

Formulation and Device Design to Increase Nose to Brain Drug Delivery System

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Abstract- Nasal drug delivery has received a great deal of attention as a convenient, reliable, and promising method for the systemic administration of drugs. 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.

It is especially for those molecules which are ineffective orally and only effective if administered by injection.

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.

This review sets out to discuss some factors affecting nasal absorption, bio-availability barriers, strategies to improve nasal absorption, new developments in nasal dosage form design and applications of nasal drug delivery system.

Index terms- Nose, Nasal drug delivery systems, Nose to Brain

INTRODUCTION

In recent time, the nasal drug delivery received a great deal of attention for its convenient, promising, and reliable way of systemic administration for drugs, especially for those drugs which are ineffective orally and those which must be administered by injections. This route provides a large surface area, porous endothelial membrane, high total blood flow, bypassing the first-pass

metabolism, and ready accessibility. Furthermore, nasal mucosa is permeable to more compounds than the gastrointestinal tract due to the absence of pancreatic, gastric enzymatic activities, and interference by gastrointestinal contents. In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route than by oral administration. Nasal therapy, has been recognized form of treatment in the Ayurvedic systems of Indian medicine, it is also called "NASAYA KARMA" (Chien YW et al., 1989).

In therapeutics, nose forms an important part of the body for faster and higher level of drug absorption with the possibility of self-administration. Drugs are ranging from small micromolecules to large macromolecules such as peptide/proteins, hormones, and vaccines, are being delivered through the nasal cavity. It is reported that lipophilic drugs are generally well absorbed from the nasal cavity with pharmacokinetic profiles often identical to those obtained following an intravenous injection with a bioavailability approaching up to 100% in many cases.

For many years drugs have been administered nasally for both topical and systemic action. Topical administration includes the treatment of congestion, rhinitis, sinusitis and related allergic or chronic conditions, and has resulted in a variety of different medications including corticoids, antihistamines, anti-cholinergic and vasoconstrictors. In recent years, increasing investigations of the nasal route have focused especially on nasal application for systemic drug delivery.

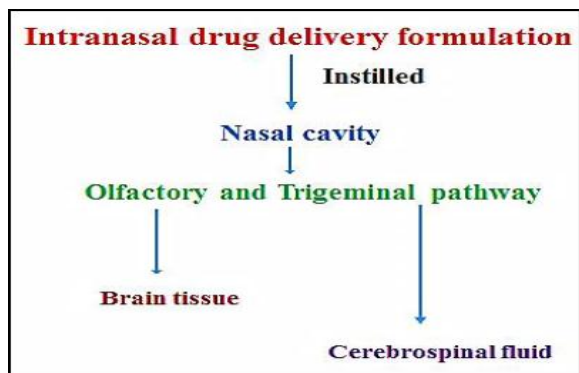


Fig. 1. Drug instillation to the nasal cavity

Only a few nasal delivery systems used in experimental studies are currently on the market to deliver therapeutics into the nasal cavities, i.e. nasal drops as multiple or single-dose formulation, aqueous nasal sprays, a nasal gel pump, pressurized MDIs and dry powder inhalers. Intranasal delivery is currently being employed in treatments for migraine, smoking cessation, acute pain relief, osteoporosis, nocturnal enuresis and vitamin-B12 deficiency. Other examples of therapeutic areas under development or with potential for nasal delivery include cancer therapy, epilepsy, anti-emetics, rheumatoid arthritis and insulin-dependent diabetes.

This review article provides a brief overview of the advantages and limitations of nasal drug delivery system and anatomy of nasal cavity, mechanism of nasal absorption, barriers to nasal absorption, strategies to improve nasal absorption, nasal drug delivery formulation issues and applications of nasal drug delivery systems.

The systemic circulation using nasal drug delivery was as follows:

1. Hepatic first-pass metabolism is avoided.
2. Improving patient compliance compared to parenteral routes as easy accessibility and needle-free drug application without the presence of trained personnel facilitates self-medication.
3. Drug degradation that is observed in the gastrointestinal tract can be bypass.
4. Using absorption enhancer, the bioavailability of large drug molecules can be improved through nasal route.
5. Rapid drug absorption and quick onset of action can be achieved easily.
6. Bioavailability though nasal route for smaller drug molecules is good.

7. Drug possessing poor stability in GIT fluids is given by nasal route.
8. Studies reveal that the nasal route is an alternate to parenteral route, especially, for protein and peptide drugs.
9. A polar compound exhibiting poor oral absorption may be particularly suited for this route of delivery.
10. Convenient for the patients, especially for those on long-term therapy, when compared with parenteral medication.

ADVANTAGES

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 GIT fluids are given by nasal route.
10. Polar compounds exhibiting poor oral absorption may be particularly suited for this route of delivery.

DISADVANTAGES

1. The nasal cavity provides a smaller absorption surface area when compared to gastrointestinal tract.
2. There is a possibility of irritation when compared to the oral delivery system since.
3. The substance and constituents added to the dosage form may cause local side effects and irreversible damage of the cilia on the nasal mucosa.

4. There could be a mechanical loss of the dosage form into the other parts of the respiratory tract like lungs due to the improper technique of administration.
5. Certain surfactants used as chemical enhancers may disrupt and even dissolve the membrane in high concentration.

LIMITATIONS

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.

ANATOMY & PHYSIOLOGY OF NASAL CAVITY

The nasal cavity is divided into two halves by the nasal septum and extends posterior to the nasopharynx, while the most anterior part of the nasal cavity, the nasal vestibule, opens to the face through the nostril. The nasal cavity consists three main regions are nasal vestibule, olfactory region and respiratory region. The surface area in the nose can be enlarges about 150cm² by the lateral walls of the nasal cavity includes a folded structure, it is a very high surface area compared to its small volume. This folded structure consists of three turbinate's: the superior, the median and the inferior (Michael et al., 2005).The main nasal airway having the narrow passages, usually it has 1-3mm wide and these narrows structures are useful to nose to carry out its main functions.

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, where as respiratory region, which has a typical airways epithelium covered with numerous microvilli, resulting in a large surface area available for drug absorption and transport (Sarkar MA, 1992). In this way the mucus layer is propelled in a direction from the anterior to-wards the posterior part of the nasal cavity. The goblet cells are present in the mucus membrane which covers the nasal turbinate and the atrium; it secretes the mucus as mucus granules which are swelling in the nasal fluid to contribute to the mucus layer.

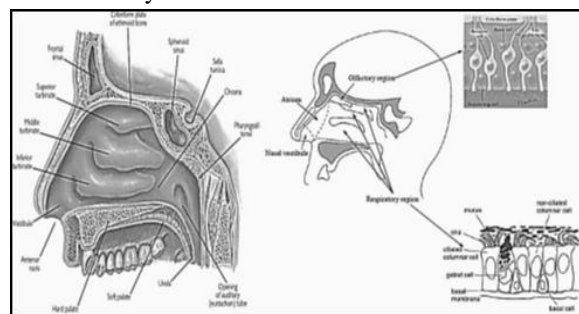


Fig. 2. Anatomy of Nose and Distinct functional areas of nasal cavity

The mucus secretion is composed of about 95% water, 2 % mucin, 1% salts, 1% of other proteins such as albumin, immunoglobulin s, lysozyme and lactoferrin, and b 1% lipids (Kaliner M et al., 1984). The mucus secretion gives immune protection against inhaled bacteria and viruses. It also performs a number of physiological functions.

1. It covers the mucosa, and physically and enzymatically protects it.
2. The mucus has water-holding capacity.
3. It exhibits surface electrical activity.
4. It permits efficient heat transfer.
5. It acts as adhesive and transport s particulate matter towards the nasopharynx.

MECHANISM OF NASAL DRUG ABSORPTION

Two mechanisms have been considered predominantly out of several mechanisms that have been proposed. The first involves an aqueous route of transport, which is also known as the paracellular route. Key feature of this mechanism involves

- 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 a drug with a molecular weight greater than 1000 Daltons

The second 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.

FACTORS INFLUENCING NASAL DRUG ABSORPTION

Several factors affect the systemic bioavailability of drugs which are administered through the nasal route. The factors can be affecting to the physiochemical properties of the drugs, the anatomical and physiological properties of the nasal cavity and the type and characteristics of selected nasal drugs delivery system. These factors play key role for most of the drugs in order to reach therapeutically effective blood levels after nasal administration. The factors influencing nasal drug absorption are described as follows.

1. Physiochemical properties of drug.
 - a. Molecular size.
 - b. Lipophilic-hydrophilic balance.
 - c. Enzymatic degradation in nasal cavity.
2. Nasal Effect
 - a. Membrane permeability.
 - b. Environmental pH
 - c. Mucociliary clearance
 - d. Cold, rhinitis.
3. Delivery Effect
 - a. Formulation (Concentration, pH, osmolarity)
 - b. Delivery effects
 - c. Drugs distribution and deposition.
 - d. Viscosity

1) Physiochemical properties of drug

Molecular size

The molecular size of the drug influence absorption of the drug through the nasal route. The lipophilic drugs have direct relationship between the MW and

drug permeation whereas water- soluble compounds depict an inverse relationship. The rate of permeation is high-ly sensitive to molecular size for compounds with $MW \geq 300$ Daltons.

Lipophilic-hydrophilic balance

The hydrophilic and lipophilic nature of the drug also affects the process of absorption. By increasing lipophi-licity, the permeation of the compound normally in-creases through nasal mucosa. Although the nasal mu-cosa was found to have some hydrophilic character, it appears that these mucosae are primarily lipophilic in nature and the lipid domain plays an important role in the barrier function of these membranes. Lipophilic drugs like naloxone, buprenorphine, testosterone and 17a-ethinyl-oestradiol are almost completely absorbed when administered intranasal route.

Enzymatic degradation in nasal cavity

In case of peptides and proteins are having low bio-availability 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 exopeptidases and endopeptidases, exopeptidases are monoaminopeptidases and diaminopeptidases. 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.

2) Nasal effect factors

Membrane permeability

Nasal membrane permeability is the most important factor, which affect the absorption of the drug through the nasal route. The water soluble drugs and particularly large molecular weight drugs like peptides and proteins are having the low membrane permeability. So the compounds like peptides and proteins are mainly absorbed through the endocytotic transport process in low amounts (Inagaki M et al., 1985). Water-soluble high molecular weight drugs cross the nasal mucosa mainly by passive diffusion through the aqueous pores (i.e. tight junctions).

Environmental pH

The environmental pH plays an important role in the efficiency of nasal drug absorption. Small water-

soluble compounds such as benzoic acid, salicylic acid, and alkaloid acid show that their nasal absorption in rat occurred to the greatest extent at those pH values where these compounds are in the nonionised form. However, at pH values where these compounds are partially ionized, substantial absorption was found. This means that the nonionised lipophilic form crosses the nasal epithelial barrier via transcellular route, whereas the more lipophilic ionized form passes through the aqueous paracellular route.

Mucociliary clearance

Mucociliary clearance is a one of the functions of the upper respiratory tract is to prevent noxious substances (allergens, bacteria, viruses, toxins etc.) from reaching the lungs. When such materials adhere to, or dissolve in, the mucus lining of the nasal cavity, they are transported towards the nasopharynx for eventual discharge into the gastrointestinal tract. Clearance of this mucus and the adsorbed/dissolved substances into the GIT is called the MCC. This clearance mechanism influence the absorption process due to the dissolved drugs in the nasal cavity are discharge by the both the mucus and the cilia, which is the motor of the MCC and the mucus transport rate is 6 mm/min. It is of utmost importance that the MCC is not impaired in order to prevent lower respiratory tract infections.

Cold, rhinitis

Rhinitis is a most frequently associated common disease, it influence the bioavailability of the drug. It is mainly classified into allergic rhinitis and common, the symptoms are hyper secretion, itching and sneezing mainly caused by the viruses, bacteria or irritants. Allergic rhinitis is the allergic airway disease, which affects 10% of population. It is caused by chronic or acute inflammation of the mucous membrane of the nose. These conditions affect the absorption of drug through the mucus membrane due the inflammation.

3) Delivery effect factors

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

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.

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 affect 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.

Viscosity

A higher viscosity of the formulation increases contact time between the drug and the nasal mucosa thereby increasing the time for permeation. At the same time, highly viscous formulations interfere with the normal functions like ciliary beating or mucociliary clearance and thus alter the permeability of drugs.

STRATEGIES FOR IMPROVING DRUG AVAILABILITY IN NASAL DELIVERY

Various strategies used to improve the availability of the drug in the nasal mucosa include:

1. Nasal residence time improvement
2. Nasal absorption enhancement
3. Modification of drug structure to change its physicochemical properties.

Nasal enzyme inhibitors

Nasal metabolism of drugs can be eliminated by using the enzyme inhibitors. Mainly for the formulation of proteins and peptide molecule development enzyme inhibitors like peptidases and proteases are used (Hus-sain MA et al., 1990). The absorption enhancers like salts and fusidic acid derivatives also shows enzyme inhibition activity to increase the absorption and bio-availability of the drug (Donnelly A et al., 1998). The other enzyme inhibitors commonly used for the enzymatic activity are trypsin, aprotinin, borovaline, amas-tatin, bestatin and boroleucin inhibitors.

Nasal Delivery Devices

Nasal drug delivery devices are versatile tool for direct drug delivery in nasal cavity by using various nasal devices. The nasal devices include Powder formulation devices and liquid Formulation devices. Liquid formulations currently completely dominate the nasal drug Market, but nasal powder formulations and devices do exist, and more are in development.

Powder formulation devices

The powder nasal devices are more convenient and it is having a maximum stability than liquid nasal devices. In powder nasal devices preservatives are not required for preparation. It is having a larger dose of drug and they improve stability of formulation. They can be free from microbial growth. The nasal

powder administration is increases the patient compliances and patient acceptance. Nasal powder devices are applicable for the number of proteins, peptides and non-peptide pharmaceutical molecules. Powder-polymer complex formulation allows easy or convenient approach to nasal delivery of drugs.

Insufflators

In this nasal devices, (Fig.3) to deliver the pharmaceutical molecule for inhalation. This device is mainly constructed in the straw or tubes which contains the pharmaceutical molecules. It is a pre-dose powder capsules.

Dry powder inhaler

Dry powder inhalers (DPIs) (Fig.3) are devices through which a dry powder formulation of an active drug is delivered for local or systemic effect via the pulmonary route. Dry powder inhalers are bolus drug delivery devices that contain solid drug, suspended or dissolved in a non-polar volatile propellant or in dry powder inhaler that is fluidized when the patient inhales. These are commonly used to treat respiratory diseases such as asthma, bronchitis, emphysema and COPD and have also been used in the treatment of diabetes mellitus. The medication is commonly held either in a capsule for manual loading or a proprietary form from inside the inhaler. Once loaded or actuated, the operator puts the mouthpiece of the inhaler into their mouth and takes a deep inhalation, holding their breath for 5-10 seconds. There are a variety of such devices. The dose that can be delivered is typically less than a few tens of milligrams in a single breath since larger powder doses may lead to provocation of cough.

Pressurized Metered-Dose Inhale (PMDI)

The pressurized metered dose inhaler is a nasal device (Fig.3) to deliver optimum amount of drug to the lungs, this is a short burst aerosolized drug that inhaled the patient. It is used for treatment of asthma, COPD and other pulmonary disorders. A PMDI devices are important to deliver the optimum amount of medication to the lungs.

Breath-powered Bi-Directional technology

The Breath-powered Bi-Directional technology (Fig.3) is a new concept for delivering the drug molecule to direct nose to brain administration. It is

novel approach for delivering the powder and liquid formulation to intranasal administration.

Liquid formulation devices

Liquid nasal devices are delivering the aqueous or watery solutions to nasal cavity. The suspension and emulsions are also transported to nasal cavity for intranasal delivery. Liquid formulation devices are useful for chronic nasal disorders.

Sprays and Solution

The solutions of drug molecule are administered in nasal cavity is act as a nasal sprays (Fig.3) and nasal solutions. The optimum dose of API is based on the amount of drug molecule or volume of drug in pharmaceutical formulations. It is most convenient approach for delivering the drug formulation for nose to brain delivery bypassing the BBB.

Instillation and rhinyle catheter

Rhinyle catheter (Fig.3) is a liquid formulation device is important to deliver the formulation by drop by drop in appropriate region of nasal cavity. Catheter dosing is measured by the filling prior to administration. This system is applicable for the experimental studies only.

Compressed air nebulizers

Nebulizers (Fig.3) are the nasal administration devices in which the drug loaded formulation in the gases state deliver to the lungs. It is a compressed air filling devices for delivering the drug formulation to nasal cavity. This device is more applicable for targeting the drug formulation to respiratory tract to give rapid on-set of action and reduces the toxic effects. This device is not applicable for drug delivering into systemic pathways.

Squeezed bottle

In this devices (Fig.3) are important for delivering the decongestants. They are smooth plastic bottles with simple jet outlet by pressing the bottle air passes in inside the container is pressed out of the small nozzle, having the optimum volume. After minimizing the pressure the air again passes to inside the bottles. Dose concentration and deposition of liquid phase delivering via Squeezed bottles they are strongly dependent on mode of administration. Dose

and droplet size of that formulation is mainly dependent on pressed application of that container.

Metered-dose pump sprays

Marketed nasal formulation such as suspension, emulsion, solution is directly delivered to intranasal pathway by using metered dose pump sprays (Fig.3). It is applicable for treatment of nasal hypersensitivity and other nasal disorders. It is based on hand operated pump mechanism. It is important to give local effect such as topical decongestants, antihistamines. These containers can be containing the pump, valve and the actuator. Dose of metered dose pump sprays depends upon the viscosity and surface tension of those formulations.

Single and duo dose spray devices

Single dose devices (Fig.3) are administered single dose of drug formulation to the intranasal pathway and duo dose device administered more than one dose of different or same drug formulation intranasal cavity. It is simple convenient and non-invasive mode for delivering the drug into nasal cavity. It is used for treatment of chronic rhinosinusitis and in a vaccine study.

Via Nase atomizer

A handheld battery-driven atomizer (Fig.3) intended for nasal drug delivery has been introduced. This device atomizes liquids by producing a vertical flow on the droplets as they exit the device. The induced vertical 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.



Fig. 3. Nasal delivery devices: Insufflators (A), Dry powder inhaler (B), Pressurized Metered-Dose Inhaler (C), Breath-powered Bi-Directional technology (D), Sprays and Solution (E), Instillation and rhinyle catheter (F), Compressed air nebulizers (G), Squeezed bottle (H), Metered-dose pump sprays (I), Single and duo dose spray devices (J), ViaNase atomizer (K)

CONCLUSION

The nasal cavity has a large surface area and a highly vascularized mucosa. Drugs absorbed by the rich network of blood vessels pass directly into the systemic circulation, thereby avoiding the first-pass metabolism. A growing body of evidence relating to nasal drug delivery suggests it might use for challenging drugs which can facilitate the pharmaceutical manufacturing and drug delivery challenges. Considering the wealth of activity and interest in the area of nasal drug delivery, together with the potential benefits from this route of administration, we should expect to see a range of novel nasal products reaching the market shortly.

Future needs and further research and development

It is not surprising to find a lot of research focusing to develop nasal drug delivery system and its contribution in therapeutic management. In general, a concise overview of the pharmacotherapy of nasal drug delivery system has highlighted that in spite of the availability of new drugs and several specialized devices.

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