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Review Article

Nasal Drug Delivery System

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ABSTRACT

Nasal route is alternative to parenteral therapy and also useful for long term therapy. Nasal route is non invasive, widely used for the local treatment may also be used for systemic therapy as drug directly goes in systemic circulation. In this article an overview of intranasal drug delivery with its various aspects like factors affecting nasal absorption are discussed. The use of the nasal route for the delivery of challenging drugs such as small polar molecules, vaccines, hormones, peptides and proteins has created much interest in nowadays. Due to the high permeability, high vasculature, low enzymatic environment of nasal cavity and avoidance of hepatic first pass metabolism are well suitable for systemic delivery of drug molecule via nose. Many drug delivery devices for nasal application of liquid, semisolid and solid formulation are investigated to deliver the drugs to the treat most crisis CNS diseases (i.e., Parkinson's disease, Alzheimer's disease) because it requires rapid and/or specific targeting of drugs to the brain. However, when considering nasal delivery devices and mechanisms, it is important to keep in mind that the prime purpose of the nasal airway is to protect the delicate lungs from hazardous exposures, not to serve as a delivery route for drugs and vaccines. New and emerging delivery technologies and devices with emphasis on BiDirectional™ delivery, a novel concept for nasal delivery that can be adapted to a variety of dispersion technologies, are described in more depth.

INTRODUCTION

The history of nasal drug delivery dates back to earlier topical applications of drugs intended for local effects. Nasal therapy also called 'Nasya karma' has been recognized form of treatment in the Ayurvedic system of Indian medicines 6. The early 1980s saw the introduction of nasal route as a promising systemic delivery alternative to other conventional drug delivery routes. Nasal route is easily accessible, convenient, and a reliable with a porous endothelial membrane and a highly vascularized epithelium that provides a rapid absorption of compounds into the systemic circulation, avoiding the hepatic first pass elimination. In addition, intranasal drug delivery enables dose reduction, rapid attainment of

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therapeutic blood levels, quicker onset of pharmacological activity, and fewer side effects. The low metabolic environment of nose has potential to overcome the limitation of oral route and duplicate the benefit of intravenous administration. In addition to that, nasal administration minimizes the lag time associated with oral drug delivery and offers non invasiveness, self-administration, patient comfort, and patient compliance, which are the hurdles in intravenous drug therapy. It was reported that lipophilic drugs are generally well absorbed from the nasal cavity with pharmacokinetic profiles, which are often identical to those obtained after an intravenous injection with a bioavailability approaching 100%, on the other hand absorption of hydrophilic drugs can be increased by means of absorption enhancers. Drugs ranging from small chemicals to large macromolecules including peptide/protein therapeutics, hormones, and vaccines, are being delivered through the nasal cavity. 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 2. It has also been considered to the administration of vaccines. Buserelin, desmopressin, calcitonin, insulin, luteinizing hormone releasing hormone, growth hormone and adreno-corticotrophic hormone are some of the peptides that have been successfully administered through the nasal route. Apart from these, steroids (corticosteroids, estradiol, progesterone, testosterone, and so on) antihypertensives (nifedipine, nitroglycerine, propranolol, hydralazine, and so on), analgesics ReviewArticle Article Article Delivery of drugs through nasal route has been potentially explored as an alternative route for administration of vaccines and biomolecules such as proteins, peptides and non peptide drugs, hence it has attracted the interest of scientific community. Inranasal therapy has been accepted form of treatment in the ayurvedic system of medicines. Nasal route is beneficial for the drugs which are unstable on oral administration because they are significantly degraded in GIT or metabolized by first pass effect in liver. Nasal route is alternative to parenteral therapy and also useful for long term therapy. Nasal mucosa is highly vascularised and most permeable giving rapid absorption and onset of action. Nasal route is non invasive, widely used for the local treatment may also be used for systemic therapy as drug directly goes in systemic circulation. Nasal route gives good absorption of small molecules, than that of large molecules can be increased by absorption promoters. In this article an overview of intranasal drug delivery with its various aspects like factors affecting nasal absorption, strategies to improve bioavailability are discussed. 1

ADVANTAGES :1,3,6,7

1. Drug degradation that is observed in the gastrointestinal tract is absent.
2. Hepatic first pass metabolism is avoided.
3. Rapid drug absorption and quick onset of action can be achieved.
4. The bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.
5. The nasal bioavailability for smaller drug molecules is good.
6. Drugs that are orally not absorbed can be delivered to the systemic circulation by nasal drug delivery.
7. Studies so far carried out indicate that the nasal route is an alternate to parenteral route, especially, for protein and peptide drugs.
8. Convenient for the patients, especially for those on long term therapy, when compared with parenteral medication.
9. Drugs possessing poor stability in g.i.t. fluids are given by nasal route.

10. Polar compounds exhibiting poor oral absorption may be particularly suited for this route of delivery.
11. Absorption of drug is rapid via highly vascularised mucosa.
12. Availability of large nasal mucosal surface area for dose absorption.
13. Onset of action is rapid.
14. Non invasive and easy for administration.
15. Bypass the BBB.
16. Convenient route for the patient on long term therapy.
17. Improved bioavailability.
18. Side effects are reduced due to low dose.
19. A self-administration is possible.
20. Direct transport into systemic circulation and CNS is Possible.
21. Offers lower risk of overdose
22. Does not have any complex formulation requirement

Profile of an 'ideal' drug candidate for nasal delivery :

An ideal nasal drug candidate should possess the following attributes:

1. Appropriate aqueous solubility to provide the desired dose in a 25–150 ml volume of formulation administration per nostril.
2. Appropriate nasal absorption properties.
3. No nasal irritation from the drug.
4. A suitable clinical rationale for nasal dosage forms, e.g. rapid onset of action.
5. Low dose. Generally, below 25 mg per dose.
6. No toxic nasal metabolites.
7. No offensive odors/aroma associated with the drug.
8. Suitable stability characteristics.

LIMITATIONS :1,3,7

1. The histological toxicity of absorption enhancers used in nasal drug delivery system is not yet clearly established.
2. Relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritation.
3. Nasal cavity provides smaller absorption surface area when compared to GIT.
4. There is a risk of local side effects and irreversible damage of the cilia on the nasal mucosa, both from the substance and from constituents added to the dosage form.
5. Certain surfactants used as chemical enhancers may disrupt and even dissolve membrane in high concentration.
6. There could be a mechanical loss of the dosage form into the other parts of the respiratory tract like lungs because of the improper technique of administration.
7. Delivery volume in nasal cavity is restricted to 25–200 μL.
8. High molecular weight compounds cannot be delivered through this route (mass cut off ~1 kDa).
9. Adversely affected by pathological conditions.
10. Large interspecies variability is observed in this route.
11. Normal defense mechanisms like mucociliary Clearance and ciliary beating affects the permeability of drug.
12. Irritation of nasal mucosa by drugs like Budesonide, Azilactine.
13. Limited understanding of mechanisms and less developed models at this stage.
14. Systemic toxicity occurring due to absorption enhancers is yet not established.
15. Smaller absorption surface compared with GIT.
16. Possibility of nasal irritation hence inconvenient compared with oral route.
17. Enzymatic barrier to permeability of drug.

ANATOMY OF NASAL CAVITY :1,2,3,4,5,6,7

Researchers became interested in the nasal route for the systemic delivery of medication due to a high degree of vascularization and permeability of the nasal mucosa. In humans and other animal species the major functions of the nasal cavity are breathing and olfaction. However, it also affords an important protective activity once it filters, heat and humidify the inhaled air before reaching the lowest airways. Passage of the nasal cavity which runs from nasal vestibule to nasopharynx has a depth of approximately 12-14cm. The total surface area of the nasal cavity in human adult is about 150 cm2 and total volume is about 15 ml. Each of two nasal cavities can be subdivided into different regions: nasal vestibule, inferior turbinate, middle turbinate, superior turbinate, olfactory region, frontal sinus, sphenoidal sinus, and cribriform plate of ethmoid bone. The nasal cavity also contains the nasal associated lymphoid tissue (NALT), which is mainly situated in the nasopharynx. Nasal cavity is lined with mucus layer and hairs which are involved in those functions are trapping inhaled particles and pathogens. Moreover, mucociliary clearance, immunological activities and metabolism of endogenous substances are also essential functions of nasal structures. The nasal cavity is covered with a mucous membrane which can be divided into two areas; nonolfactory and olfactory epithelium, in this non-olfactory area includes the nasal vestibule which is covered with skin-like stratified squamous epithelium cells, whereas respiratory region, which has a typical airways epithelium covered with numerous microvilli, resulting in a large surface area available for drug absorption and transport . Nasal cavity is divided by middle septum into two symmetrical halves, each one opening at the face through nostrils and extending posterior to the nasopharynx. Both symmetrical halves consist of four areas (nasal vestibule, atrium, respiratory region and olfactory region) that are distinguished according to their anatomic and histological characteristics

Nasal vestibule

Most anterior part of the nasal cavity is nasal vestibule, just inside the nostrils, and presents an area about 0.6 cm2. Nasal hairs are present in this area, also called vibrissae, which filter the inhaled particles. Histologically, this nasal portion is covered by a stratified squamous and keratinized epithelium with sebaceous glands.

Atrium

Intermediate area between nasal vestibule and respiratory region is atrium. Its anterior section is constituted by a stratified squamous epithelium and the posterior area by psudostratified columnar cells presenting microvilli.

Respiratory region

Largest part of the nasal cavity is respiratory region, also called conchae, is the cavity and it is divided in superior, middle and inferior turbinates which are projected from the lateral wall. The nasal respiratory mucosa, considered the most important section for delivering drugs systemically, is constituted by the epithelium, basement membrane and lamina propria. The nasal respiratory epithelium consists of pseudostratified columnar epithelial cells, globet cells, basal cells and mucous and serous glands .Many of the epithelial cells are covered on their apical surface with microvilli and the major part of them also has fine projections, called cilia.

Olfactory region

Location of olfactory region is at the roof of the nasal cavity and extends a short way down the septum and lateral wall. Its neuro-epithelium is the only part of the CNS that is directly exposed to the external environment. Similarly to the respiratory epithelium, the olfactory one is also pseudostratified but contains specialized olfactory receptor cells important for smell perception.

Mucus membrane of nose and its composition

The nasal mucus layer is only 5 μm thick and it is organized in two distinct layers: an external, viscous and dense, and an internal, fluid and serous. Overall, nasal mucus layer consists of 95% of water, 2.5-3% of mucin and 2% of electrolytes, proteins, lipids, enzymes, antibodies, sloughed epithelial cells and bacterial products.

Epithelial cells

basically, there are two functions of these cells,

1. Provide a physical barrier to the invasion of infectious microorganisms and allergic particles;
2. Work in conjunction with mucus glands and cilia to secrete and remove mucus and foreign particles from the nasal cavity .

Blood supply to nasal cavity Vasculature of the nasal cavity is richly supplied with blood to fulfill the basic functions such as heating and humidification, olfaction, mucociliary clearance and immunological functions. The nasal vascular bed is so designed that rapid exchange of fluid and dissolved excipients between blood vessels and nasal tissue can be done easily. The capillary flow in the nasal mucosa was reported to be 0.5 ml/g/min . Sphenopalatine artery a branch of maxillary artery. Anterior ethmoidal artery a branch of ophthalmic artery. Branches of the facial artery supplying the vestibule of the nasal cavity.

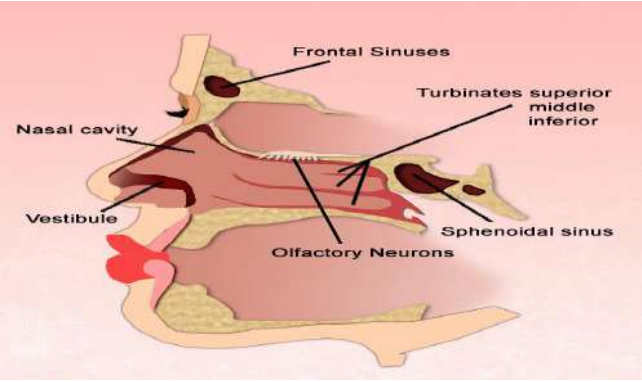

Figure 1: Anatomy of Nasal cavity

MECHANISM OF DRUG ABSORPTION FROM NOSE :

In the absorption of drug from the nasal cavity first step is passage through the mucus, large/charged particles may find it more difficult to cross. But small unchanged particles easily pass through this layer. Mechanisms for absorption through the nasal mucosa include paracellular transport via movement between cell and transcellular or simple diffusion across the membrane.

1. The first mechanism includes aqueous route of transport, which is also called as the paracellular route. This is slow and passive route. Poor bioavailability was observed for drugs with a molecular weight greater than 1000 Daltons, because inverse relationship exists between molecular weight and absorption.
2. Transcellular process is the second mechanism of transport through a lipoidal route 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. For example, Chitosan, a natural biopolymer opens tight junctions between epithelial cells to facilitate drug transport.

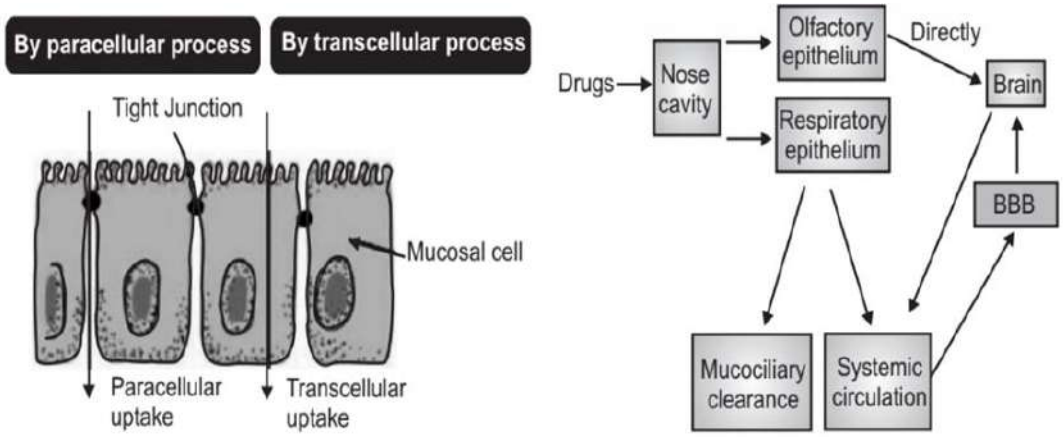

Figure 2: Mechanism of Drug Absorption from Nose

BARRIERS TO NASAL ABSORPTION : 3

Nasal drug delivery system is considered has a profitable route for the formulation scientist because it has easy and simple formulation strategies. Intra-nasally administered drug products therapeutic efficacy and toxicities are influenced by number of factors .Following factors are the barriers to the absorption of drugs through nasal cavity.

I. Low bioavailability Lipophilic drugs are generally well absorbed from the nasal cavity compared to polar drugs. The pharmacokinetic profiles of lipophilic drugs are often identical to those obtained after an intravenous injection and bioavailability approaching 100%. A good examples of this is the nasal administration of Fentanyl where the Tmax for both intravenous and nasal administration have been shown to be very rapid (7 min or less) and the bioavailability for nasal anterior part of the nasal cavity can decrease clear- administration was near 80%. The most important factor limiting the nasal absorption of polar drugs and especially large molecular weight polar drugs such as peptides and proteins is the low membrane permeability. Drugs can cross the epithelial cell membrane either by the transcellular route exploiting simple concentration gradients, by receptor mediated or vesicular transport mechanisms, or by the paracellular route through the tight junctions between the cells. Polar drugs with molecular weights below 1000 Da will generally pass the membrane using the latter route. Larger peptides and proteins have been shown to be able to pass the nasal membrane using an endocytotic transport process but only in low amounts .

II. Low membrane transport Another importance factor is low membrane transport is the general rapid clearance of the administered formulation from the nasal cavity due to the mucociliary clearance mechanism. This is especially the case for drugs that are not easily absorbed across the nasal membrane. It has been shown that for both liquid and powder formulations, that are not mucoadhesive, the half life of clearance is in the order of 15–20 min .It has further been suggested that the deposition of a formulation in the anterior part of the nasal cavity can decrease clear- ance and promote absorption as compared to deposition further back in the nasal cavity. Most nasal sprays of various makes have been shown to deliver the formulation to a limited area in the anterior part of the nasal cavity as opposed to nasal drops which will be delivered to a larger area further back in the nasal cavity. The use of bioadhesive excipients in the formulations is an approach to overcome the

rapid mucociliary clearance. The clearance may also be reduced by depositing the formulation in the anterior, less ciliated part of the nasal cavity thus leading to improved absorption

III. Enzymatic Degradation- Another contributing (but normally considered less important) factor to the low transport of especially peptides and proteins across the nasal membrane is the possibility of an enzymatic degradation of the molecule either within the lumen of the nasal cavity or during passage across the epithelial barrier. These sites both contain exo-peptidases such as mono- and di-aminopeptidases that can cleave peptides at their N and C termini and endopeptidases such as serine and cysteine, which can attack internal peptide bonds. The use of enzyme inhibitors and/or saturation of enzymes may be approaches to overcome this barrier.

Different factors affecting nasal drug absorption :

Various factors affect bioavailability of nasally administered drugs as follows;

I . **Biological Factors**

- Structural features
- Biochemical changes

II **Physiological factors**

- Blood supply and neuronal regulation
- Nasal secretions
- Mucociliary clearance and ciliary beat frequency
- Pathological conditions
- Environmental conditions.
- Membrane permeability.
- Distribution

III **Physicochemical Properties of Drugs**

- Molecular weight
- Size
- Solubility
- Lipophilicity
- pka and Partition coefficient
- Chemical form of drug.
- Polymorphism.
- Chemical state.
- Physical state.
- Formulation

IV Physicochemical Properties of Formulation

- Physical form of formulation
- pH
- Osmolarity
- Volume of solution applied and drug concentration
- Viscosity
- Enzymetic degredation

I Biological factors

1. Structural features

There are five different sections of nasal cavity: nasal vestibule, atrium, respiratory area, olfactory region and the nasopharnyx. These structures and the type of cells, density and number of cells present in that region influence the permeability. Absorption enhancers used in combination with drugs increase the permeation of compounds.

2. Biochemical changes

Enzymatic barrier to the delivery of drugs is nasal mucosa because of the presence of a large number of enzymes, which include oxidative and conjugative enzymes, peptidases and proteases. These enzymes are responsible for the degradation of drugs in the nasal mucosa and result in creation of a pseudo-first-pass effect. Metabolism of nasal decongestants, alcohols, nicotine and cocaine IS due to p450 dependent monoxygenase system. Protease and peptidase were responsible for the pre-systemic degradation and subsequent lower permeation of various peptide drugs, such as calcitonin, insulin, LHRH and desmopressin.. To overcome these degradations various approaches have been used. These include the use of protease and peptidase inhibitors such as bacitracin, amastatin, boroleucin and puromycin.

II Physiological factors

a. Blood supply and neuronal regulation

Nasal mucosa is highly permeable site. High blood supply due to parasympathetic stimulation gives congestion and low blood supply due to sympathetic stimulation gives relaxation, regulate the rise and fall in the amounts of drug permeated, respectively. Based on the above observations, we can conclude that the increased permeability of a compound is due to parasympathetic stimulation.

Nasal secretions

Nasal secretions are produced by anterior serous and seromucus glands. Mucus production is approximately 1.5–2 l ml daily. The permeability of drug through the nasal mucosa is affected by:

Viscosity of nasal secretion

The viscous surface layer will inhibit the ciliary beating if the sol layer of mucus is too thin and mucociliary clearance is impaired if sol layer is too thick, because contact with cilia is lost. Permeation of the drug is affected due to impairment of mucociliary clearence by altering the time of contact of drug and mucosa.

Solubility of drug in nasal secretions

For permeation of drug solublisation is necessary. A drug needs to have appropriate physicochemical characteristics for dissolution in nasal secretions.

Diurnal variation Nasal secretions

Are also affected by circadian rhythm. Permeation of drug is altered at night due to secretions and clearance rates are reduced. Chronokinetics dictate the pattern and rate of permeation in such cases.

pH of nasal cavity variation in pH

Is observed between 5.5–6.5 in adults and 5.0–7.0 in infants. Permeation of drug is greater if the nasal pH is lower than pKa of drug because under such conditions the penetrant molecules exist as unionized species. Increase or decrease in the permeation of drug is observed because ionization is affected by change in pH of mucus, depending on the nature of the drug. pH of formulation should be between 4.5 to 6.5 for better absorption and should also have good buffering capacity.

Mucociliary clearance (MCC)

And ciliary beating Whenever a substance is nasally administered, it is cleared from the nasal cavity in ~21 min by MCC because mucociliary clearance is the normal defense mechanism of the nasal cavity which clears substances adhering to nasal mucosa and cleared in GIT by draining into nasopharynx. Drug permeation is enhanced by increasing contact time between drug and mucus membrane because reduced MMC; whereas, increased MCC decreases drug permeation.

Pathological conditions:

Mucociliary disfunctioning, hypo or hypersecretions, irritation of the nasal mucosa occurs due to diseases such as the common cold, rhinitis, atrophic rhinitis and nasal polyposis, and drug permeation is affected by this.

Environmental conditions:

Moderate reduction in the rate of MCC occurs at the temperature of 240C, it has been predicted that a linear increase in ciliary beat frequency occurs with increase in temperature.

Membrane permeability:

Absorption of the drug through the nasal route is affected by membrane permeability which is most important factor. The large molecular weight drugs and water soluble drugs like peptides and proteins have low membrane permeability hence absorbed through endocytic transport in fewer amounts.

Drugs distribution and deposition

The drug distribution in the nasal cavity is one of the important factors, which affect the efficiency of nasal absorption. The mode of drug administration could effect the distribution of drug in nasal cavity, which in turn will determine the absorption efficiency of a drug. The absorption and bioavailability of the nasal dosage forms mainly depends on the site of disposition. The anterior portion of the nose provides a prolonged nasal residential time for disposition of formulation, it enhances the absorption of the

drug. And the posterior chamber of nasal cavity will use for the deposition of dosage form; it is eliminated by the mucociliary clearance process and hence shows low bioavailability .The site of disposition and distribution of the dosage forms are mainly depends on delivery device, mode of administration, physicochemical properties of drug molecule.3

III. Physicochemical properties of drug:

Molecular weight and size:

Drug permeation is determined by molecular weight, molecular size, hydrophilicity and lipophilicity of the compound. For compounds 1 kDa, bioavailability can be directly predicted from knowledge of MW. In general, the bioavailability of these large molecules ranges from 0.5% to 5%. Physicochemical properties of the drug don't significantly affect permeation of drug LT 300 Da, which will mostly permeate through aqueous channels of the membrane. By contrast, for compounds with MW 300 Da rate of permeation is highly sensitive.

Solubility:

Major factor in determining absorption of drug through biological membranes is drug solubility. As nasal secretions are more watery in nature, a drug should have appropriate aqueous solubility for increased dissolution. Lipophilic drugs have less solubility in the aqueous secretions. Water soluble drugs are absorbed by passive diffusion and lipophilic drugs via active transport depending on their solubility.

Lipophilicity:

The permeation of the compound normally increases through nasal mucosa with increase in lipophilicity. It appears that nasal mucosa is primarily lipophilic in nature and the lipid domain plays an important role in the barrier function of these membranes although they have some hydrophilic characteristics. Systemic bioavailability of many drugs is decreased due to excess hydrophilicity in such cases prodrug approach is beneficial.

Pka and partition coefficient:

As per the pH partition theory, unionized species are absorbed better compared with ionized species and the same fact is true in the case of nasal absorption. There is constant relationship between pKa and nasal absorption of these drugs. With an increase in lipophilicity or the partition coefficient of the drugs its concentration in biological tissues increases. The absorption rate of aminopyrine increased with the increase in pH and was found to fit well to the theoretical profile Major factor governing nasal absorption is partition coefficient. Polymorphism: Polymorphism is the important parameter in the nasal drug product development which is administered in particulate form. Polymorphism is known to affect dissolution of drugs and their absorption through biological membranes is affected by polymorphism. This factor should be carefully considered in the dosage form development for the nasal delivery.

Chemical state of drug:

Absorption of the drug is determined by the chemical form of the drug in which it is presented to nasal mucosa. Chemically alter a drug molecule by adding a bio-cleavable lipophilic moiety is the alternative for improving absorption of the drug which is not having desired absorption properties. The prodrug approach provides many additional challenges which need to be overcome in the drug product developmental process. The toxicity of the prodrug itself needs to be fully evaluated .

Physical state of drug:

Particle size and morphology of drug are two main important properties for particulate nasal drug products. These both parameters should be controlled to obtain suitable drug dissolution properties in the nostrils. Too fine particles below 5 microns should be avoided because it may get inhaled in lungs. Generally, particles in the 5–10 micron range are deposited in the nostrils.

Formulation (Concentration, pH, Osmolarity) : The pH of the formulation and nasal surface, can affect a drug's permeation. To avoid nasal irritation, the pH of the nasal formulation should be adjusted to 4.5–6.5 because lysozyme is found in nasal secretions, which is responsible for destroying certain bacteria at acidic pH. Under alkaline conditions, lysozyme is inactivated and the tissue is susceptible to microbial infection. In addition to avoiding irritation, it results in obtaining efficient drug permeation and prevents the growth of bacteria. Concentration gradient plays very important role in the absorption / permeation process of drug through the nasal membrane due to nasal mucosal damage. Examples for this are nasal absorption of L-Tyrosine was shown to increase with drug concentration in nasal perfusion experiments. Another is absorption of salicylic acid was found to decline with concentration. This decline is likely due to nasal mucosa damage by the permanent. The osmolarity of the dosage form affects the nasal absorption of the drug; it was studied in the rats by using model drug. The sodium chloride concentration of the formulation affects the nasal absorption. The maximum absorption was achieved by 0.462 M sodium chloride concentration; the higher concentration not only causes increased bioavailability but also leads to the toxicity to the nasal epithelium.3

VI. Physicochemical properties of formulation:

Physical form of formulation: Physical form of the formulation is very important in nasal drug absorption. Liquid formulations are less effective than powder form in delivering insulin in rabbits. Less efficient systemic nasal drug delivery observed with more viscous formulation. Scientist found that somewhat more sustained effects of desmopressin are observed with addition of viscous agent but total bioavailability is not enhanced. Viscous formulations may help in minimizing nasal drip. pH: extent of drug ionization IS determined by pH partition hypothesis hence it is related to formulation pH. Nasal formulation should be adjusted to appropriate pH to avoid irritation, to obtain efficient absorption and to prevent growth of pathogenic bacteria. Ideal formulation pH should be adjusted between 4.5 and 6.5. pH of the nasal surface is 7.39 and the pH of nasal secretions is 5.5–6.5 in adults and 5.0–6.7 in infants and children.

Enzymatic degradation in nasal cavity :

In case of peptides and proteins are having low bioavailability across the nasal cavity, so these drugs may have possibility to undergo enzymatic degradation of the drug molecule in the lumen of the nasal cavity or during passage through the epithelial barrier. These both sites are having exo-peptidases and endopeptidases, exo-peptidases are mono-aminopeptidases and di-aminopeptidases. These are having capability to cleave peptides at their N and C termini and endopeptidases such as serine and cysteine, which can attack internal peptide bonds.3

- **Formulations based on Nasal Delivery System :**

Liquid dosage forms

- **Nasal drops**

Nasal drops are one of the most simple and convenient delivery systems among all formulations. The main disadvantage of this system is the lack of dose precision.

- **Nasal sprays**

Both solution and suspension formulations can be formulated into nasal sprays. Due to the availability of metered dose pumps and actuators, a nasal spray can deliver an exact dose anywhere from 25 -200 μL.

- **Nasal emulsions,**

micro emulsions Intranasal emulsions have not been studied as extensively as other liquid nasal delivery systems. Nasal emulsions offer the advantages for local application mainly due to the

viscosity. Semi-solid dosage forms Semi-solid systems, for example gels, ointments and liquid systems containing polymers that gel at particular pH changes are usually employed for designing the nasal drug delivery systems.

- **Nasal gels**

Nasal gels are thickened solutions or suspensions, of high-viscosity. The advantages of a nasal gel include the reduction of post-nasal dripping due to its high viscosity, reduction of the taste impact due to reduced swallowing, reduction of anterior leakage of the formulation. Solid dosage forms Solid dosage forms are also becoming popular for intranasal drug delivery, although these formulations are more suitable for pulmonary drug delivery and similar applications, since it can cover the vasculature within the epithelium of nasal mucosa.

- **Nasal powders**

Powder dosage forms may be developed if solution and suspension dosage forms cannot be developed, mainly due to lack of drug stability. The advantages of a nasal powder dosage form are the absence of preservative and superior stability of the drug in the formulation. However, the suitability of the powder formulation is dependent on the solubility, particle size, aerodynamic properties and nasal irritancy of the active drug and/or excipients. Novel drug formulations Several claims have been made in favour of developing nasal formulations containing liposomes, microspheres and nanoparticles for intranasal drug delivery. These systems can include, besides the drug, enzymatic inhibitors, nasal absorption enhancers or/and mucoadhesive polymers in order to improve the stability, membrane penetration and retention time in nasal cavity.

- **Liposomes**

Liposomes are phospholipids vesicles composed by lipid bilayers enclosing one or more aqueous compartments and wherein drugs and other substances can be included. Liposomal drug delivery systems present various advantages such as the effective encapsulation of small and large molecules with a wide range of hydrophilicity and pKa values . In fact, they have been found to enhance nasal absorption of peptides such as insulin and calcitonin by increasing their membrane penetration. This has been attributed to the increasing nasal retention of peptides. Protection of the entrapped peptides from enzymatic degradation and mucosal membrane disruption.

- **Microspheres**

Microsphere technology has been widely applied in designing formulations for nasal drug delivery. Microspheres are usually based on mucoadhesive polymers (chitosan, alginate), which present advantages for intranasal drug delivery. Furthermore, microspheres may also protect the drug from enzymatic metabolism and sustain drug release, prolonging its effect.

- **Nanoparticles**

Nanoparticles are solid colloidal particles with diameters raging from 1-1000 nm. They consist of macromolecular materials and can be therapeutically used as adjuvant in vaccines or as drug carriers, in which the active substance is dissolved, entrapped, encapsulated, adsorbed or chemically attached. Nanoparticles may offer several advantages due to their small size, but only the smallest nanoparticles penetrate the mucosal membrane by paracellular route and in a limited quantity because the tight junctions are in the order of 3.9-8.4 Å.1

- **NASAL DRUG DELIVERY DEVICES :**

The details and principles of the mechanics of particle generation for the different types of nasal aerosols have been described in detail by Vidgren and Kublik in their comprehensive review from 1998 and will only be briefly described here, with focus instead on technological features directly impacting particle deposition and on new and

emerging technologies and devices. Liquid formulations currently completely dominate the nasal drug market, but nasal powder formulations and devices do exist, and more are in development. Table 1 provides an overview of the main types of liquid and powder delivery devices, their key characteristics, and examples of some key marketed nasal products and emerging devices and drug–device combination products in clinical development (Table 1).

- **Devices for liquid formulations :**

The liquid nasal formulations are mainly aqueous solutions, but suspensions and emulsions can also be delivered. Liquid formulations are considered convenient particularly for topical indications where humidification counteracts the dryness and crusting often accompanying chronic nasal diseases. In traditional spray pump systems, preservatives are typically required to maintain microbiological stability in liquid formulations. Studies in tissue cultures and animals have suggested that preservatives, like benzalkonium chloride in particular, could cause irritation and reduced ciliary movement. However, more recent human studies based on long-term and extensive clinical use have concluded that the use of benzalkonium chloride is safe and well tolerated for chronic use. For some liquid formulations, in particular peptides and proteins, limited stability of dissolved drug may represent a challenge. Drops delivered with pipette Drops and vapor delivery are probably the oldest forms of nasal delivery. Dripping breast milk has been used to treat nasal congestion in infants, vapors of menthol or similar substances were used to wake people that have fainted, and both drops and vapors still exist on the market (e.g., www.vicks.com). Drops were originally administered by sucking liquid into a glass dropper, inserting the dropper into the nostril with an extended neck before squeezing the rubber top to emit the drops. For multi-use purposes, drops have to a large extent been replaced by metered-dose spray pumps, but inexpensive single-dose pipettes produced by "blow-fill-seal" technique are still common for OTC products like decongestants and saline. An advantage is that preservatives are not required. In addition, due to inadequate clinical efficacy of spray pumps in patients with nasal polyps, a nasal drop formulation of fluticasone in single-dose pipettes was introduced in the EU for the treatment of nasal polyps. The rationale for this form of delivery is to improve drug deposition to the middle meatus where the polyps emerge. However, although drops work well for some, their popularity is limited by the need for head-down body positions and/or extreme neck extension required for the desired gravity-driven deposition of drops. Compliance is often poor as patients with rhinosinusitis often experience increased headache and discomfort in head-down positions.

- **Delivery of liquid with rhinyle catheter and squirt tube :**

A simple way for a physician or trained assistant to deposit drug in the nose is to insert the tip of a fine catheter or micropipette to the desired area under visual control and squirt the liquid into the desired location. This is often used in animal studies where the animals are anesthetized or sedated, but can also be done in humans even without local anesthetics if care is taken to minimize contact with the sensitive mucosal membranes. This method is, however, not suitable for self-administration. Harris et al. described a variant of catheter delivery where 0.2 ml of a liquid desmopressin formulation is filled into a thin plastic tube with a dropper. One end of the tube is positioned in the nostril, and the drug is administered into the nose as drops or as a "liquid jet" by blowing through the other end of the thin tube by the mouth. Despite a rather cumbersome procedure with considerable risk of variability in the dosing, desmopressin is still marketed in some

countries with this rhinyle catheter alongside a nasal spray and a tablet for treatment of primary nocturnal enuresis, Von Willebrand disease, and diabetes insipidus.

- **Squeeze bottles :**

Squeeze bottles are mainly used to deliver some over-thecounter (OTC) products like topical decongestants. By squeezing a partly air-filled plastic bottle, the drug is atomized when delivered from a jet outlet. The dose and particle size vary with the force applied, and when the pressure is released, nasal secretion and microorganisms may be sucked into the bottle. Squeeze bottles are not recommended for children.

Figure 3 : Squeeze bottles

- **Metered-dose spray pumps :**

Metered spray pumps have, since they were introduced some four decades ago, dominated the nasal drug delivery market (Table 1). The pumps typically deliver 100 µl (25– 200 µl) per spray, and they offer high reproducibility of the emitted dose and plume geometry in in vitro tests. The particle size and plume geometry can vary within certain limits and depend on the properties of the pump, the formulation, the orifice of the actuator, and the force applied. Traditional spray pumps replace the emitted liquid with air, and preservatives are therefore required to prevent contamination. However, driven by the studies suggesting possible negative effects of preservatives, pump manufacturers have developed different spray systems that avoid the need for preservatives. These systems use a collapsible bag, a movable piston, or a compressed gas to compensate for the emitted liquid volume (www.aptar.com and www.rexam.- com). The solutions with a collapsible bag and a movable piston compensating for the emitted liquid volume offer the additional advantage that they can be emitted upside down, without the risk of sucking air into the dip tube and compromising the subsequent spray. This may be useful for some products where the patients are bedridden and where a headdown application is recommended. Another method used for avoiding preservatives is that the air that replaces the emitted liquid is filtered through an aseptic air filter. In addition, some systems have a ball valve at the tip to prevent contamination of the liquid inside the applicator tip (www.aptar.com). These preservative-free pump systems become more complex and expensive, and since human studies suggest that preservatives are safe and well tolerated, the need for preservative-free systems seems lower than previously anticipated. More recently, pumps have been designed with side-actuation and introduced for delivery of fluticasone furoate for the indication of seasonal and perennial allergic rhinitis. The pump was designed with a shorter tip to avoid contact with the sensitive mucosal surfaces. New designs to reduce the need for priming and re-priming, and pumps incorporating pressure point features to improve the dose reproducibility and dose counters and lock-out mechanisms for enhanced dose control and safety are available (www.rexam.com and www.aptar.com). Importantly, the in vivo deposition and clinical performance of metered-dose spray pumps can be enhanced for some applications by adapting the pumps to a novel breathpowered "Bi-Directional™" delivery technology described in more detail below.

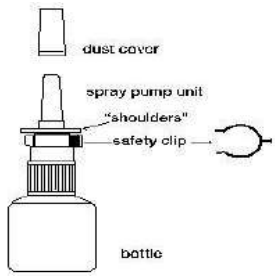

Figure 4: Metered-dose spray pumps

- **Single- and duo-dose spray devices :**

Metered-dose spray pumps require priming and some degree of overfill to maintain dose conformity for the labeled number of doses. They are well suited for drugs to be administered daily over a prolonged duration, but due to the priming procedure and limited control of dosing, they are less suited for drugs with a narrow therapeutic window. For expensive drugs and vaccines intended for single administration or sporadic use and where tight control of the dose and formulation is of particular importance, single-dose or duo-dose spray devices are preferred (www.aptar.com). A simple variant of a single-dose spray device (MAD) is offered by LMA (LMA, Salt Lake City, UT, USA; www.lmana.com). A nosepiece with a spray tip is fitted to a standard syringe. The liquid drug to be delivered is first drawn into the syringe and then the spray tip is fitted onto the syringe. This device has been used in academic studies to deliver, for example, a topical steroid in patients with chronic rhinosinusitis and in a vaccine study. A pre-filled device based on the same principle for one or two doses (Accuspray™, Becton Dickinson Technologies, Research Triangle Park, NC, USA; www.bdpharma.com) is used to deliver the influenza vaccine FluMist (www.flumist.com), approved for both adults and children in the US market .A similar device for two doses was marketed by a Swiss company for delivery of another influenza vaccine a decade ago. This vaccine was withdrawn due to occurrence of adverse events (Bell's palsy) potentially related to the cholera toxin adjuvant used. The device technology is now owned by a Dutch vaccine company (Crucell N.V. Leiden, the Netherlands; www.crucell.com), but to our knowledge is not currently used in any marketed products. The single- and duo-dose devices mentioned above consist of a vial, a piston, and a swirl chamber. The spray is formed when the liquid is forced out through the swirl chamber. These devices are held between the second and the third fingers with the thumb on the actuator. A pressure point mechanism incorporated in some devices secures reproducibility of the actuation force and emitted plume characteristics. Currently, marketed nasal migraine drugs like Imitrex (www.gsk.com) and Zomig (www.az.com; Pfeiffer/Aptar single-dose device) and the marketed influenza vaccine FluMist (www.flumist.com; Becton Dickinson single-dose spray device) are delivered with this type of device (Table 1). With sterile filling, the use of preservatives is not required, but overfill is required resulting in a waste fraction similar to the metered-dose, multi-dose sprays. To emit 100 µl, a volume of 125 µl is filled in the device (Pfeiffer/Aptar single-dose device) used for the intranasal migraine medications Imitrex (sumatriptan) and Zomig (zolmitriptan) and about half of that for a duo-dose design .

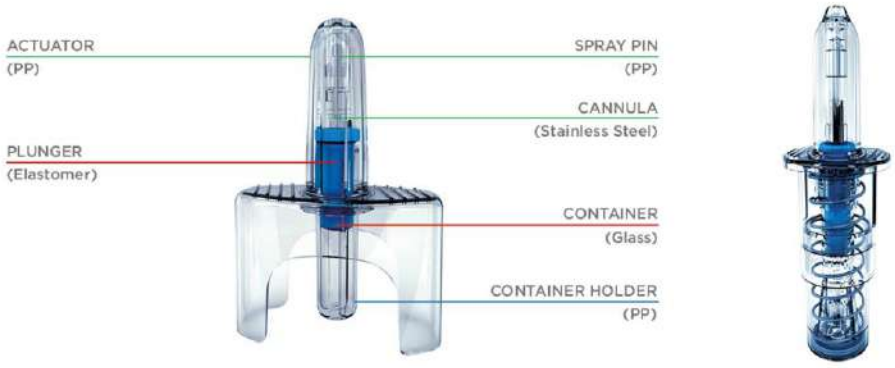

Figure 5: Single and duo-dose spray devices

- **Nasal pressurized metered-dose inhalers (pMDIs) :**

Most drugs intended for local nasal action are delivered by spray pumps, but some have also been delivered as nasal aerosols produced by pMDIs. Following the ban on ozonedepleting chlorofluorocarbon (CFC) propellants, the number of pMDI products for both pulmonary and nasal delivery diminished rapidly, and they were removed from the US market in 2003. The use of the old CFC pMDIs for nasal products was limited due to complaints of nasal irritation and dryness. The particles from a pMDI are released at a high speed and the expansion of a compressed gas, which causes an uncomfortable "cold Freon effect" .The particles emitted from the traditional pMDIs had a particle velocity much higher than a spray pump (5,200 vs. 1,500 cm/s at a distance 1–2 cm from the actuator tip) .The issues related to the high particle speed and "cold Freon effect" have been reduced with the recently introduced hydrofluoroalkane (HFA)-based pMDI for nasal use offering lower particle speeds .Recently, the first nasal pMDI using HFA as propellant to deliver the first generation topical steroid beclomethasone dipropionate (BDP) was approved for allergic rhinitis in the USA .Like spray pumps, nasal pMDIs produce a localized deposition on the anterior non-ciliated epithelium of the nasal vestibule and in the anterior parts of the narrow nasal valve, but due to quick evaporation of the spray delivered with a pMDI, noticeable "drip-out" may be less of an issue.

Mismatch between geometry of anterior nose and the spray plume

The pressure created by the force actuating a spray pump drives the liquid through the swirl chamber at the tip of the applicator and out through the circular nozzle orifice .The combination of radial and axial forces creates a swirling thin sheet of liquid that, after some millimeters, becomes unstable and breaks up into "ligaments" before forming the particles (break-up length). Importantly, a hollow spray cone is formed with particles mainly at the periphery. The key parameters influencing the properties of the plume and subsequently the deposition pattern of the particles are the swirl effect, nozzle orifice dimensions, the spray cone angle, and the break-up length. Inthavong et al. reported for a spray with a nozzle diameter of 0.5 mm, a spray cone angle of 30°, and a break-up length of about 3.5 mm, and the diameter at the break-up point is already 4 mm. One study reported the smallest spray cone diameters (Dmax/Dmin) for a spray angle with 54.6° to be 2.34/1.92 and 3.30/3.08 cm at distances of 1.0 and 2.5 cm from the nozzle .Another study reported a spray cone diameter of 2.52/1.58 at 3 cm from the nozzle for a spray angle of 39° . Even if the spray pump is inserted as deep as 10–15 mm into the nostril, there is an obvious mismatch between the dimensions and shape of the circular

plume (diameter≈2 cm) and the narrow triangular valve opening. With most of the particles in the periphery of the plume, it becomes quite evident that the majority of the particles will impinge in the non-ciliated mucosal walls of the vestibule anterior to the valve. Particles actually penetrating the valve will do so primarily through the lower and wider part of the triangle, a delivery pattern that is accentuated if delivery is performed during sniffing. Although the aerosol-generating mechanisms are different, a similar mismatch would exist between constricting geometry of the nasal vestibule and the conical-shaped plumes produced by other powered devices like pMDIs, nebulizers/atomizers, and many powder devices (see below).

- **Powered nebulizers and atomizers :**

Nebulizers use compressed gasses (air, oxygen, and nitrogen) or ultrasonic or mechanical power to break up medical solutions and suspensions into small aerosol droplets that can be directly inhaled into the mouth or nose. The smaller particles and slow speed of the nebulized aerosol are advocated to increase penetration to the target sites in the middle and superior meatuses and the paranasal sinuses. Indeed, nasal inhalation from a nebulizer has been shown to improve deposition to the upper narrow part of the nose when compared to a metered-dose spray pump, but with 33 % and 56 % of the delivered dose deposited in the lungs in the subjects assessed. In light of this problem of lung delivery, it is unsurprising that nasal inhalation of nebulized antibiotics intended for topical action in patients with chronic rhinosinusitis resulted in coughing and increased need for inhaled medications following nasal inhalation.

Figure 6 : Powdered Nebulizer And Atomizer

- **VibrENT pulsation membrane nebulizer :**

A new nebulizer intended for delivery to the nose and sinuses in patients with chronic rhinosinusitis utilizing a pulsating aerosol generated via a perforated vibrating membrane has recently been introduced (VibrENT PARI Pharma GmbH). The pulsation in combination with small particles is assumed to offer better penetration to the sinuses, and instruction on specific breathing technique during delivery is advocated to minimize inhalation . Delivery of an aerosol with small particles with a mass median aerodynamic diameter (MMAD) of 3.0 μm was performed with two different techniques and compared to a spray pump. Aerosol administration into one nostril for 20 s at a rate of mass output of 0.3 ml/min, with an exit filter attached to the other nostril during nasal breathing, resulted in 4.5 % of the fraction deposited in the nose (63 %) reaching the sinuses (i.e., 2.8 % of the delivered dose), 27 % in the exit filter, and significant lung deposition (10 %). Nasal aerosol delivery was also performed when the subjects were instructed to maintain the soft palate closed while a flow resistor was connected to the left nostril. Following this procedure, 70 % of the radioactivity was deposited in the nose, 30 % in the exit filter, a negligible fraction in the lungs, and 7 % of the fraction in the nose (i.e., 4.9 % of the delivered dose) was found in the sinuses . Following delivery of 100 μl with a traditional spray pump, 100 % of the dose was found in the nose with no deposition in the lungs and non-significant deposition in the sinuses. Correction

for background radiation and decay was performed, but correction for tissue attenuation was not performed, which is likely to change the relative distribution and potentially increase the fraction actually deposited in the lungs .Nevertheless, the results suggest that the use of a pulsating aerosol in combination with the breathing technique and an exit resistor may enhance deposition in the sinuses in healthy volunteers. However, the clinical relevance of these results from healthy volunteers for rhinosinusitis patients with blocked sinus openings remains to be determined. The proposed breathing technique used to prevent lung deposition may also prove challenging as compared to the automatic integration of velum closure and the drug delivery process, as achieved when using the exhalation breath in operation of the delivery device, such as provided by OptiNose's Bi-Directional™ delivery technology, which can also utilize an exit resistor to create positive pressure in the nose and sinuses. Furthermore, a very distinct "hot spot" was observed for both the nebulizer and spray pump delivery, but no assessment of regional deposition in the nose was performed in the study with the pulsating aerosol nebulizer.

- **Aeroneb Solo vibrating mesh nebulizer**

Distinct anterior deposition in the valve area with nebulizers is confirmed in another very recent publication comparing nasal inhalation from a nasal sonic/pulsating jet nebulizer (Atomisor NL11S® sonic, DTF-Medical, France) and a new nasal mesh nebulizer system designed to minimize lung inhalation (Aeroneb Solo®, Aerogen, Galway, Ireland; DTFAerodrug, Tours, France) with the same mean particle size (5.6±0.5 μm). The new system consists of two integrated components: the nebulizer compressor administering a constant airflow rate transporting the aerosol into one nostril via a nozzle and a pump simultaneously aspirating from a second nozzle in the other nostril at the same airflow rate while the subject is instructed to avoid nasal breathing. The new nasal mesh nebulizer produced more deposition in terms of volume of liquid (27 % vs. 9 %, i.e., 0.81 vs. 0.27 ml) in the nasal cavity. The much higher fraction found in the nasal cavity in this study is probably a result of the shorter nebulizing time and smaller delivered volume in the study testing the PARI pulsating nebulizer (20 s at a rate of 0.3 ml/min to each nostril versus delivery of 3 ml for up to 10 min) before assessment of deposition was performed . With much longer delivery time, a substantial fraction of the dose delivered beyond the nasal valve will be cleared to the gastrointestinal (GI) tract. Aerosol distribution deposition showed a distinct maximum value at 2 cm from the nostril for both nebulizers corresponding to deposition in the nasal valve region. Furthermore, aerosol distribution deposition in the vertical plane showed a similar profile for both nebulizers with a distinct maximum close to the floor of the nose (0.75 cm for the mesh nebulizer and 1.2 cm for the sonic jet nebulizer) . Importantly, the delivery efficiencies for both nebulizers and delivery techniques appear very low with only 27 % vs. 9 %, i.e., 0.81 vs. 0.27 ml, possibly due to the long delivery time and resulting differences in mucociliary and other mechanisms of clearance. In other words, a study assessing deposition after several minutes of delivery is likely to underestimate the actual exposure to the posterior ciliated part of the nose compared to the study assessing deposition after a short period of delivery of less than 1 min (20 s×2).

- **Clinical relevance of deposition results with nebulizers**

Lung deposition and relatively low nasal delivery fractions are issues with nasal nebulizers. Although lung deposition appears to be reduced with simultaneous aspiration from the contralateral nostril and with specific breathing instructions, this complex mechanism for use, coupled with the need for careful patient

compliance with breathing, may be challenging, especially in children or other special populations. The study design, comparing not only two different nebulization techniques but also very different breathing techniques, makes interpretation of the results comparing the nasal nebulizers in terms of deposition efficacy and clinical significance very difficult. The rationale for using small particles and sonic/pulsation techniques is to increase the delivery into the sinuses, but at the expense of low delivery efficacy and significant potential for lung deposition. Moreover, despite the intended advantages of the vibrating mesh nebulizer that employs aspiration from the contralateral nostril, the quantification of deposition in the different planes (cartography) demonstrates the typical highly preferential deposition in the anterior (anterior 2–3 cm) and lower (lower 1–2 cm) parts of the nasal cavity. This pattern of deposition suggests the nebulizer is not effectively delivering to the prime target sites for chronic rhinosinusitis and nasal polyposis (i.e., the middle and superior meatuses or sinuses). To date, no clinical data has been published with the new nebulizer systems . One approach to avoiding lung deposition is the BiDirectionalTM technology employed in OptiNose devices; this technology ensuring operation of the nebulizer only on generation of a pressure sufficient to close the palate, avoiding the problems associated with suction pumps and special breathing instructions. However, clinical data using this approach with a nebulizer has also not been published.

- **ViaNase atomizer :**

A handheld battery-driven atomizer intended for nasal drug delivery has been introduced (ViaNase by Kurve Technology Inc., Lynnwood, WA, USA). This device atomizes liquids by producing a vortical flow on the droplets as they exit the device (www.kurvetech.com). The induced vortical flow characteristics can be altered in circular velocity and direction to achieve different droplet trajectories . As discussed above, it is not clear that vortex flow is desirable for penetration past the nasal valve; however, it has been suggested that this technology is capable of targeting the sinuses, and some gamma-deposition images suggesting delivery to the sinuses have been published. However, no information related to impact of prior surgery or numerical quantification of nasal or sinus deposition verifying the claimed improved deposition to the upper parts of the nose has been published . The ViaNase device has been used to deliver nasal insulin in patients with early Alzheimer's disease (AD), and clinical benefit has been demonstrated . In these studies, delivery of insulin was performed over a 2-min period by nasal inhalation. However, when insulin is delivered with this device, lung deposition is likely to occur, and some concerns related to airway irritation and reduction in pulmonary function have been raised in relation to long-term exposure to inhaled insulin when Exubera was marketed for a short period as a treatment for diabetes . This example highlights the issue of unintended lung delivery, one important potential clinical problem associated with using nebulizers and atomizers producing respirable particles for nasal drug delivery.

- **Impel nitrogen-driven atomizer :**

A nasal atomizer driven by highly pressurized nitrogen gas is under development by Impel Inc. (www.impel.com). The device is intended to enable drug delivery to the upper parts of the nose in order to achieve N2B delivery . To date, only animal data has been presented, making it difficult to evaluate its potential in human use, as nasal deposition and the assessment of nasal deposition in animal models vary significantly from humans. As previously noted, however, pMDIs are associated with a number of limitations. It therefore remains to be seen if a pressurized "open-palate" nebulizer will be capable of creating the desired delivery pattern.

- **Powder devices :**

Powder medication formulations can offer advantages, including greater stability than liquid formulations and potential that preservatives may not be required. Powders tend to stick to the moist surface of the nasal mucosa before being dissolved and cleared. The use of bioadhesive excipients or agents that slow ciliary action may decrease clearance rates and improve absorption . A number of factors like moisture sensitivity, solubility, particle size, particle shape, and flow characteristics will impact deposition and absorption .

The function of nasal powder devices is usually based on one of three principles (Table 1):

1. Powder sprayers with a compressible compartment to provide a pressure that when released creates a plume of powder particles fairly similar to that of a liquid spray;
2. Breath-actuated inhalers where the subject uses his own breath to inhale the powder into the nostril from a blister or capsule; and
3. Nasal insufflators describe devices consisting of a mouthpiece and a nosepiece that are fluidly connected. Delivery occurs when the subject exhales into the mouthpiece to close the velum, and the airflow carries the powder particles into the nose through the device nosepiece similar to the rhinyle catheter described above. The principle can be applied to different dispersion technologies and has been further developed and extended into the breath-powered Bi-Directional™ delivery technology (see below)

- **Nasal powder inhalers :**

& Astra Zenaca markets budesonide powder delivered with the Turbuhaler multi-dose inhaler device modified for nasal inhalation (Rhinocort Turbuhaler® ; www.az.com). It is marketed for allergic rhinitis and nasal polyps in some markets as an alternative to the liquid spray, but it does not seem to offer any particular advantage . In a study comparing twice daily treatment with aqueous budesonide spray (128 µg×2) and the Rhinocort Turbuhaler® (140 µg×2) in nasal polyp patients, both treatments significantly reduced polyp size compared to placebo, but with no difference between the active treatments. However, nasal symptom scores were significantly more reduced in the liquid spray compared to the powder. A gamma-deposition study with Rhinocort Turbuhaler) has shown predominantly anterior deposition with a “hot spot” at the nasal valve area and about 5 % lung deposition . If corrected for tissue attenuation in the lungs, it is likely that the fraction would be substantially higher. Aptar group (www.aptar.com) offers a simple blisterbased powder inhaler. The blister is pierced before use and the device nosepiece placed into one nostril. The subject closes the other nostril with the finger and inhales the powder into the nose. A powder formulation of apomorphine for Parkinson’s using this blister-based powder inhaler (BiDose™/Prohaler™) from Pfeiffer/ Aptar was in clinical development by Britannia, a UK company recently acquired by Stada Pharmaceutical (www.stada.de). Apparently, further development has been discontinued. & Nippon Shinyaku Co., Ltd. (www.nippon-shinyaku.- co.jp) markets in Japan a topical steroid (dexamethasone cipecilate) delivered with a powder-based inhalation device for allergic rhinitis. The device (Twin-lizer™) has two chambers with capsules inside. The capsule is pierced, and when the subject inhales from the nosepiece, the powder is deagglomerated and delivered into the nose with the airflow. Nasal powder sprayers & SBNL Pharma (www.snbl.com) recently reported data on a Phase 1 study described in a press release (www.snbl.com) with a zolmitriptan powder cyclodextrin formulation (µco™ System) for enhanced absorption, described previously in an in

vitro study [81]. The zolmitriptan absorption was rapid, and the relative bioavailability was higher than the marketed tablet and nasal spray (www.snbl.com). The company has their own capsule-based, single-dose powder devices (Fit-lizer) [82]. When inserted into a chamber, the top and bottom of the capsule is cut off by sharp blades. A plastic chamber is compressed by hand, compressed air passes through a one-way valve and the capsule during actuation, and the powder is emitted. In vitro testing shows high-dose reproducibly and minimal residuals, but no data on particle size distribution or in vivo deposition and clearance patterns appear to be available. The company has also completed a Phase 2 study with the drug granisetron for the indication of delayed chemotherapy-induced nausea and vomiting based on the same formulation technology and delivered with the Fit-lizer™ device [81]. They have also announced plans to develop a powder-based influenza vaccine (www.snbl.com). & Bespak (www.bespak.com), the principle for UnidoseDP™, is similar to the Fit-lizer device. An air-filled compartment is compressed until a pin ruptures a membrane to release the pressure to emit the plume of powder. Delivery of powder formulations of a model antibody (human IgG) has been tested in a nasal cast model based on human MRI images. Approximately 95 % of the dose was delivered to the nasal cavity, but the majority of it was deposited no further than the nasal vestibule with only about 30 % deposited into deeper compartments of the nasal cavity [83]. The company report in their website that they have entered into a collaboration to develop an undisclosed nasal powder product with this device (www.bespak.com). & Aptar group (Pfeiffer/Valois) (www.aptar.com) offers a powder device (Monopowder) based on the same principle as the devices above but with a plunger that when pressed creates a positive pressure that ruptures a membrane to expel the powder. The device has been used in studies in rabbits, but no data from human deposition or clinical studies have been published [84]. & BD (www.bdpharma.com) also has a powder device (SoluVent™) where a positive pressure is created with a plunger that pierces a membrane to expel the powder. A device based on this technology is being tested with powder vaccines. Nasal powder insufflators & Trimel (www.trimel.com) has acquired a device originally developed by a Danish company (Direct Haler). There are two versions of this device that looks like a small drinking straw. One version is intended for pulmonary drug delivery where subjects inhale through the small tubular device and one for nasal drug delivery where subjects blow into one end of the tube while the other end is inserted into the vestibule of the nostril. The device can in principle be viewed as a powder version of the rhinyle catheter for liquid delivery. This tubular device includes a middle section with corrugations. The corrugations allow flexion of the device and create turbulence that deagglomerates the powder. One end of the small tubular device is inserted between the lips and the other into the nasal vestibule. The subject then exhales through the device to expel the powder from the tube and into the nostril. As when using the rhinyle catheter, exhalation into the device causes the soft palate to automatically elevate to separate the oral cavity and the nasal passages, preventing lung inhalation during delivery. No clinical data with the device is available apart from a small gamma study in a patent stating that the device produced clearance and areas of deposition that were not significantly different from a “state-of-the-art” powder inhalation device (device details not identified) .
& OptiNose (www.optinose.com) has developed a breath powered Bi-Directional™ nasal delivery technology for liquid and powder medications which utilizes the exhaled breath to deliver the drug into the nose, but with additional key

distinguishing features that importantly impact drug deposition and clearance patterns and clinical device performance.

Figure 7: Nasal powder inhaler

- **Breath-powered**

Bi-Directional™ technology—a new nasal drug delivery concept

This novel concept exploits natural functional aspects of the upper airways to offer a delivery method that may overcome many of the inherent limitations of traditional nasal devices. Importantly, the breath-powered Bi-Directional™ technology can be adapted to any type of dispersion technology for both liquids and powders. Breath-powered Bi-Directional™ devices consist of a mouthpiece and a sealing nosepiece with an optimized frusto-conical shape and comfortable surface that mechanically expands the first part of the nasal valve (Figs. 1, 2, and 3). The user slides a sealing nosepiece into one nostril until it forms a seal with the flexible soft tissue of the nostril opening, at which point, it mechanically expands the narrow slit-shaped part of the nasal triangular valve. The user then exhales through an attached mouthpiece. When exhaling into the mouthpiece against the resistance of the device, the soft palate (or velum) is automatically elevated by the positive oropharyngeal pressure, isolating the nasal cavity from the rest of the respiratory system. Owing to the sealing nosepiece, the dynamic pressure that is transferred from the mouth through the device to the nose further expands the slit-like nasal passages. Importantly, the positive pressure in the entry nostril will, due to the sealing nosepiece, balance the oropharyngeal pressure across the closed velum to prevent the velum from being "over-elevated," thus securing an open flow path between the two nasal passages behind the nasal septum and in front of the elevated velum. This "breath-powered" mechanism enables release of liquid or powder particles into an air stream that enters one nostril, passes entirely around the nasal septum, and exits through the opposite nostril, following a "Bi-Directional™" flow path. Actuation of drug release in devices employing this approach has been described using manual triggering as well as mechanisms automatically triggered by flow and/or pressure. By optimizing design parameters, such as the nosepiece shape, the flow rate, the particle size profile, and release angle, it is possible to optimize delivery to target sites beyond the nasal valve, avoid lung deposition, and to assure that particles are deeply deposited without exiting the contralateral nostril. The Bi-Directional™ devices currently in phase 3 clinical trials are a multi-dose liquid device incorporating a standard spray pump and a capsule-based powder multi-use device with disposable drug chamber and nosepiece (Fig. 3), but other configurations are possible. Importantly, the Bi-Directional™ delivery concept can be adapted to a variety of dispersion technologies for both liquids and powders.

Table 1 Overview of the main types of liquid and powder delivery devices, their key characteristics, and examples of some key marketed nasal products and emerging devices and drug–device combination products in clinical development.

LIQUID DEVICES		Product Stage	Example substances	Example indications	Dosing	Mechanism	Actuation	Relevant website
Vapour	Vapour inhaler	Marketed	Menthol	Rhinitis, common cold	Multidos	Vaporisation	Nasal inhalation	www.vicks.com
Drops								
	Rhinyl catheter	Marketed product	Desmopressin	Diabetes incipidus	Single dose	Mechanical	Breath powdered	www.fering.com
	Multi-dose droppers	Marketed	Decongestants	Rhinitis, Common cold	Multidose	Mechanical	Hand actuated	
	Unit-dose pipettes	Marketed	Topical steroids	Nasal polyps	Single dose	Mechanical	Hand actuated	www.gsk.com
Mechanical spray pumps								
	Squeeze bottle	Marketed	Decongestants	Rhinitis, Common cold	Multidose	Mechanical	Hand actuated	www.novarits.com
	Multidose metered-dose spray pump							
		Marketed	Topical steroids	Allergic & Perinneal rhinitis	Multidose	Marketed	Topical steroids	Allergic & Perinneal rhinitis
		Marketed	Desmopressin	Primary nocturnal enuresis	Multidose	Mechanical	Hand actuated	www.fering.com
		Marketed	Ketrorolac	Pain	Multidose	Mechanical	Hand actuated	www.luitpoldcom

	Single - dose spray pumps	Marketed	Triptans	Migraine & Cluster headache	Single dose	Mechanical	Hand actuated	www.gsk.com www.az.com
		Marketed	Vaccine	Influenza vaccine	Single dose	Mechanical	Hand actuated	www.bd.com
	Bi-dir Multi-dose spray pump	Product in Phase 3	Fluticasone propionate	CRS with Nasal polyps	Multi-dose	Mechanical	Breath powered	www.optinose.com
Gas driven spray systems/atomizers	Electrically powered Nebulizers/ Atomizers							
		Pulsation membrane nebulizer	Marketed device	Topical steroids	Sinusitis and nasal polyps	Multi-dose	Electical	Electical
		Vibrating mech nebulizer	Marketed device	Topical drugs	Sinusitis and nasal polyps	Multi-dose	Electical	Electical
POWDER DEVICES		**Product stage**	**Substances**	**Indication (s)**	**Dosing**	**Mechanism**	**Actuation**	**Example website (s)**
Mechanical powder sprayers								
	Powder spray device (capsule based) (SNBL)	Phase 2	Zlomitriptan	Migraine	Single dose	Mechanical	Hand actuated	www.snbl.com
	Powder sprays (Aptar/Vallois)	Device	Not known	Not known	Single dose	Mechanical	Hand actuated	www.bdl.com www.aptar.com
	Powder spray device (BD)	Marketed device	Not known	Not known	Single dose	Mechanical	Hand actuated	www.bespak.com

Breath actuated inhalers								
	Multi-dosepowderinhaler(AZ)	Rhinocort Turbohaler	Budesonide	Allergic rhinitis, Nasal polyps	Multi-dose	Mechanical	Nasal inhalation	www.az.com
	Single/duo dose capsule inhaler (Nippon-Shinyaku)	Twin-lizer	Dexamethasone cipecilate	Allergic rhinits	Single /duo dose	Mechanical	Nasal inhalation	www.nippons hinyaku.com
Insufflators								
	Insufflator - (Trimel)	Preclinical	Undisclosed	Allergic rhinitis	Single dose	Mechanical	Exhalation driven	www.trimelph armaceuticals.com
	Breath powered Bi-directional delivery (OptiNose)	Phase 3 trials	Sumatriptan powder	Migraine	Single dose	Mechanical	Breath powered	www.optinose.com

CONCLUSION :

Nasal drug delivery is a novel platform and it is a promising alternative to injectable route of administration. There is possibility in the near future that more drugs will come in the market in the form of nasal formulation intended for systemic treatment. Development of a drug with a drug delivery system is influenced by several factors. For the treatment of long illnesses such as diabetis, osteoporosis, fertility treatment novel nasal products are also expected to be marketed. Bioavailability of nasal drug products is one of the major challenges in the nasal product development. In contrast, a huge amount of money is investigated by pharmaceutical companies in the development of nasal products, because of growing demand of nasal drug products in global pharmaceutical market. So for the avoidance of side effect and improve effectiveness of nasal products we should pay attention to basic research in nasal drug delivery.1,3,10 Despite important improvements in the technical device attributes that can offer more reproducible and reliable in vitro performance, this has to a limited extent translated into improved clinical performance. While in vitro performance testing is undoubtedly of value for product quality assessment, predictive value for in vivo clinical performance is highly questionable. As stated in a recent review, well controlled clinical studies are currently required to quantify changes in both symptoms and functional parameters, and ultimately to determine the efficacy of novel drug/ device combinations.

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