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Nasal drug delivery system: A innovative approach

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Abstract

Nasal drug administration has been used as an alternative route for the systemic availability of drugs restricted to intravenous administration. This is due to the large surface area, porous endothelial membrane, high total blood flow, the avoidance of first-pass metabolism, and ready accessibility. 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.

Keywords: Nasal drug delivery, systemic circulation, bioavailability, permeation enhancers

Introduction

Nasal mucosa has been considered as a potential administration route to achieve faster and higher level of drug absorption because it is permeable to more compounds than the gastrointestinal tract due to lack of pancreatic and gastric enzymatic activity, neutral pH of the nasal mucus and less dilution by gastrointestinal contents ^[1]. Nasal therapy, has been recognized form of treatment in the Ayurvedic systems of Indian medicine, it is also called “NASAYA KARMA” ^[2]. Intranasal drug delivery is a useful delivery method for drugs that are active in low doses and show no minimal oral bioavailability such as proteins and peptides ^[3]. One of the reasons for the low degree of absorption of peptides and proteins via the nasal route is rapid movement away from the absorption site in the nasal cavity due to the mucociliary clearance mechanism ^[4].

For nasal drug delivery various systems such as: nasal spray, nasal pumps, gels, microemulsion, suspensions, powders and thermoreversible mucoadhesive gels have been studied ^[5].

Advantages ^[1,6]

- 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) Drugs that are orally not absorbed can be delivered to the systemic circulation by nasal drug delivery.
- 6) Studies so far carried out indicate that the nasal route is an alternate to parenteral route, especially, for protein and peptide drugs.
- 7) Drugs possessing poor stability in g.i.t. fluids are given by nasal route.
- 8) Polar compounds exhibiting poor absorption may be particularly suited for this route of delivery.

Limitations ^[7,8]

- 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.

An 'ideal' drug candidate for nasal delivery ^[9]

An ideal nasal drug candidate should possess the following attributes:

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

Anatomy and Physiology of Nasal Cavity

The nasal route for the systemic delivery of medication due to a high degree of vascularization and permeability of the nasal mucosa ^[10]. 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 ^[11]. 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 ^[12]. 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 ^[13].

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 ^[12].

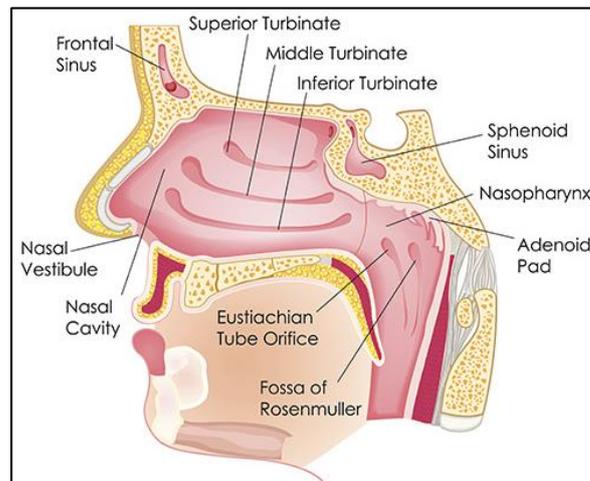


Fig 1: Schematic of a sagittal section of nasal cavity

- 1. Nasal vestibule:** Most anterior part of the nasal cavity is nasal vestibule, just inside the nostrils, and presents an area about 0.6 cm² ^[14]. 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.
- 2. 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 pseudostratified columnar cells presenting microvilli ^[15, 16].
- 3. 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 turbinate 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, goblet cells, basal cells and mucous and serous glands ^[17]. 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.
- 4. 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 ^[15, 16].
- 5. 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.
- 6. 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 [18].

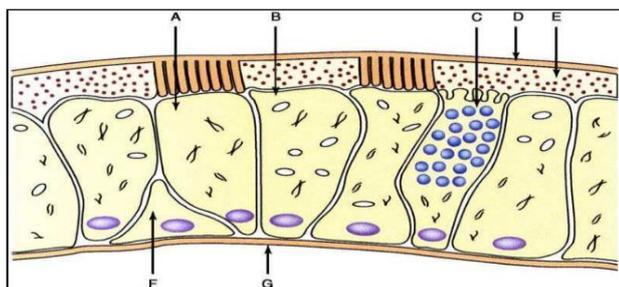


Fig 2: Cell type of the nasal epithelium

Mechanism of Nasal Absorption

The absorbed drugs from the nasal cavity must pass through the mucus layer; it is the first step in absorption. The principle protein of the mucus is mucin, it has the tendency to bind to the solutes, hindering diffusion. Additionally, structural changes in the mucus layer are possible as a result of environmental changes (i.e. pH, temperature, etc.) [19]. So many absorption mechanisms were established earlier but only two mechanisms have been predominantly used, such as:

- First mechanism- It involves an aqueous route of transport, which is also known as the Para cellular route but slow and passive. There is an inverse log-log correlation between intranasal absorption and the molecular weight of water-soluble compounds. The molecular weight greater than 1000 Daltons having drugs shows poor bioavailability [20].
- Second mechanism- It involves transport through a lipoidal route and it is also known as the transcellular process. It is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drug also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junctions [20].

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. The factors influencing nasal drug absorption are described 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.
 - 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 highly sensitive to molecular size for compounds with MW \geq 300 Daltons [21].

Lipophilic-hydrophilic balance

The hydrophilic and lipophilic nature of the drug also affects the process of absorption. By increasing lipophilicity, the permeation of the compound normally increases through nasal mucosa. Lipophilic drugs like naloxone, buprenorphine, testosterone and 17 α -ethinyl- oestradiol are almost completely absorbed when administered intranasal route [22, 23].

Enzymatic degradation in nasal cavity

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 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 [24].

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 [25]. 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 [26].

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 [27]. 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 [28].

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 [14].

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 [29].

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 [30].

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 [31]. 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 to Improve Nasal Absorption

Various strategies used to improve the bioavailability of the drug in the nasal mucosa which includes

- To improve the nasal residence time
- To enhance nasal absorption
- To modify drug structure to change physicochemical properties.

1. 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 [32]. The absorption enhancers like salts and fusidic acid derivatives also shows enzyme inhibition activity to increase the absorption and bioavailability of the drug [33].

2. Permeation enhancers

The permeation enhancers are mainly used for the enhancement of absorption of the active medicament. Generally, the absorption enhancers act via one of the following mechanisms:

- Inhibit enzyme activity;
- Reduce mucus viscosity or elasticity;
- Decrease mucociliary clearance;
- Open tight junctions; and
- Solubilize or stabilize the drug.

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.

Qualities of Ideal penetration enhancer

- a) It should lead to an effective increase in the absorption of the drug.
- b) It should not cause permanent damage or alteration to the tissues
- c) It should be non irritant and nontoxic.
- d) It should be effective in small quantity
- e) The enhancing effect should occur when absorption is required
- f) The effect should be temporary and reversible
- g) It should be compatible with other excipients.

Classification of chemical penetration enhancer [34]

- ✓ Surfactants: Polyoxyethylene-9-lauryl ether (Laureth-9), Saponin
- ✓ Bile salts: Trihydroxy salts (glycol- and taurocholate), Fusidic acid derivatives (STDHF)
- ✓ Chelators: Salicylates, Ethylenediaminetetraacetic acid (EDTA)

- ✓ Fatty acid salts: Oleic acid, Caprylate (C8), Caprate (C10), Laurate (C12)
- ✓ Phospholipids: Lysophosphatidylcholine (lyso-PC), Didecanoyl – PC
- ✓ Glycyrrhetic acid derivatives: Carbenozolone, Glycyrrhizinate
- ✓ Cyclodextrins: α , β , and γ - cyclodextrins and their derivatives
- ✓ Glycols: n- glycofurols and n- ethylene glycols

3. Prodrug approach

Prodrug approach is mainly meant for optimizing favorable physicochemical properties such as solubility, taste, odor, stability, etc. Prodrug is usually referred as pro moiety, it is to cover the undesired functional groups with another functional groups. This prodrug approach is mainly for improving the nasal bioavailability especially for the proteins and peptides to enhance the membrane permeability along with increased enzymatic stability [35]. The prodrug undergoes enzymatic transformation to release the active medicament, when it crosses the enzymatic and membrane barrier. The absorption of peptides like angiotensin II, bradykinin, caulein, carnosine, enkephalin, vasopressin and calcitonin are improved by prepared into enamine derivatives, these agents showed absorption enhancement with prodrug approach.

4. Structural modification

Modification of drug structure without altering pharmacological activity is one of the lucrative ways to

improve the nasal absorption. The chemical modification of drug molecule has been commonly used to modify the physicochemical properties of a drug such as molecular size, molecular weight, pka and solubility are favorable to improve the nasal absorption of drug. Example, chemical modification of salmon calcitonin to ecatonin (C-N bond replaces the S-S bond) showed better bioavailability than salmon calcitonin [36].

5. Particulate drug delivery

Particle design is an increasingly important role in absorption enhancement. Microspheres, nanoparticles and liposomes are all systems which can be used as carriers to encapsulate an active drug. The properties of these can be varied to maximize therapeutic efficacy. Overall, this can result in increased absorption efficacy and stability and reduced toxicity of the active ingredient. Systems can be designed to be mucoadhesive to increase the retention time and facilitate sustained release. Microspheres are mainly increase the absorption and bioavailability by adhering to the nasal mucosa and increase the nasal residence time of drug [37]. The microspheres prepared by using polymers like dextran, chitosan, biodegradable starch microspheres successfully improved the bioavailability of various drugs. Liposomes are amphiphilic in nature are well characterized for favorable permeation of drugs through the biological membranes, so the water soluble drugs have been delivered to nasal drugs. Cationic liposomes are having good permeation capacity than negatively charged anionic liposomes [2].

Table 1: Nasal drug absorption enhancers and mechanisms

Class of compound	Example	Possible action	Reference
Fatty acids	Dideconoylphosphatidylcholine, lysophosphatidylcholine	Membrane disruption	[38]
Surfactants	Sodium lauryl sulphate, saponin, polyoxyethylene-9-lauryl ether	Membrane disruption	[39 – 42]
Bile salts	Sodium deoxycholate, sodium glycocholate, sodium taurodihydrofusidate	Open tight junctions, enzyme inhibition	[43 – 45]
Cyclodextrines and derivatives	α -, β -, γ -cyclodextrin DM β -, HP β -cyclodextrin	Open tight junctions	[46, 47]
Enzyme inhibitors	Bestatin, amastatia	Enzyme inhibition	[48]
Bio-adhesive materials	Carbopol, starch microspheres, chitosan	Reduce nasal clearance, open tight junctions	[49]

Nasal Drug Delivery System Dosage Forms

The selection of dosage form depends upon the drug being used, proposed indication, patient population and last but not least, marketing preferences.

A. Liquid Nasal Formulations

Liquid preparations are the most widely used dosage forms for nasal administration of drugs. They are mainly based on aqueous state formulations. Their humidifying effect is convenient and useful, since many allergic and chronic diseases are often connected with crusts and drying of mucous membranes. Microbiological stability, irritation and allergic rhinitis are the major drawbacks associated with the water-based dosage forms because the required preservatives impair mucociliary function [50].

1. Instillation and rhinyle catheter Catheters are used to deliver the drops to a specified region of nasal cavity easily. Place the formulation in the tube and kept tube one end was positioned in the nose, and the solution was delivered into the nasal cavity by blowing through the other end by mouth [51, 52].

2. Compressed air nebulizers Nebulizer is a device used to

administer medication in the form of a mist inhaled into the lungs. The compressed air is filling into the device, so it is called compressed air nebulizers. The common technical principal for all nebulizers, is to either use oxygen, compressed air or ultrasonic power, as means to break up medical solutions/ suspensions into small aerosol droplets, for direct inhalation from the mouthpiece of the device [53].

3. Squeezed bottle Squeezed nasal bottles are mainly used as delivery device for decongestants. They include a smooth plastic bottle with a simple jet outlet. While pressing the plastic bottle the air inside the container is pressed out of the small nozzle, thereby atomizing a certain volume. By releasing the pressure again air is drawn inside the bottle. This procedure often results in contamination of the liquid by microorganisms and nasal secretion sucked inside [54].

4. Metered-dose pump sprays Most of the pharmaceutical nasal preparations on the market containing solutions, emulsions or suspensions are delivered by metered-dose pump sprays. Nasal sprays, or nasal mists, are used for the nasal delivery of a drug or drugs, either locally to

generally alleviate cold or allergy symptoms such as nasal congestion or systemically, see nasal administration. Although delivery methods vary, most nasal sprays function by instilling a fine mist into the nostril by action of a hand-operated pump mechanism. The three main types available for local effect are: antihistamines, corticosteroids, and topical decongestants Metered- dose pump sprays include the container, the pump with the valve and the actuator.

B. Powder Dosage Forms

Dry powders are less frequently used in nasal drug delivery. Major advantages of this dosage form are the lack of preservatives and the improved stability of the formulation. Compared to solutions, the administration of powders could result in a pro- longed contact with the nasal mucosa.

1. Insufflators: Insufflators are the devices to deliver the drug sub-stance for inhalation; it can be constructed by using a straw or tube which contains the drug substance and sometimes it contains syringe also. The achieved particle size of these systems is often increased compared to the particle size of the powder particles due to insufficient deaggregation of the particles and results in a high

coefficient of variation for initial deposition areas. Many insufflator systems work with pre-dosed powder doses in capsules [51].

2. Dry powder inhaler: Dry powder inhalers (DPIs) 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 [55]. 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.

Table 2: Formulation of intranasal dds

Pharmaceutical excipients	Type of dosage form	Comments
Permeation enhancers e.g., 1. Cyclodextrins 2. Fusidic acid derivatives 3. Phosphatidylcholines 4. Microspheres and liposomes 5. Bile salts and surfactants	Powders, gels, solutions	Improve the bioavailability of drugs particularly molecular weight above 1000 Da Causes nasal epithelial toxicity
Solvents e.g., ethanol, polyethylene, propylene glycols, etc.	Gels, solutions	To increase the concentration of drug in vehicle and reduce the dose volume. May act as a permeation enhancer
Viscosity modifiers e.g., cellulose derivatives	Gels, solutions	To improve nasal residential time
Mucoadhesive polymers e.g., carbopol, polycarbophil, cellulose derivatives, lecithin, and chitosan	Powders, gels, solutions	To improve the nasal residential time
Preservatives e.g., benzalkonium chloride	Gels, solutions	To maintain sterility of dosage form, may alter the nasal residential time
Enzyme inhibitors e.g., bestatin, amastatin, boroleucine, fusidic acids, and bile salts	Powders, gels, solutions	To improve the bioavailability of protein and peptides
Tonicity modifiers/buffers e.g. sodium chloride, citrate buffer	Solutions	To avoid the nasal epithelial toxicity

C. Pressurized MDIs

A metered-dose inhaler (MDI) is a device that delivers a specific amount of medication to the lungs, in the form of a short burst of aerosolized medicine that is inhaled by the patient. It is the most commonly used delivery system for treating asthma, chronic obstructive pulmonary disease (COPD) and other respiratory diseases. The medication in a metered dose inhaler is most commonly a bronchodilator, corticosteroid or a combination of both for the treatment of asthma and COPD. Other medications less commonly used but also administered by MDI are mast cell stabilizers, such as (cromoglicate or nedocromil).

The advantages of MDIs are their portability and small size, availability over a wide do-sage range per actuation, dose consistency, dose accu-racy, protection of the contents and that they are quickly ready for use [56].

Propellants in MDIs typically make up more than 99 % of the delivered dose. Actuation of the device releases a single

metered dose of the formulation which contains the medication either dissolved or suspended in the propellant. Breakup of the volatile propellant into droplets, followed by rapid evaporation of these droplets, results in the generation of an aerosol consisting of micrometer-sized medication particles that are then inhaled.

D. Nasal Gels

Nasal gels are high-viscosity thickened solutions or suspensions. Until the recent development of precise dosing devices, there was not much interest in this system. The advantages of a nasal gel include 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 delivery to mucosa for better absorption [57].

The deposition of the gel in the nasal cavity depends on the mode of administration, because due to its viscosity the

formulation has poor spreading abilities. Without special application techniques it only occupies a narrow distribution area in the nasal cavity, where it is placed directly. Recently, the first nasal gel containing Vitamin B12 for systemic medication has entered the market.



Fig 3: Devices used for Nasal delivery

Evaluation of Nasal Drug Formulations [12, 58]

In vitro nasal permeation studies Various approaches used to determine the drug diffusion through nasal mucosa from the formulation. There are two different methods to study diffusion profile of drugs,

A) *In vitro* diffusion studies

The nasal diffusion cell is fabricated in glass. The water-jacketed recipient chamber having total capacity of 60 ml and a flanged top of about 3mm; the lid has 3 opening, each for sampling, thermometer, and a donor tube chamber. The donor chamber is 10 cm long with internal diameter of 1.13 cm, and a donor tube chamber has total capacity of 60 ml and a flanged top of about 3mm; the lid has 3 openings, each for sampling, thermometer. 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, it 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. Samples (0.5 ml) from recipient chamber are with draw at predetermined intervals, and transferred to amber colored ampoules. The temperature is maintained at 37 °C throughout the experiment.

B) *In Vivo* Nasal Absorption studies

Rat model

The surgical preparation of rat for *in vivo* nasal absorption study is carried out as follows: The rat is anaesthetized by intraperitoneal injection of sodium pentobarbital. An incision is made in the neck and the trachea is cannulated with a polyethylene tube. Another tube is inserted through the oesophagus towards the posterior region of the nasal cavity. The passage of the nasopalatine tract is sealed so that the drug solution is not drained from the nasal cavity through the mouth. The drug solution is delivered to the nasal cavity through the nostril or through the cannulation tubing. Femoral vein is used to collect the blood samples. As all the probable outlets of drainage are blocked, the drug can be only absorbed and transported into the systemic circulation by penetration and/or diffusion through nasal mucosa.

In-vivo bioavailability studies

In-vivo bioavailability study is conducted on healthy male rabbits. Study consists of three groups each containing six rabbits and fasted for 24 h. One group treated with conventional preparation, second group kept as control (i.e.

not received any test substances) and third group of test formulation. Water is given ad libitum during fasting and throughout the experiment. For the collection of blood samples the marginal ear vein of the rabbits used and sample of about 2 ml collected in heparinized centrifuge tubes at 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 h after the drug administration. The blood samples are centrifuged at $3000 \times g$ for 15 min to obtain the plasma and stored at -20°C until analysis. The extraction of drug from plasma can be carried out as reported previously and then analyze using the HPLC system.

Conclusion

Nasal drug delivery system is a promising alternative route of administration for the several systemically acting drugs with poor bioavailability and it has advantages in terms of improved patient acceptability and compliance compared to parenteral administration of drugs. The intranasal route is an accessible alternative route for drug administration. This route provides future potential for several drugs through the development of safe and efficacious formulations for simple, painless and long-term therapy. Nasal product will include drugs for acute and long term diseases and also vaccines with better local or systemic protection against infections. From this route drugs can be directly target to the brain in order to attain a good therapeutic effect in CNS with reduced systemic side effects. The nose is a complex organ with multiple functions. The nasal cavity provides a highly vascularized surface of the nasal mucosa for the absorption of drugs.

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