many drugs have better bioavailability by nasal route than by oral route. This has been attributed to rich vasculature and a highly permeable structure of the nasal mucosa coupled with avoidance of hepatic first-pass elimination, gut wall metabolism and/or destruction in the gastrointestinal tract. The physiology of the nose presents obstacles, but offers a promising route for non-invasive systemic delivery of numerous therapies and debatably drug delivery route to the brain. Intranasal microemulsions, gels and microspheres have gained increased interest in recent years as a delivery system for protein and peptides through nasal route. Since building a more efficient nasal drug delivery device requires not only better device design but a far more versatile technology platform; one that delivers optimal nasal deposition, with formulation flexibility to work successfully with the many variables of the formulation itself. Thus present review focuses on innovations in nasal drug delivery devices.

Key Words: Transmucosal nasal delivery, bioavailability, non-invasive, brain, device design, formulation flexibility

## INTRODUCTION:

Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vagina, ocular and oral cavity) offer distinct advantages over peroral administration for systemic drug delivery. These advantages includes possible bypass of the first pass effect, avoidance of pre-systemic elimination of gastro intestinal tract and depending on the particular drug. The nasal cavity as a site for local and systemic drug delivery has been investigated by many research groups[1-4] and the route has already reached commercial status with several drugs including calcitonin[5, 6]. However, the potential irritation and irreversible damage to the ciliary action application of nasal dosage forms, as well as the large intra and inter subject variability in mucus secretion in the nasal mucosa could significantly effect drug absorption from this site.

Currently, many nasal drug products on the market are indicated for the treatment of local disease such as allergic rhinitis, pain and for centrally acting drugs where the direct pathway from the nose to brain might offer a quicker and further specific therapeutic effect. Many low-molecular-weight, non-polar drugs (<300Da) in solution form are able to infiltrate the nasal epithelium with effortlessness. The effectiveness of a particular delivery system is also affected by its formulation as a liquid[7], powder[7], gel[8], microsphere[9], liposome[10] or nanoparticle[11]. Intranasal drug delivery is now recognized to be a useful and reliable alternative to oral and parenteral routes. In general, among the primary targets for intranasal administration are pharmacologically active compounds with poor stability in gastrointestinal fluids, poor intestinal absorption and/or extensive hepatic first-pass elimination, such as peptides, proteins and polar drugs [12].

The nasal delivery seems to be a favorable way to circumvent the obstacles for blood-brain barrier (BBB) allowing the direct drug delivery in the biophase of central nervous system (CNS)-active compounds. In addition, intranasal absorption avoids the gastrointestinal and hepatic pre-systemic metabolism, enhancing drug bioavailability in comparison with that obtained after gastrointestinal absorption[13, 14]. Hence, it appears to be an appropriate route for the treatment of not only acute or chronic nasal diseases, but also for a range of acute or chronic conditions requiring considerable systemic drug exposure [12]. Since building a more efficient nasal drug delivery device requires not only better device design but a far more versatile technology platform; one that delivers optimal nasal deposition, with formulation flexibility to work successfully with the many variables of the formulation itself. Present review focuses on the innovations in nasal drug delivery devices. Additionally this review also outlines anatomical and physiological features of nasal cavity, the major factors affecting nasal drug delivery.

## REASON FOR DEVELOPMENT OF NASAL DELIVERY

Nasal drug delivery is a useful delivery method for drugs that are active in low doses and show no or minimal oral bioavailability. The nasal route circumvents hepatic first pass elimination associated with the oral delivery: it is easily accessible and suitable for self-medication. Currently, tow classes of nasally delivered therapeutics are on the market. The first one comprises low molecular weight and hydrophobic drugs for the treatment of the nasal mucosa and sinus, including decongestants, topical steroids, antibiotics and other (OTC) products. The second

class encompasses a few drugs, which have sufficient nasal absorption for displaying systemic effects. Important candidates are the compounds, generally administered by injection and hardly absorbed after oral administration, due to their instability in gastrointestinal tract, poor absorption properties, and their rapid and extensive biotransformation[15-17].

Table 1: Benefits of nasal drug delivery comparison to alternate delivery methods[12-14]

| Key Features | Nasal | Oral | I.V. |
|---|---|---|---|
| **High Drug Level** | Yes | No | Yes |
| **Rapid Onset** | Yes | No | Yes |
| **Painless** | Yes | Yes | No |
| **Self Administration** | Yes | Yes | No |
| **Low Resource Utilization** | Yes | Yes | No |
| **Bypasses BBB** | Yes | No | No |
| **Patient Compliance** | High | Low | High |
| **Hepatic First Pass Metabolism** | No | Yes | No |
| **After Taste** | Low | No | High |
| **Peptide drug Degradation** | Low | High | No |
| **Emesis** | No | Yes | No |

## MECHANISM OF DRUG ABSORPTION THROUGH NASAL MUCOSA:

The first step in the absorption of drug from the nasal cavity is passage through the mucus[16]. Small, unchanged particles easily pass through this layer. However, large or charged particles may find it more difficult to cross. Mucin, the principle protein in the mucus, has the potential to bind to solutes, hindering diffusion. Additionally, structural changes in the mucus layer are possible as a result of environmental changes (i.e. pH, temperature, etc.)[18]. Subsequent to a drug's passage through the mucus, there are several mechanisms for absorption through the mucosa [19]. These include transcellular or simple diffusion across the membrane, paracellular transport *via* movement between cell and transcytosis by vesicle carriers[18]. Obstacles to drug absorption are potential metabolism before reaching the systemic circulation and limited residence time in the cavity.

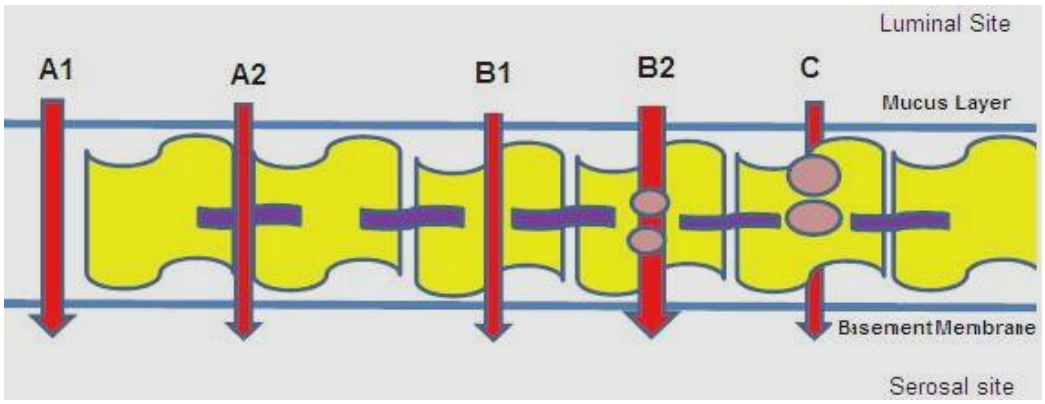


*Figure 1: (A) Paracellular route (A1) Intercellular spaces, (A2) Tight junctions, (B) Transcellular route (B1) Passive diffusion, (B2) Active transport, (C) Transcytosis*

The first mechanism involves an aqueous route of transport, which is also known as the paracellular route (Figure 1). This route is slow and passive. Insulin, mannitol and propranolol were absorbed through this mechanism. There is an inverse log-log correlation between intranasal absorption and the molecular weight of water-soluble compounds. Literature survey revealed that good bioavailability was observed for drugs with a molecular weight up to 1000 Daltons. But with the help of permeation enhancers good bioavailability can be enhanced to at least 6000 Daltons[20]. The second mechanism involves transport through a lipoidal route that is also known as the transcellular process and is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drugs also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junctions[22]. For example, Chitosan, a natural biopolymer from shellfish, opens tight junctions between epithelial cells to facilitate drug transport[21].

## RECENT NASAL DRUG DELIVERY DEVICES AND TECHNIQUES:

Building a more efficient nasal drug delivery device requires not only better device design but a far more versatile technology platform; one that delivers optimal nasal deposition, with formulation flexibility to work successfully with the many variables of the formulation

itself. Drug formulation and delivery devices can be mutually adapted and matched for optimal characteristics to reach the desired therapeutic target.

**A. ChiSys™ *Nasal Delivery*[22]:**

West Drug Delivery of Lionville, Pa (US) and Nottingham, UK, have developed ChiSys, a patent protected versatile transmucosal delivery system based on the bioadhesive excipient chitosan. Chitosan is an interesting and versatile molecule, as it has been used extensively in a number of field ranging from wound-healing, slimming aid and cosmetics to a wastewater treatment flocculent. Recently, chitosan has been the subject of interest in a number of pharmaceutical and drug delivery studies, as evidenced by its many appearances in literature. West believes chitosan works well as a bioadhesive excipient; it is theorised that its positively charged molecules interact with the negatively charged sialic acid residues present in mucus, thereby retaining drug compound at the mucosal surface for an extended period of time.

**B. DirectHaler™ *Technology*[23]:**

Direct-Haler A/S has invented and developed a novel nasal delivery device and nasal delivery principle. The innovation takes advantage of the patient's anatomy to improve nasal delivery effectiveness and convenience. The integrated nasal device and delivery method enables nasal delivery of very fine particles, without the risk of pulmonary deposition. The DirectHaler Nasal device has successfully been used in clinical trials, and has confirmed patient acceptability. The single-use, disposable device is for both mono and bi-dose delivery, in a pre-metered, prefilled dose format. The device offers effective, accurate, repeatable and hygienic dosing, and is intuitively easy-to-use (Figure 2).

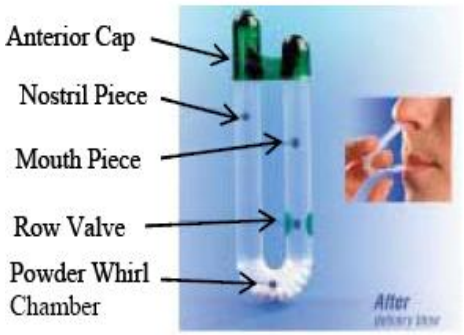


*Figure 2: DirectHaler Nasal: Device innovation and delivery method innovation*[23]

***How* DirectHaler *deliver the drug?***

When air is being blown out of the mouth against a resistance, the airway passage between the oral and nasal cavities automatically closes. The same reflex is activated when a person blows up a balloon; none of the air escapes through the nose. This anatomical feature is activated when the patient uses DirectHaler Nasal for blowing their nasal dry-powder dose into their nostril. Thus, the dose is captured in the nasal cavity, where it is intended to act or to be absorbed into the systemic circulation. After completion of the dose delivery blow, the nasal/oral connection returns to its normal open state.

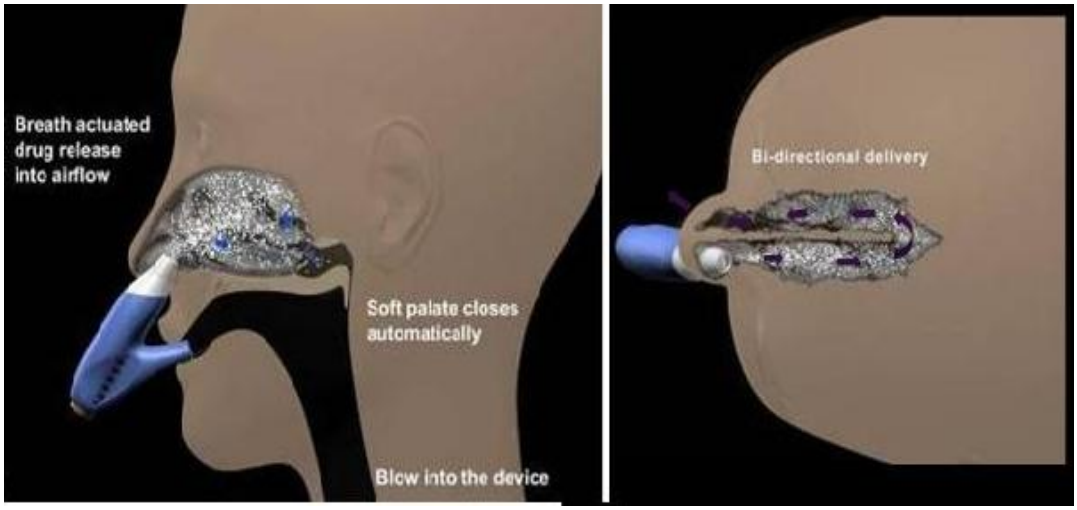


*Figure 3: BiDirectional Nasal delivery*[25]

**C. Bi-Directional *Nasal Delivery*[24-26]:**

Bi-directional nasal delivery devices offer a unique solution for nasal delivery of drugs and vaccines. Bi-directional delivery devices improve distribution to the nasal mucosa in general and can target the sinus ostia and organized nasal lymphatic tissues, while at the same time preventing lung deposition. Breath actuation and controlled particle release secure a reliable, efficient and

safe delivery of vaccines to the target sites within the nasal passages with maximum patient comfort. Breath Powered, Bi-directional Delivery consists of a mouthpiece and a sealing nozzle;

- ✓ Blowing into the device cause the soft palate to close, isolating the nasal cavity
- ✓ As the patient continues to blow the device is triggered, releasing drug into the air flow and carrying it deep into the nasal cavity
- ✓ At the back of the nose, the air flow passes through a communication between the nasal passages and exits through the other nostril in the opposite direction

By permitting delivery of nasal formulation to the target sites in the nose, benefits can be gained from increased absorption and lower dose. Any dispersion technology for liquid and powder particles can be combined with the bi-directional nasal delivery concept, adding to its versatility (Figure 3, 4).

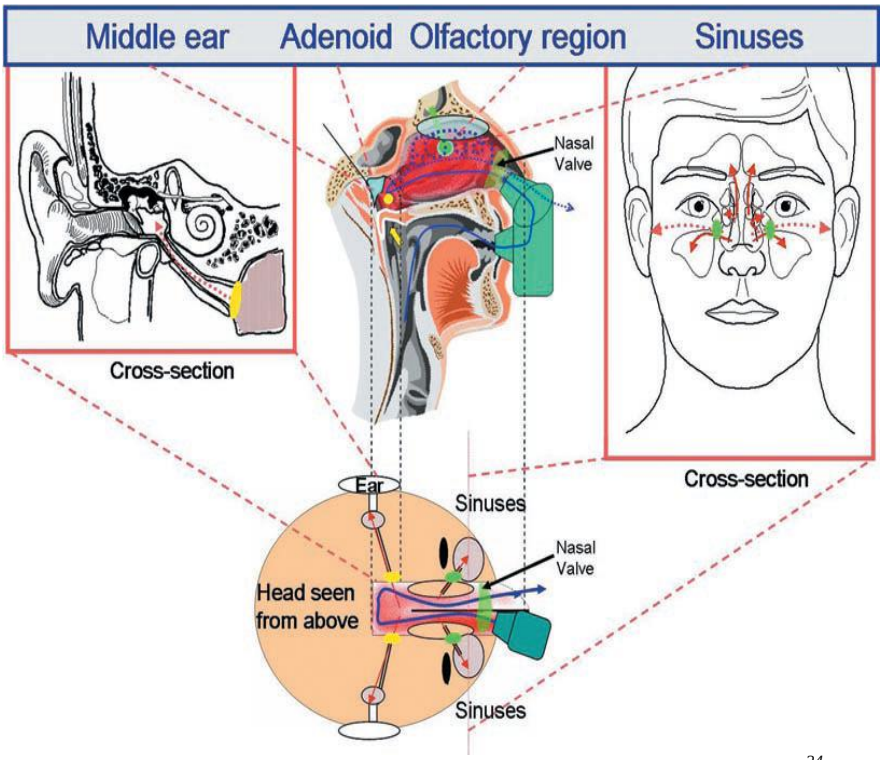


*Figure 4: Target sites that are better served by bi-directional delivery*[24]

Deposition studies of bi-directional delivery using gamma scintigraphy have shown significantly improved deposition patterns compared with traditional nasal spray pumps. Phase I nasal vaccination trials have shown a several fold increase in the immune response as compared with vaccine delivery by traditional spray devices. Patient acceptance and compliance for the bi-directional device are excellent thanks to the two-point device fixation and breathe actuation. Bidirectional delivery can be useful in vaccine delivery, topical and systemic nose to brain delivery.

**D. CONTROLLED PARTICLE DISPERSION(CPD)™:**[27]

Controlled Particle Dispersion (CPD) is a technology platform that pharmaceutical companies can use to deliver most compounds regardless of characteristics or target conditions. Whether the applications are systemic or topical, solutions or suspensions, CPD meets the demands of today and tomorrow's full nasal delivery product line. CPD offers a vast improvement in efficacy and performance while presenting design flexibility for maximum compliance. Rather than build a single device, Kurve Technology developed CPD – a comprehensive nasal drug delivery technology platform. Using new principals such as vortical flow, CPD effectively disrupts inherent nasal cavity airflows to deliver compounds to the entire nasal cavity, the olfactory region and the paranasal sinuses. CPD optimizes droplet size and trajectory to saturate the nasal cavity, lengthens compound residence time, and minimizes deposition to the lungs and stomach. This leads to more effective and efficient treatments than delivery via traditional nasal spray bottles that deliver compounds only as far as the anterior portion of the nasal cavity.

**CPD's adjustable variables include:**

- ✓ Droplet size variability from 3 to 50 µm
- ✓ Atomization rate
- ✓ Delivery of solutions, suspensions and dry powder
- ✓ Small and large molecules, Proteins and peptides
- ✓ Preservative-free, unit-dose ampoules
- ✓ Targeted deposition including to the paranasal sinuses and the olfactory region
- ✓ Variable medication volumes in the device and in the nasal cavity
- ✓ Wide viscosity range

**E. Advanced nasal spray medications:**

They are simple and easy to administer, noninvasive and virtually pain free method for nasal drug delivery. Other benefits of advanced nasal spray:

- ✓ Reduce irritation as they are preservative-free
- ✓ Demonstrate rapid onset of action and efficient absorption
- ✓ Provide for precise, metered doses
- ✓ Enable greater patient compliance

Nasal sprays are an alternative to injections because they eliminate needles and the associated risk of contamination from blood. Also, while only a trained health professional can perform an injection, patients, caregivers and professionals can readily use nasal sprays with minimal instruction or assistance. Compared to oral, sublingual and sometimes intramuscular injections, drugs administered nasally are absorbed more quickly. [28]

Orally administered drugs like midazolam and hydromorphone tend to be rapidly metabolized by the intestinal tract and liver and have greater variability in their absorption and bioavailability than nasally delivered drugs. ITI (Ikano therapeutics Inc.) studies show that smaller doses of the same two nasally administered drugs produce faster absorption rates and bioavailability yet with similar plasma concentrations as the orally delivered forms. Gastrointestinal-related side effects may also be reduced because nasally delivered medication bypasses the gut[59]. ITI products improve the likelihood that patients will take regular and accurate doses of their medication because nasal devices are compatible with active lifestyles and reduce the potential for waste and abuse[28].

### F. MAD Nasal-Mucosal Atomizer:

MAD Nasal-Mucosal Atomization Device delivers intranasal medication in a fine mist which enhances absorption and improves bioavailability for fast and effective drug delivery. By eliminating the need to establish an IV, delivery is rapid which is useful for treating various emergencies, ENT, anesthesia and pediatric conditions[29] (Figure 5).

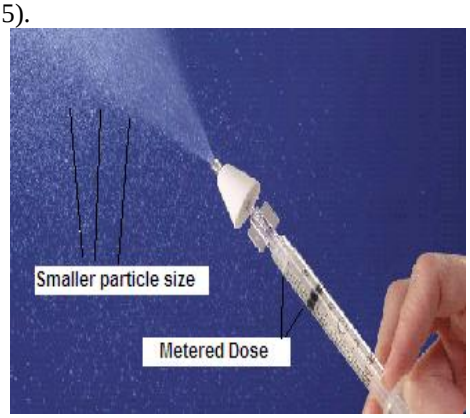


*Figure 5: MAD Nasal-Mucosal Atomization Device [29]*

***MAD Nasal Features and Benefits:***

No needle - No shot → Safe and Painless

Medications absorb directly into the brain via olfactory mucosa → Rapidly Effective

Exact dosing, exact volume, Atomizes in any position → Controlled administration

Drug administration is quick, No sterile technique is required → Minimal Resource Utilization

### G. NasoNeb™ Nasal Nebulizer[30]

A new double barrel atomization device from ASL Pharmacy® offers hope for chronic sinusitis patients. The NasoNeb™ Nasal Nebulizer may be used for the administration of compounded tobramycin, clarithromycin, mupirocin, meropenem and other antibiotics, anti-fungals, mucolytics and corticosteroids (Figure 6).


Figure 6: NasoNeb™ Nasal Nebulizer[30]

### H. Preservative Free Systems (P.F.S.) [61]

Preservatives are commonly used in drug formulations and they are generally well tolerated when used in small amounts for occasional treatments. However in the case of nasal spray delivery, preservatives can be irritating to the patient mucosa causing some unpleasant itching, but more seriously can also slow down or even stop the mucociliary clearance which is an essential natural mechanism for the protection of the upper airways.

Preservatives can also make the work of the formulation scientist more challenging by causing some stability/compatibility issues, and/or by modifying the smell and/or taste of the drug product.

To help formulation scientists reduce and eliminate preservatives from nasal spray formulations, drug delivery device manufacturers have successfully developed and marketed specific multidose spraying devices called Preservative Free Systems (P.F.S.).

There are two main categories of technologies currently used for P.F.S:

***Fully sealed systems*:** This technology was developed by Valois Pharma. The pumps are non-vented which means contamination from the environment cannot enter the container- by design - and come into contact with the drug product. In addition specific actuators equipped with a mechanical tip seal prevents contamination of the formulation in the actuator between actuations

***Vented pumps equipped with a micro-filter*:** Several manufacturers are using this technology. These pumps are designed in such a way that the air is sterile-filtered at the inlet via the micro-filter. These pumps are also used in conjunction with specific self-sealing valves in the actuator tip. An alternative approach is to use a specific actuator with a bacteriostatic material (generally silver derivatives or ions) that is released into the drug formulation in the actuator tip.

## NEEDS AND FUTURE PROSPECTIVE OF NASAL DRUG DELIVERY TECHNOLOGIES:

In the field of drug delivery, drug delivery technologies will play a key role in the success or failure of the industry. The need for non-invasive delivery systems continues due to

patients' poor acceptance and compliance with existing delivery regimes, limited market size for drug companies and drug uses, coupled with high cost of disease management. The current needs of the industry are improved solubility/stability, biological half-life and bioavailability enhancement of poorly absorbed drugs. Key issues facing the biopharma industry are to improve safety, improve efficacy for organ targeting, and improved compliance via sustained release or increasing residence time of drug at the site of application. New technologies include improved nasal formulations; site specific release, carrier-based systems, advanced spray formulations, atomized mist technology, preservative free system and integrated formulation development are strictly needed for success of drug delivery through nasal mucosa.

For success of nasal drug delivery Researchers may focus on:

- ✓ Development of delivery technologies to increase efficacy and reduce side effects by target delivery with variations potential of the drug
- ✓ Development of new technologies to deliver macromolecules with utilization of biotechnology and high technology
- ✓ Development of integrated/improved nasal formulations
- ✓ Development of integrated device development for successful delivery of therapeutics

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