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NEWER ADVANCEMENT IN NASAL DRUG DELIVERY SYSTEM

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ABSTRACT

Over the past two decades, intranasal drug delivery has shown tremendous promise for systemic delivery of therapeutic agents, although the potential of the nose as a route of administration has been known since ancient time. Psychotropic and hallucinogenic agents have been used as snuff in many parts of the world for hundreds of years. Because of rich vasculature and highly permeable structure, nasal route could be used as an alternative to parenteral routes of delivery. Nasal route circumvents hepatic first pass metabolism and gut wall enzyme mediated degradation. Nasal route is easily accessible for self-administration without the help of health professionals, and no needle stick hazards are associated with nasal administration. Other advantages of nasal drug delivery systems include rapid onset of action, reduced risk of overdose and improved patient compliance. However, there are several disadvantages of nasal route of administration including impermeability of nasal mucosa to lipophillic and high molecular weight drugs, mucotoxicity associated with long term use of formulation, requirement of expensive delivery device, and dose inaccuracy.

INTRODUCTION: Nasal drug delivery system offers lucrative way of drug delivery both topical and systemic therapies. The high permeability, high vasculature and low enzymatic environment of nasal cavity are well suitable for systemic delivery of drug molecules via nose with remarkable bioavailability. The noninvasiveness and self administrative nature of nasal also attracts the formulation scientists to deliver protein and peptides compounds.

Despite of all the advantages, the bioavailability of nasally administered products are affected by many barriers such as physiological, physicochemical and formulation barriers. Nasal absorption obeys passive and active transport pathways [1-2]. The absorption mechanism intramucosal transportation is regulated by simple diffusion, facilitated transport and active transport.

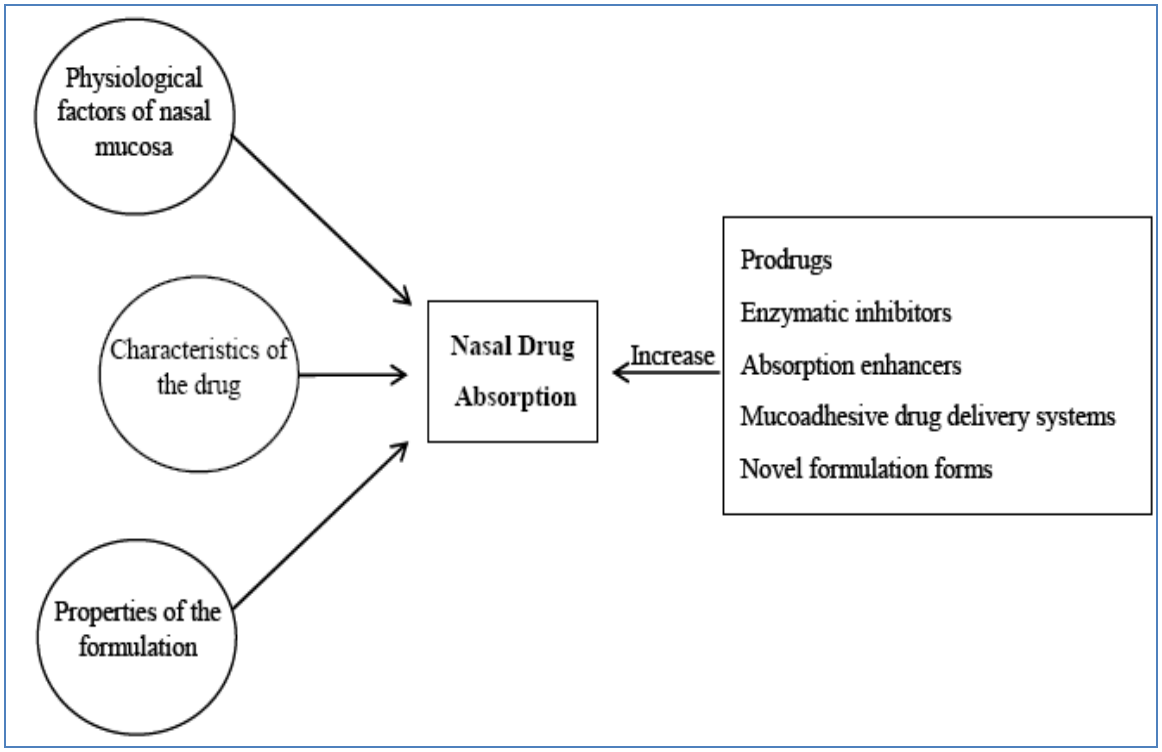
Merits:

- Avoidance of hepatic first-pass metabolism
- Rate of absorption comparable to IV medication
- Rapid onset of pharmacological action
- User-friendly, painless, non-invasive, needle-free administration mode

Demerits:

- Once administered, rapid removal of the therapeutic agent from the site of absorption is difficult
- Pathologic conditions such as cold or allergies may alter significantly the nasal bioavailability

Strategies to increase Nasal Drug Absorption [3]: Although the intranasal route is efficient for topic, systemic and CNS delivery of a wide range of drugs, it cannot be applied for many others due to their low nasal bioavailability. Briefly, bioavailability of nasally administered drugs is particularly restricted by low drug solubility, rapid enzymatic degradation in nasal cavity, poor membrane penetration and rapid mucociliary clearance.



OVERVIEW OF THE NASAL FORMULATIONS AVAILABLE IN MARKET

PRODUCT	DRUG	INDICATION	MANUFACTURER
Stadol NS® Nasal Spray	Butorphanol tartatrate	Management of pain including migraine	Bristol Myers Squibb
Miacalcin® Nasal Spray	Calcitonin- Salmon	Treatment of hypercalcemia and osteoporosis	Novartis
DDAVP® Nasal Spray	Desmopressin acetate	Diabetes insipidus	Aventis Pharmaceuticals
Migranal® Nasal Spray	Dihydroegotamine	Treatment of migraine	Novartis
Medihaler- ISO® Spray	Isoproterenol sulfate	--	3M Pharmaceuticals INC
Nitrolingual® Spray	Nitroglycerin	Prevention of angina pectoris due to coronary artery disease	G Pohl Boskamp GMBH and Co.
Synarel® Nasal Solution	Nafarelin acetate	Central precocious puberty, endometriosis	Roche Laboratories
Nicotrol® Inhalation	Nicotine	Smoking cessation	Pharmacia
Syntocinon® Nasal Spray	Oxytocin	Promote milk ejection in breast feeding mothers	Novartis
Imitrex® Nasal Spray	Sumatriptan	Migraine	Glaxo SmithKline
Relenza® Powder for Inhalation	Zanamivir	Treatment of uncomplicated acute illness due to influenza A and B	Glaxo SmithKline

NASAL DRUG DELIVERY TECHNIQUES:

Delivery Devices: Delivery devices have a profound impact on drug deposition, for example the tendency for anterior versus more uniform distribution achieved by nasal sprays and solutions, respectively. The simple presentation as nasal drops is simple, economic, and convenient, but it is likely that more sophisticated presentations will be required for many compounds in development. At present typical delivery devices include solutions, nasal sprays (solutions and suspensions), gels, and powders [4].

Snorting: The method of intranasal medication delivery likely impacts the success of the procedure. Elicit drug users employ a technique called 'snorting' whereby they take a highly concentrated powder form of a drug such as cocaine or heroin and rapidly sniff the drug into the nostril. This causes deposition of the powder onto the nasal mucosa and rapid transfer of the drug into the circulation and brain. This technique requires an experienced and cooperative user and is unlikely to be effective in medical therapeutic situations.

Drug Delivery as drops using a Syringe or Dropper: A second method of intranasal drug delivery is to take a solubilized medication (liquid form) and drip it into the nose a few drops at a time, allowing it to run down onto the nasal mucosa. This can be done using a syringe or in some instances using the packaged form of the medication to drip it directly into the nose. To use this technique, most generic medications will need to be removed from within their storage bottle using a syringe. The syringe can then act as the measuring/dosing device as well as the dropper.

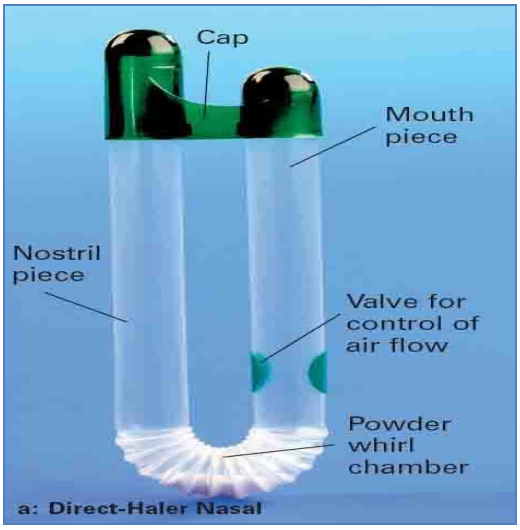
Sprayed or Atomized Medication Delivery: Sprayed or atomized intranasal medication delivery is a more recent technique adopted by the pharmaceutical industry due to improved usability issues as well as improved bioavailability data. This delivery technique

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 [5-7].

Furthermore, the usability 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 / atomized as a mist, less is likely to be blown back out 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 devices (atomizers) now exist for delivery of a variety of generic nasal medications.

TYPES OF ATOMISERS:

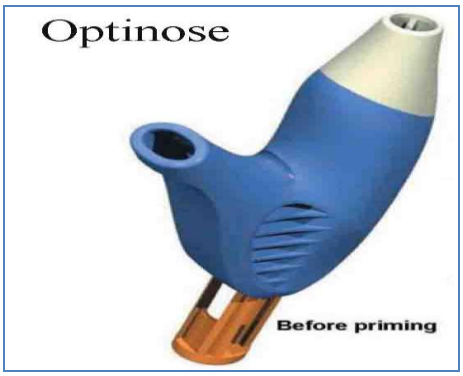
ACCUSPRAY NASAL ATOMIZER



DIRECT-HALER POWDER DRUG NASAL DELIVERY

MAD (MUCOSAL ATOMIZATION DEVICE) NASAL

OptiNose is developing devices for nasal delivery of vaccines and drugs with topical or systemic action. OptiNose manipulates the particle size and aerodynamics and results in widespread delivery of the drug over the entire nasal mucosa and minimizing inhalation of small particles into the lungs.



VIANASE ELECTRONIC ATOMIZER

Nebulized versus Atomized: Nebulized medications as a method to delivery systemic drugs. While the lung has a large absorptive surface area, there are several problems with this delivery method for routine systemic and CNS delivery of drugs. First, nebulizers deliver very little drug to the actual target tissue (the lung) - most is lost into the environment, some to the relatively non-absorptive tissue between the oral opening and the alveoli and very little actually reaches the end destination. More concerning is the unknown toxicity.

While a drug that irritates the nasal mucosa is not optimal, it is also probably not outright dangerous especially if used on occasion. A drug that damages lung tissue is an entirely different matter and practitioners should be hesitant to deliver a drug to the pulmonary tissue until and unless they are sure it is safe. Finally and certainly of significant importance to most of the indications discussed for nasal drug delivery on this web site is the length of time it takes to nebulize a medication (many minutes) to the time it takes to atomize the same volume (1-2 seconds). In conclusion the requirements for ideal nasal drug delivery devices includes [8];

- Accurate and repeatable dosing
- Consistent delivery to the optimal site of action
- Protection for preservative free formulations in multidose presentations
- Patient independent actuation
- Compliance monitors and aids

APPLICATIONS [9-10]:

- Delivery of non-peptide pharmaceuticals
- Delivery of peptide-based pharmaceuticals
- Delivery of diagnostic drugs

Delivery of Non- Peptide Pharmaceuticals: Drugs with extensive pre-systemic metabolism, such as progesterone, estradiol, propranolol, nitroglycerin and sodium chromoglyate can be rapidly absorbed through the nasal mucosa with a systemic bioavailability of approximately 100%.

Delivery of peptide-based pharmaceuticals: Peptides & proteins have a generally low oral bioavailability because of their physico-chemical instability and susceptibility to hepato-gastrointestinal first-pass elimination e.g., Insulin, Calcitonin, Pituitary hormones etc. Nasal route is proving to be the best route for such biotechnological products

3. Delivery of diagnostic:

- Phenol sulfonaphthalein- kidney function
- Secretin- pancreatic disorders
- Pentagastrin- secretory function of gastric acid

CONCLUSION: Considering the widespread interest in nasal drug delivery and the potential benefits of intranasal administration, it is expected that novel nasal products will continue to reach the market. They will include not only drugs for acute and long term diseases, but also novel nasal vaccines with better local or systemic protection against infections. The development of drugs for directly target the brain in order to attain a good therapeutic effect

in CNS with reduced systemic side effects is feasible.

However, it was also stated that intranasal route presents several limitations which must be overcome to develop a successful nasal medicine. Physiological conditions, physicochemical properties of drugs and formulations are the most important factors determining nasal drug absorption. The use of prodrugs, enzymatic inhibitors, absorption enhancers, mucoadhesive drug delivery systems and new pharmaceutical formulations are, nowadays, among the mostly applied strategies. Each drug is one particular case and, thus, the relationship between the drug characteristics, the strategies considered and the permeation rate is essential. The era of nasal drug delivery is growing. However, new efforts are needed to make this route of delivery more efficient and popular.

The nasal route is generating increasing interest as a route for the administration of local treatments and a cost-effective and patient-friendly alternative to injection for systemic delivery .The special advantages of nasal delivery make it attractive for (i) crisis treatment where rapid onset of action is desirable (e.g., pain, migraine, panic attacks), (ii) systemic delivery of compounds that at present can only be delivered by injection (peptides=pro-Proteins=vaccination), and (iii) direct targeting of the CNS (polar drugs for the treatment of CNS disorders).

To take full advantage of these opportunities offered by nasal delivery, innovative approaches to overcome the biological barriers to delivery are being developed. Advances in formulation design, nasal delivery systems, penetration enhancers, enzyme inhibitors, and bioadhesive polymers require an understanding of the biological barriers that they seek to overcome. Furthermore, appropriate models in which to evaluate new delivery strategies are required. These should be capable of identifying any toxic effects of formulations or excepients, while avoiding misleading results brought about by poor experimental design or model selection. In vitro optimization should be undertaken to explore fully fundamental concepts and optimize formulations prior to in vivo testing, thereby improving the chances of success and complying with the ethical principles of replacement, refinement, and reduction of animal experimentation.

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