A RECENT REVIEW ON ALTERNATIVE SYSTEM OF PARENTERAL DELIVERY: NASAL DRUG DELIVERY SYSTEM.

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ABSTRACT

In modern pharmaceutics, the nose had been considered primarily as a route for local drug delivery. Nasal drug delivery for systemic effects has been practiced since ancient times. Nose is the important part of body for inhalation process. But when it is used as the route of drug delivery, attained the great attraction for various drugs because nose provides faster and higher level of drug absorption with possibility of self-administration. Hydrophobic and low molecular drugs can easily penetrate through nasal mucosa with less degradation. Fast absorption can be achieved due to large absorption surface area and high vascularisation. In emergency nasal route can be used as alternative route of parenteral. This review provide an overview of the complete information about nasal drug delivery system such as anatomy and of nose, advantage, limitations, mechanism of drug absorption, factors affecting of nasal drug delivery, absorption improvement aspects, types of nasal drug delivery system and evaluation of nasal drug delivery system.

KEYWORDS: Nose, Parenteral, Nasal Delivery, Absorption

INTRODUCTION

Therapy through intranasal administration has been an accepted form of treatment in the Ayurvedic system of Indian Medicine. In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route than by oral administration (1).

Even though a number of challenges are still to be overcome, especially with respect to toxicity, the potential of nasal drug delivery (NDD), including the ability to target drugs across the blood–brain barrier (BBB), are very high and continues to stimulate academic and industrial research groups so that we will keep witnessing increasing number of advanced nasal drug delivery products. To optimize nasal administration, bioadhesive hydrogels, Bioadhesive microspheres (dextran, albumin and degradable starch) and liposomes have been studied (2).

Many nasal products for the topical treatment of conditions such as rhinitis and sinusitis have of course been marketed for decades. More recently, several systemic nasal formulations of, for example, hormones, vaccines and compounds for the treatment of migraine, have also reached the market – and more still are progressing through clinical development.

As Michael Sheckler of Javelin Pharmaceuticals (formerly IDDS) reports herein, Greystone Associates predicts that the nasal drug delivery market will enjoy annual growth of 24% between 2004 and 2007, increasing the market value from around US$2 billion to US$4.3 billion (3).

AN ADVANCED ORGAN WITH MANY FUNCTIONS: NOSE:

The nasal passages are complex aerodynamic structures optimized during evolution to protect the lower airways. Specifically, large particles (>5-10μm) are efficiently filtered out, and infective agents are presented to the abundant nasal immune system. The inspired air has

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to be warmed and moistened, within fractions of a second, to transform cold winter air into conditions more reminiscent of a tropical summer. Last, but not least, the nose is a delicate sensory organ designed to provide us with the greatest pleasures, but also to warn and protect us against dangers. The functionality of the nose is achieved by its structure and the complex, narrow nasal geometry. Amazingly, the relatively short air-path in the nose accounts for half of the total airway resistance during inhalation. In the nasal valve (the anterior triangular narrow segments in the nose) the flow rate can approach the speed of a hurricane. Beyond the nasal valve is a much larger space divided into slit-like passages by the nasal turbinates. Here the airflow is slowed down and disrupted, allowing close contact between the air and the mucosa. It is this close contact that enables effective filtering and conditioning of the inspired air. Imagine leaves blowing in the wind through a narrow alleyway; the leaves will pile up behind edges and behind the corners at the exit of the alleyway. A similar process happens in the nose. Particles are deposited on the mucosa behind the valve from where the mucociliary transport mechanism carries them backwards to eventually be swallowed. Figure 1 showing the anatomy of Nose (4, 5).

Figure 1: Anatomy of nose (6).

PHYSIOLOGY OF NOSE:

The nasal physiologic functions, such as warming and humidification, are vital for upper airway function. It has been estimated that an adult inspires up to 10,000 liters of air daily. Nasal breathing is healthy breathing as the air is treated in many ways by the structures of the nose, paranasal sinuses and the peculiarities of their lining mucosa.

A. Filtering the air

Filtration of environmental particles occurs first in the nasal cavity. Nasal mucus traps incoming particulate matter. The largest particles are filtered by nasal hairs (vibrissae).

B. Moistening the air

Humidification is another important process of nasal physiology. The nasal cavity is covered with a highly vascular mucosa that warms and humidifies incoming air, increasing the relative humidity to 95% before air reaches the nasopharynx.

C. Warming the air

Inhaled air must have a temperature between at least 33 and 35 degree Celsius to not cause pathological reactions at the level of the alveoli. Again, by the turbulence, the cold air is forced to make contact with the warm surface of the mucosa and thus heated during its passage. A number of nasal neurovascular reflexes occur as well. If needed, underlying capillaries will dilate and warm up the upper laying mucosa, giving more heat to the passing air.

D. The sense of smell

Nasal aerodynamics also contributes to the olfactory system. In addition, the active process of sniffing allows environmental particles to reach the olfactory system located at the skull base. Even the smallest particles are detected by the olfactory receptors, warning us about danger, food, or any other biologically meaningful sign detectable through the sense of smell.

E. The nasal cavity as a sound box
The nose and sinuses serve as contributing factors in voice modification. Authors have noted that nasal aerodynamics may have a role in modifying high frequency sounds and consonants. The resonance created within the nasal cavity is characteristic, similar to a fingerprint and for each person is different (except in identical twins). Nasal pathologies such as polyps or rhinitis will directly influence the resonance spectrum and we will “hear” that the person has a cold or something has changed in his/her voice (2, 6).

**ADVANTAGES:**

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<th>Sr. No.</th>
<th>Advantages</th>
<th>Factors</th>
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<tr>
<td>1.</td>
<td>Improving patient compliance</td>
<td>Needle free (painless)</td>
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<td></td>
<td></td>
<td>Trained person not required</td>
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<td>2.</td>
<td>Good penetration</td>
<td>In case of lipophilic drugs,</td>
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<td></td>
<td></td>
<td>In case of low molecular weight</td>
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<td>3.</td>
<td>rapid absorption and onset of action</td>
<td>Due to relative large surface area</td>
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<td></td>
<td></td>
<td>High vascularisation</td>
</tr>
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<td>4.</td>
<td>Avoidance of the harsh environment</td>
<td>less chemical and enzymatic degradation</td>
</tr>
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<td>5.</td>
<td>low dose required</td>
<td>Free from first pass metabolism</td>
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<td>6.</td>
<td>Direct delivery of drug to central nervous system</td>
<td>Via olfactory region, thus bypass the blood brain barrier</td>
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**LIMITATIONS:**

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<th>Sr. No.</th>
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<th>Factors</th>
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<tr>
<td>1.</td>
<td>Risk of local side effect and irreversible damage of cilia on nasal mucosa</td>
<td>Due to constituents added to dosage forms</td>
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<td>2.</td>
<td>Disrupt and even dissolve the nasal membrane</td>
<td>Due to high concentration of absorption enhancers</td>
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<td>3.</td>
<td>Reduce the capacity of nasal absorption</td>
<td>Due to nasal atrophic rhinitis and severe vasomotor rhinitis</td>
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<td>4.</td>
<td>Low bioavailability</td>
<td>Due to enzymatic degradation and metabolism at mucosal surface.</td>
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**MECHANISM OF NASAL DRUG ABSORPTION:**

Several mechanisms have been proposed but the following two mechanisms have been considered predominantly.

- The first mechanism involves an aqueous route of transport, which is also known as the paracellular route. This route is slow and passive. There is an inverse log-log correlation between intranasal absorption and the molecular weight of water-soluble compounds. Poor bioavailability was observed for drug with a molecular weight greater than 1000 Daltons.

- The second mechanism involves transport through a lipoidal route is also known as the transcellular process and is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. For examples, chitosan, a natural biopolymer from shellfish, opens tight junctions between epithelial cells to facilitate drug transport (1).

**FACTORS AFFECTING NASAL DRUG ABSORPTION:**

The factors influencing nasal drug absorption are as follows:

1. Physiochemical properties of drug.
• Molecular size.
• Lipophilic-hydrophilic balance.
• Enzymatic degradation in nasal cavity.

2. Nasal Effect
   • Membrane permeability.
   • Environmental pH
   • Mucociliary clearance
   • Cold, rhinitis.

3. Delivery Effect
   • Formulation (Concentration, pH, osmolarity)
   • Delivery effects
   • Drugs distribution and deposition.
   • Formulation effect on mucociliary clearance.
   • Toxic effect on ciliary function and epithelial membranes (1, 11).

**ABSORPTION ENHANCEMENT:**
Factors that affect the delivery of drug across nasal mucosa such as surfactants, dose pH, osmolality, viscosity, particle size and nasal clearance, drug structure can be used to advantage to improve absorption.

1. **DRUG CONCENTRATION, DOSE AND DOSE VOLUME:**
   Drug concentration, dose and volume of administration are three interrelated parameters that impact the performance of the nasal delivery performance. Nasal absorption of L-Tyrosine was shown to increase with drug concentration in nasal perfusion experiments. However, in another study, aminopyrine was found to absorb as a function of concentration. In contrast, absorption of salicylic acid was found to decline with concentration. This decline is likely due to nasal mucosa damage by the permanent.

2. **FORMULATION PH:**
   The pH of a nasal formulation is important for the following reasons:
   • To avoid irritation of nasal mucosa.
   • To allow the drug to be available in unionized form for absorption.
   • To prevent growth of pathogenic bacteria in the nasal passage.
   • To maintain functionality of excipients such as preservatives.
   • To sustain normal physiological ciliary movement. 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. It is therefore advisable to keep the formulation at a pH of 4.5 to 6.5 keeping in mind the physiochemical properties of the drug as drugs are absorbed in the unionized form.

3. **BUFFER CAPACITY:**
   Nasal formulations are generally administered in small volumes ranging from 25 to 200μL with 100 μL being the most common dose volume. Hence, nasal secretions may alter the pH of the administered dose. This can affect the concentration of unionized drug available for absorption. Therfore, an adequate formulation buffer capacity may be required to maintain the pH in situ.

4. **GELLING/VISCOFYING AGENTS OR GEL-FORMING CARRIERS:**
   According to various studies, increasing solution viscosity may provide means of prolonging the therapeutic effect of nasal preparations. A drug carrier such as hydroxypropyl cellulose was effective for improving the absorption of low molecular weight but did not produce the same effect for high molecular weight peptides. Use of a combination of carriers is often recommendation from a safety (nasal irritancy) point of view.

5. **SOLUBILISERS:**
   Aqueous solubility of drug is always a limitation for nasal drug delivery in solution conventional solvents such as glycols, small quantities of alcohol, Transcutol (diethylene glycol monoethyl ether), medium chain glycerides and Labrasol (saturated polyglycolyzed C₈-C₁₀ glycerides) can be used to enhance the solubility of drugs. Other options include the use of surfactants or cyclodextrins such as HP-β-cyclodextrin that serve as a biocompatible solubilizer and stabilizer in combination with lipophilic absorption enhancers. In such cases, their impact on nasal irritancy should be considered.

6. **PRESERVATIVES:**
   Most nasal formulations are aqueous based and need preservatives to prevent microbial growth. Parabens, benzalkonium chloride, phenyl ethyl alcohol, EDTA and benzoyl alcohol are some of the commonly used preservatives in nasal formulations.

7. **ANTIOXIDANTS:**
   A small quantity of antioxidants may be required to prevent drug oxidation. Commonly used antioxidants are sodium metabisulphite, sodium bisulfite, butylated hydroxytoluene and tocopherol. Usually, antioxidants do not affect drug absorption or cause nasal irritation. Chemical/physical interaction of antioxidants and
preservatives with drugs, excipients, manufacturing equipment and packaging components should be considered as part of the formulation development program (1, 11).

STRATEGIES FOR IMPROVING DRUG AVAILABILITY IN NASAL DELIVERY:

Various strategies used to improve the availability of the drug in the nasal mucosa include:
1. To improve the nasal residence time
2. To enhance nasal absorption
3. To modify drug structure to change physicochemical properties

1. TO IMPROVE THE NASAL RESIDENCE TIME:

Mucociliary clearance acts to remove the foreign bodies and substances from nasal mucosa as quickly as possible. One way of delaying clearance is to apply the drug to the anterior part of the nasal cavity, an effect that is largely determined by the type of dosage form used. The preparation could also be formulated with polymers such as methylcellulose, hydroxy propyl methyl cellulose or polyacrylic acid, in which incorporation of polymer increases viscosity of the formulation and also acts as a bioadhesive with mucus. Increase in residence time does not necessarily lead to increase the absorption; this concept can be illustrated by considering insulin solution with similar viscosity containing carbopol and CMC. Here carbopol enhance the absorption whereas CMC solution doesn’t enhance the absorption of insulin. If we increase the viscosity, slow diffusion of drug from matrix causes retention in absorption with CMC. In case of carbopol causes enhancement of absorption due to opening the intracellular junctions. One more lucrative way to increase the nasal residence time is using biodegradable microspheres as a carrier for drug delivery. Biodegradable microspheres swell in presence of water thereby increasing the viscosity. This phenomenon leads to increase the nasal residential time.

2. ENHANCING NASAL ABSORPTION:

The mechanism of action of absorption enhancer is increasing the rate at which drug passes through the nasal mucosa. Many enhancers act by altering the structure of epithelial cells in some way, but they should accomplish this while causing no damage or permanent change to nasal mucosa. General requirement of an ideal penetration enhancer are as follows:
- It should not cause permanent damage or alteration to the tissue
- It should be nonirritant and nontoxic
- It should lead to an effective increase in the absorption of the drug
- It should be compatible with other excipients.
- The enhancing effect should occur when absorption is required
- It should be effective in small quantity
- The effect should be temporary and reversible

CLASSIFICATION OF PENETRATION ENHANCER:

Chemical penetration enhancers are widely used in the nasal drug delivery. Classification of chemical penetration enhancer includes, following

- Solvents
- Surfactants.
- Pyrrolidones
- 1- Dodecyl azacycloheptan-2-one
- Alkyl methyl sulphoxides

3. MODIFYING DRUG STRUCTURE:

Modification of drug structure without altering pharmacological activity is one of the lucrative ways to improve the nasal absorption. Here modification of physiochemical properties such as molecular size, molecular weight, pKa and solubility, are favorable for nasal drug absorption (1, 12).

FORMULATION DEVELOPMENT RESEARCH IN NASAL DRUG DELIVERY:

Most of the over the counter nasal preparation are formulated as solution, to treat the nasal symptoms of allergic rhinitis and common cold. A simple drug solution is adequate for this purpose as it produces better dispersion over greater surface area. The nasal residence time of such formulation is short (3-20 min) and exhibit high inter individual variability. This route provides fast peak levels in circulation. Large number of drugs has been evaluated for systemic bioavailability after transnasal administration in experimental animal models. Transnasal administration of drugs in diverse dosage forms such as sprays, powders, and microspheres has been attempted for improved residence and bioavailability. The nasal delivery is receiving attention for management of postoperative pain; mucosal administration requires only a 1.1-1.5 time higher dose of fentanyl than i.v. dose. The nasal delivery of vaccines is a very attractive route of administration in terms of efficacy (1, 13).

TYPE OF NASAL DRUG DELIVERY SYSTEMS:

The selection of delivery system depends upon the drug being used, proposed indication, patient population
and last but not least, marketing preferences. Some of these delivery systems and their important features are summarized below:

1. NASAL DROPS:
   Nasal drops are one of the most simple and convenient systems developed for nasal delivery. The main disadvantage of this system is the lack of the dose precision and therefore nasal drops may not be suitable for prescription products. It has been reported that nasal drops deposit human serum albumin in the nostrils more efficiently than nasal sprays.

2. 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 from 25 to 200 μm. The particles size and morphology (for suspensions) of the drug and viscosity of the formulation determine the choice of pump and actuator assembly.

3. NASAL GELS:
   Nasal gels are high-viscosity thickened solutions or suspensions. Until the recent development of precise dosing device, there was not much interest in this system. The advantages of a nasal gel includes the reduction of post-nasal drip due to high viscosity, reduction of taste impact due to reduced swallowing, reduction of anterior leakage of the formulation, reduction of irritation by using soothing/emollient excipients and target to mucosa for better absorption.

4. NASAL POWDER:
   This dosage form may be developed if solution and suspension dosage forms cannot be developed e.g., due to lack of drug stability. The advantages to the nasal powder dosage form are the absence of preservative and superior stability of the formulation. However, the suitability of the powder formulation is dependent on the solubility, particles size, aerodynamic properties and nasal irritancy of the active drug and /or excipients. Local application of drug is another advantage of this system.

5. LIPOSOMES:
   These are phospholipid vesicles composed by bilayer enclosing one or more aqueous compartments, in these compartments drug can be entrapped or adsorbed.

6. MICROSPHERES:
   Microsphere has important role in nasal drug delivery with enhance absorption, sustained release, and also has great importance because it protects drug from enzymatic degradation (1, 9).

EVALUATION OF NASAL FORMULATIONS:

1. IN VITRO NASAL PERMEATION STUDIES:
   Various approaches used to determine the drug diffusion through nasal mucosa from the formulation. The two important methodologies to study the diffusion profile of the drug are discussed below.

IN VITRO DIFFUSION STUDIES:
   The nasal diffusion cell is fabricated in glass. The water-jacketed recipient chamber has total capacity of 60 ml and a flanged top of about 3 mm; the lid has 3 opening, each for sampling, thermometer, and a donor tube chamber. The 10 cm long donor chamber, and a donor tube chamber has total capacity of 60 ml and a flanged top of about 3 mm; the lid has 3 openings, each for sampling, thermometer, and a donor tube chamber the 10 cm long donor chamber tube has internal diameter of 1.13 cm. The nasal mucosa of sheep was separated from sub layer bony tissues and stoned in distilled water containing few drops at genatamycin injection. After the complete removal of blood from muscosal surface, is attached to donor chamber tube. The donor chamber tube is placed such a way that it just touches the diffusion medium in recipient chamber. At predetermined intervals, samples (0.5 ml) from recipient chamber are drawed and transferred to amber colored ampoules. The samples withdrawn are suitably replaced. The samples are estimated for drug content by suitable analytical technique. Throughout the experiment the temperature is maintained at 37°C (14, 15).

2. IN VIVO NASAL ABSORPTION STUDIES:
   ANIMAL MODELS FOR NASAL ABSORPTION STUDIES:
   The animal models employed for nasal absorption studies can be of two types, viz., whole animal or in vivo model and an isolated organ perfusion or ex vivo model.
   In vivo models are Rat model, Rabbit model, monkey model and dog model.

EX VIVO NASAL PERFUSION MODELS:
   Surgical preparation is the same as that is for in vivo rat model. During the perfusion studies, a funnel is placed between the nose and reservoir to minimize the loss of drug solution. The drug solution is placed in a reservoir maintained at 37°C and is circulated through the
nasal cavity of the rat with a peristaltic pump. The perfusion solution passes out from the nostrils (through the funnel) and runs again into the reservoir. The drug solution in the reservoir is continuously stirred. The amount of drug absorbed is estimated by measuring the residual drug concentration in the perfusing solution. The drug activity due to stability problems may be lost during the course of experiment. This is especially true for peptide and protein drugs that may undergo proteolysis and aggregation. Rabbit can also be used as the animal model for ex vivo nasal perfusion studies. The rabbit is anaesthetized with parenteral urethane-acepromazine. A midline incision is made in the neck and the trachea is cannulated with a polyethylene neonatal endotracheal tube. The oesophagus is isolated and ligated. The distal end of the oesophagus is closed with suture and flexible tygon tubing is inserted into the proximal end and advanced to the posterior part of the nasal cavity. The nasopalatine tract (that connects nasal cavity to the mouth) is closed with an adhesive to avoid drainage of drug solution from the nasal cavity. The drug in isotonic buffer solution is recirculated using a peristaltic pump (1, 16).

CONCLUSION:

In present era, nasal drug delivery system has been considered as potential and favorable route of drug delivery because it provides patient compliance, easy to administration, bypass first pass metabolism, excellent penetration, low dose required, rapid absorption and gives desirable effects. By using any of the mechanisms proposed, this route holds future potential for numerous drugs through the development of safe and efficacious formulations which would be useful for a simple, painless and long-term therapy. It is very likely that in the near future more drugs will come in the market intended for systemic absorption in the form of nasal formulation.

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