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Review Article

Novel Nasal Devices for the Efficient Drug Delivery: A Systemic Review

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ABSTRACT

Now a day, nasal drug delivery has occupied an important place in the field of drug delivery technology. A range of medicaments can be successfully delivered at the site of action using drug delivery devices. A successful nasal drug delivery device seems to deliver medication efficiently, necessarily non-invasive, helps in rapid onset of action, patient friendly for self administration and should exhibit minimal side effects. Since constructing an efficient drug delivery device, capable of achieving sufficient local, systemic or brain distribution of drug is a challenge, usually requires a robust and innovative technology. Fortunately, the nose offers easy access to a large mucosal surface, well suited for delivery of many therapeutics including proteins and peptides. Present review deals with such novel nasal drug delivery devices, more specifically, OptiNose, ViaNase, Direct Haler, MAD-nasal ™ mucosal atomizer, which have proven their proficiency in delivering medications. The clinical status of the therapeutics administered by these devices along with their regulatory requirements has also been extended.

INTRODUCTION

Fabrication of a more efficient nasal drug delivery device, one that delivers optimal nasal deposition, requires not only better device design, but also an advanced and more versatile technology with formulation flexibility to work successfully with the many variables of the formulation. Now a day, Nasal delivery technology is arousing interest amongst the potential partners viz. the pharmaceutical industry and the investment community. Drug formulation and delivery devices can be mutually adapted and matched for optimal characteristics to reach the desired therapeutic target. The nasal route circumvents hepatic first pass elimination associated with the oral delivery; in addition it is easily accessible and suitable for self-medication. The large surface area of the nasal mucosa offers a rapid onset of therapeutic effect and enhances the potential for direct nose to brain delivery. Intranasal delivery is convenient, non-invasive, having rapid onset of action, high bioavailability, essentially painless, does not require sterile preparations, easy to administered by the patient or a physician in emergency conditions, all of which may maximize patient compliance. [1-3]

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Of course, nasal drug delivery research faces significant challenges, including-accurate targeting the correct sites within the nose, avoiding unwanted deposition in the stomach and lungs, microbial contamination of multi-use devices, successful development of preservative free formulations, and the incorporation of dose-counting mechanisms. Nasal drug delivery is a useful delivery method for drugs that are active in low doses and show no or minimal oral bioavailability. Currently, two classes of nasally delivered therapeutics are on the market. The first one comprises of low molecular weight and hydrophobic drugs for the treatment of the nasal mucosa and sinus, including decongestants, topical steroids, antibiotics and other over the counter products. The second class encompasses a few drugs, which have sufficient nasal absorption for displaying systemic effects. The most promising candidates would be the compounds, generally administered by injection and hardly absorbed after oral administration. [4-6]

The Regulatory Perspective

The regulatory guideline for nasal sprays recommends that it should be tested as combined products, device and formulation together, to determine reproducible delivery.

Achieving clinical efficacy relies on understanding and controlling the interactions between device and formulation, which together dictate performance and manufacturing products that behave in a consistent way. *In-vitro* testing is specified for a range of variables, droplet size being one important parameter. Droplet size measurements are used to assess the following parameters.

Quality: The consistency of performance, over the lifetime of the product, from batch to batch, or after storage.

Safety: Droplets of 10 micron and below may pass through the nasal passages, penetrating into the lungs. Consequently, active pharmaceutical ingredient in this fraction will enter the body by pulmonary absorption, rather than by the intended route. Quantifying the extent of this risk, and assessing the associated clinical effect, is essential for the effective nasal drug delivery development.

Efficacy: Droplet size influences the site of deposition within the nasal passages which in turn may affect bioavailability. [7]

NASAL DRUG DELIVERY DEVICES:

OptiNose

OptiNose is a novel drug delivery device which is used in reliable and efficient drug delivery *via* nasal route. The breath powered delivery concept was developed to overcome the anatomical and physiological characteristics of the nasal airways that limit the delivery efficiency of traditional delivery technologies. The OptiNose devices are designed to be the first and only devices which truly sum up all the unique characteristics of the nasal cavity to effectively deliver drugs more consistently and reliably to all regions of the nasal cavity. This device is now in increasing demand due to its broad spectrum use in systemic, local, nose to brain and vaccine delivery. To reduce the levels of risk, time and cost, components from existing device technologies are usually incorporated whenever possible, through alliances with the suppliers of these components. Nasal delivery *via* this device is advantageous as it is convenient, non-invasive, executes rapid onset of action, and high bioavailability. In depth knowledge of nasal anatomy and physiology reinforced by detailed studies, have provided the information enabling OptiNose to understand how to optimize drug delivery while reducing or eliminating side effects. [8]

This device has a flexible mouthpiece and a shaped sealing nosepiece designed for a suitable fit. The nosepiece is first inserted to form a seal with the nostril and then the user exhales forcefully into the mouthpiece. The sealing nose piece introduces the naturally warmed and humidified exhaled air into the nasal cavity. This process automatically elevates and seals the soft palate to separate the oral cavity from the nasal cavity, as occurs when inflating a balloon. The positive pressure transferred into the nose due to the sealing nosepiece also further expands the nasal valve and the narrow slit-like passage to propel the particles to the target sites beyond the valve region. Importantly, the transferred air pressure in the nasal cavity correctly balances the air pressure applied to the soft palate from the oropharynx, thus preventing excessive elevation of the soft palate which may obstruct the passage of air posteriorly around the nasal septum. The entered air passes first to posterior region around the nasal septum and then anteriorly to exit through the opposite nostril. This flow pattern is called as bidirectional as shown in figure 1.

In bidirectional flow pattern concept is based on the following mechanism: During exhalation against a resistance the soft palate closes due to positive pressure, separating the nasal and oral cavities. Consequently, it becomes possible to use smaller particles in a nasal spray and still avoid lung deposition by exhaling through the mouth during nasal administration. For the duration of closure of the soft palate there is a communication pathway between the two nostrils, located behind the walls separating the two passages. Under these circumstances, it is possible for airflow to enter via one nostril and leave by the other. Bi-directional delivery concept offers a range of new and attractive nasal destinations not reached by traditional nasal spray pumps. The ability to deliver steroids to the nasal mucosa and entrances to the sinuses will lead to a dramatic increase in the effectiveness of these drugs – resulting in a marked improvement in the condition, a reduced need for surgery and an improved quality of life. Figure 2 displays the gamma scintigraphy images showing superiority of OptiNose technology in dose deposition in the nasal cavity. [9-13]

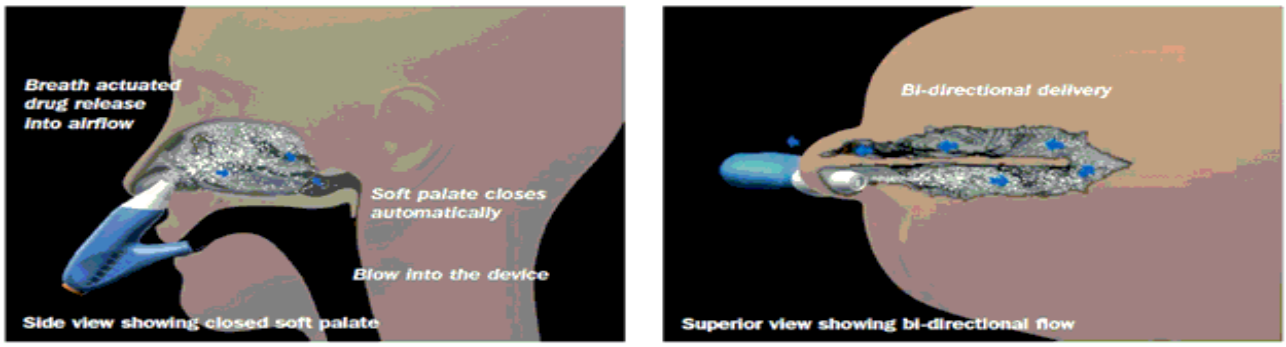

Figure 1: Two interlinked anatomical principles underlying bi-directional drug delivery.

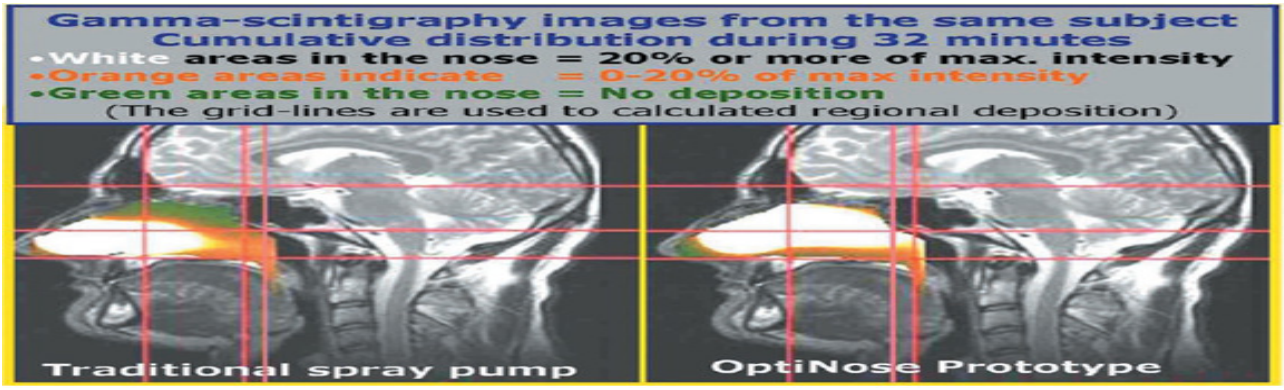

Figure 2: Gamma scintigraphy images, comparing deposition following traditional and bi-directional delivery

1) Powder Delivery Device: OptiNose's breath-powered nasal delivery technology, shown in figure 3, significantly improves delivery to the target sites deep into the nasal cavity. The powder delivery device has a disposable drug-containing section and a reusable device body that can be packaged along with a number of drug-containing sections. The disposable drug-containing section contains the powdered drug within standard size 3- inhalation capsules.

Figure 3: Multidose powder delivery device

To operate the powder delivery device, a disposable section is inserted into the device body and the piercing button on the side is depressed once. Two steel pins connected to the button pierce the capsule and are automatically retracted by spring action when the button is released. The user slides the nosepiece of the device into the nostril and the mouthpiece is inserted between the lips. The user then takes a deep breath closes the lips around the mouthpiece and exhales, thus delivering drug directly into the nasal cavity.

2) Liquid Delivery Device: Figure 4 displays the liquid delivery device, in use; the subject inserts the sealing nozzle of the device into one nostril and blows into the mouthpiece against a resistance. Then the user manually activates the device by pressing the bottom of the bottle, releasing the resistance to the exhaled breath and allowing the exhaled breath and drug particles to create a medication-carrying airflow into the user's nasal cavity. [13]

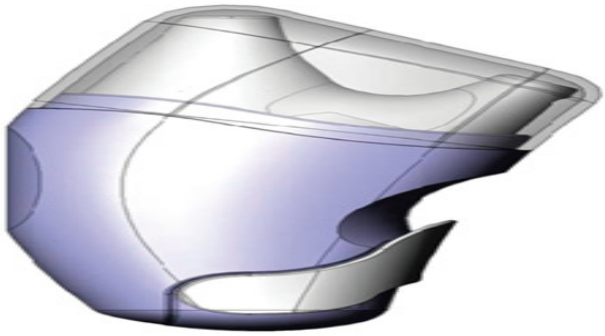

Figure 4: Multidose liquid delivery device

3) OptiNose Benefits

1. *Breath Powered:* This unique and simple OptiNose approach to self-administration is positively viewed by patients worldwide. This approach to administration is likely to contribute to improved consistency, reliability and targeting of delivery of drug into the nasal cavity.
2. *Improved Efficacy and Lower Doses:* Direct delivery of medication into the body without first passing through the stomach or liver may reduce doses. It may also make it possible to bring new or old medications to the public which would otherwise not be developed. This may also enable delivery of medications like proteins, peptides and vaccines without the need for needles and people trained to use them.
3. *Reduced Side Effects:* While exhaling, the soft palate is closed off resulting in a significant reduction in "drip" down the back of the throat. In addition to avoiding the historical nasal spray problem of bad taste, OptiNose delivery greatly reduces lung and gastrointestinal exposure to medication, which can improve safety. The ability to use lower doses of medication may also improve tolerability and safety of certain medications.
4. *Patient's convenience:* The device is comfortable because of its fixed position during use compared with a traditional spray pump. In addition, the naturally warmed and humidified air from the lungs may reduce the discomfort often experienced when a traditional spray is released alone into the nasal cavity.
5. *Design:* The OptiNose drug delivery technology is ergonomic, takes advantage of several off-the-shelf components, and has no electromechanical or other costly design elements creating regulatory or manufacturing risk. The design is often referred to as "simple and elegant".
6. *Platform Applications:* Central Nervous System disorders, pain, oncology, vaccine delivery, small and large (biologic) molecules for multiple therapeutic applications. [14]

ViaNase ™

A handheld battery-driven nasal atomizer has been introduced by Kurve Technology Inc., Lynnwood, WA, USA. ViaNase™, shown in figure 5, is an advanced nasal drug delivery device with the ability to optimally saturate the entire nasal cavity, including the olfactory region and paranasal sinuses. ViaNase ™ offers effective and efficient delivery of a wide range of topical, systemic, and nose-to-brain drug therapies. Its pocket–size and patient-friendly operation facilitate compliance.

Figure 5: Schematic diagram of ViaNase™ device by Kurve technology, USA.

ViaNase ™ with Controlled Particle Dispersion (CPD) ™ technology allows formulations to negotiate the complicated structure and varied airflows of the nasal cavity. The major precedence of ViaNase ™ includes consistent dosing, having superior efficacy, preservative-free unit dose ampoules, patient friendly operations, pocket sized portability.

CPD™, developed by Kurve Technology Inc. USA, provides the opportunity to change drug delivery as it is known today, creating a paradigm shift in the industries for treating various sorts of diseases and ailments. Nowadays ViaNase™ is possessing broad spectrum of applications that includes-

1) Local Drug Delivery: The CPD's ability to saturate the nasal mucosa and deliver to the paranasal sinuses can dramatically improve treatment of conditions such as rhinitis, chronic rhinosinusitis, cold and influenza. Intranasal corticosteroids (INSs) effectively reduce the nasal inflammation that is a prime cause of allergic rhinitis. By acting early and throughout the allergy process, INSs block more allergy mediators, treating the symptoms caused by nasal inflammation such as nasal congestion, sneezing, and runny or itchy nose. This class of medicine is considered first-line therapy when nasal congestion is the primary symptom of the patient's rhinitis.

2) Systemic Drug Delivery: Mucosal delivery provides non-invasive, rapid absorption and onset of action without hepatic first pass effect of the drug. The major disadvantage of most nasal drug delivery devices is they only apply medication to the closest one-third of the nasal cavity, thus limiting drug absorption for treatment of systemic diseases. CPD's optimal mucosal saturation and depth of drug penetration will lead to improved systemic treatment of conditions such as osteoporosis and migraine headaches. However, good drug candidates for intranasal delivery are any that undergo extensive first-pass metabolism, display intermittent absorption, or require quick therapeutic onset.

3) Nose to Brain Transport: The blood-brain barrier that separates the brain interstitial fluid from the circulating blood provides an efficient barrier for the diffusion of most drugs from the blood to receptors in the central nervous system (CNS). This limits drug treatment of CNS diseases, such as Parkinson's and Alzheimer's diseases. In recent years, interest has been expressed in the use of the nasal route to deliver drugs to the brain, exploiting the olfactory pathway

4) Intranasal Vaccine Administration: Intranasal administration of vaccines has recently proven to be one of the most efficient ways for inducing both mucosal and systemic antibody responses in experimental animals. The needle-free nature of nasal delivery also offers anticipation of improved patient compliance. In recent testing at the Center for Disease Control and Prevention, three different ViaNase ™ device configurations aerosolized live attenuated measles virus without loss of potency.

Nasal delivery of local and systemic medical therapies is rapidly becoming a suitable treatment method for various medical conditions. Current technologies have significant challenges in being effective if the drug reaches and covers a greater area of the affected nasal mucosa. Main treatments, such as those for chronic rhino-sinusitis, have been unavailable to physicians due to ineffective drug delivery. CPD™, developed by Kurve technology, provides the opportunity to change drug delivery as it is known today. In addition, results of clinical studies comparing intranasal drug distribution of traditional nebulizers and nasal spray pumps with the ViaNase ™ electronic atomizer using CPD™ technology is showed in Figure 6 and summarized in Table 1. [15-18]

Figure 6: Comparison between deposition pattern between traditional spray pumps and ViaNase™ by Kurve technology

Table 1: Comparison of ViaNase with Spray Pumps

Characteristic features	ViaNase™	Spray pumps	Comments
Saturates nasal cavity	Yes	No	Spray pump only penetrate front 1/3rd of nasal cavity
Penetrates para nasal sinuses	Yes	No	Only known device that delivers drug to this region
Odourless, tasteless and painless	Yes	No	Spray pumps produce nasal irritation, unpleasant taste and headache which diminishes patient compliance
Minimal stomach deposition	Yes	No	-
Minimal lung deposition	Yes	Yes	-
Easy to use	Yes	No	80% of patients use spray pump incorrectly, ViaNase is extremely easy to use
Quick treatment times	Yes	Yes	Both under 60 seconds.

DirectHaler ™ Technology

DirectHaler ™ is novel drug delivery device, for efficient and convenient delivery of medicament

into nasal cavity. 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, as shown in figure 7, 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. When air is being blown out of the mouth against a resistance, the airway passage between the oral and nasal cavities automatically closes. This anatomical feature is activated when the patient uses DirectHaler ™ Nasal device 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.

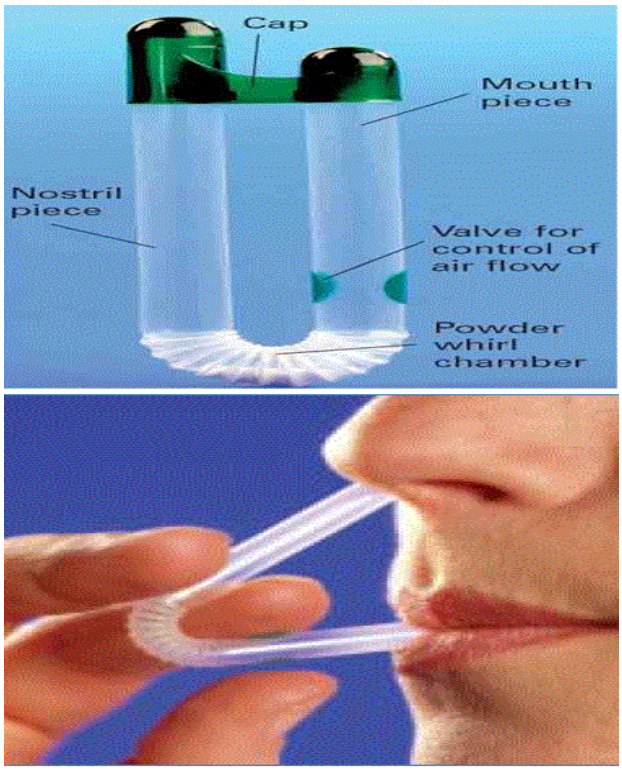

Figure 7: Schematic presentation of Direct Haler™ Nasal device and its way of usage

This delivery method holds the potential to become the dominant delivery principle in nasal drug delivery, merits over other technology is summarized in the Table 2. DirectHaler ™ is the first drug delivery to take advantage of this device dependent reflex for enhancing nasal drug delivery. A range of nasally delivered products has been on the market during recent decades, belonging to therapeutic areas such as allergic rhinitis treatment, migraine relief, hormone replacement therapy (HRT) and common cold relief. The products have applied nasal delivery systems based primarily on four different formulations: liquid nasal drops; liquid nasal sprays; pressurized metered dose inhalers; and dry-powder inhalers and insufflators. The DirectHaler ™ Nasal device and delivery method can outweigh all these formulations.

Table 2: Advantages of DirectHaler over other drug delivery systems

Disadvantages reported on current nasal delivery system	Solved by DirectHaler™ nasal
Risk of liquid dose dripping out from nostril after dose delivery	Dry powder formulation adhere to the nasal mucosa
Risk of pulmonary dose deposition	No risk of pulmonary deposition
Unpleasant "Cold blow" and "Hand blow" of medication from powdered metered dose inhaler	Tempered and pleasant blow
Acceptability problems for liquid formulations with preservatives for chronic use	No preservatives
Risk of liquid dose being swallowed immediately after delivery, thus giving unpleasant taste	No risk of immediate swallowing, and taste sensation

While using DirectHaler ™ the patient contributes the blow energy using their own breath. The DirectHaler™ nasal device & method automatically activates the anatomical reflex that closes the airway passage between the nasal and oral cavities. The activated reflex removes the risk of pulmonary deposition of drug particles. DirectHaler™ provides a novel opportunity for overcoming the recognized problems, associated with currently marketed nasal delivery device.

The innovative result of DirectHaler™ nasal devices can be "clicked" together to constitute such a compact bi-dose. DirectHaler™ is extremely straight forward and cost effective to manufacture, fill and assemble using high speed standard mass production technology.

Combining an oral dose with DirectHaler™ can be used for two different delivery routes- i.e. Local action pertaining to nasal mucosa and systemic action related to enteral route. [19-21]

MAD - Nasal Mucosal Atomizer

Sprayed or atomized intranasal medication delivery, as shown in figure 8, is a more recent technique adopted by the pharmaceutical industry due to improved usability issues as well as improved bioavailability data. This delivery technique combines a method of measuring a unit dose of medication – either via a syringe or unit dose pump with a spray tip that fragments the medication into fine particles as it is being sprayed into the nose. It appears that this method of delivery results in a broader distribution of the medication across the nasal mucosa and an increased bioavailability of the drug.

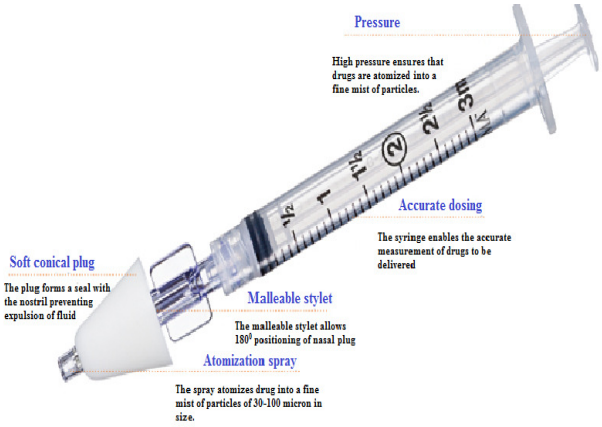

Figure 8: MAD Nasal Mucosal Atomizer

The accessibility issue makes this nasal spraying of medications far easier to employ the patient can have the medication delivered from any position (sitting, lying down, prone, on side) and since it only takes a second to administer the dose they do not need to be restrained. Finally, because the medication is sprayed as a mist, it is less likely to be blown back out of the nose into the external environment. For all these reasons, most pharmaceutical nasal medications are now packaged with a spray applicator rather than a dropper. In addition, syringe driven and pump driven spraying atomizers now exist for delivery of a variety of generic nasal medications. [22-23] Since, intravenous (IV) delivery is less than ideal, switching to MAD Nasal™ Device to deliver safe, painless, and rapidly effective treatment with minimal resource utilization is better option. With no danger of needle sticks, no need to sterilize the delivery site, and no cumbersome and time consuming IV setup, this intranasal mucosal atomization device delivers a mist of atomized medication that offers rapid absorption across mucosal membranes to the blood stream. [24-25]

The ideal volume for intranasal administration is 0.2-0.3ml and the maximum recommended volume per nostril is 1ml. If dose is greater than 0.5ml, application should be in two separate doses allowing 5-10 minutes apart for each dose. Detailed specification pertaining to MAD NASAL™ device is furnished in Table 3. [26-27]

Table 3: MAD NASAL™ device specifications

Typical Particle Size	**30-100 micron**
System Dead Space	0.13 ml MAD100 & MAD140/0.07 ml MAD300
Tip Diameter	0.7 inches (4.3mm)
Applicator Length (MAD300)	1.65 inches (4.2cm)

CONCLUSION

The novel and innovative nasal drug delivery devices mentioned in this review article, have potential of providing eternal opportunities in the field of drug delivery. Nasal drug delivery has immense potential to treat both acute and chronic diseases. This delivery system is beneficial in conditions like Parkinson's disease, Alzheimer's disease, since it possess rapid and specific targeting of drugs to the brain and it is a suitable route to produce immune response against various diseases like anthrax, influenza etc., by delivering the vaccines through the nasal mucosa. In the future we should expect to see a range of novel nasal products reaching the market.

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