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Review Article

Importance of Different Novel Nasal Drug Delivery System-A Review

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ABSTRACT

The intranasal delivery system is preferable route for administration of the drug for local, systemic as well as central nervous system drug delivery. Advantages of nasal spray dosage form such as it is cost-effective, easy to use/carry and self-administrable, it has high patient compliance make this dosage form growing opportunity for nasal drug delivery. This article outlined the relevant aspects of nasal anatomy, physiology and histology, and the biological, physicochemical and pharmaceutical factors that must be considered during the formulation development of nasal spray. It is intuitively expected that this review will help to understand nasal formulation and it's in- vitro characteristics.

Keywords: Anatomy of nose, Nasal drug delivery system, nasal spray, nasal powder.

INTRODUCTION

Intranasal drug delivery system is recognized to be a useful and reliable alternative to oral and parenteral routes. The nasal route can be used for both local and systemic drug delivery. For localized nasal drug delivery is usually used to treat conditions related to the nasal cavity, such as congestion, rhinitis, sinusitis and related allergic conditions. A diverse range of drugs including corticosteroids, anti-histamines, anti-cholinergic and vasoconstrictors can be administered locally. Now days achieving a systemic drug action using the nose as the entry portal into the body has received more attention. Also, the nasal delivery seems to be a favorable way to circumvent the obstacles for bloodbrain barrier (BBB) allowing the direct drug delivery in the biophase of central nervous system (CNS)-active compounds. Now a day's multiple types of formulation are used to administer drug by nasal rout, which includes nasal spray, nasal drop, nasal powder, nasal gels & nasal insert etc. Administration of drugs through the nose in the spray dosage form is a noninvasive method that gives rapid onset of drug action. Because the nasals spray dosage form is cost-effective, easy to use/carry and self-administrable, it has high patient compliance. Therefore, nasal drug delivery has become a popular route of drug administration and has strong growth opportunity[1].

Only relatively recently have speciallydesigned devices emerged that can target the delivery of sprays or powders to the olfactory region of the nose, thereby enabling delivery of the drug directly to the central nervous system. The present review outlines anatomical, physiological and histological features of nasal cavity and the major factors affecting nasal drug delivery, the properties of drugs and formulation characteristics that determine decisively the pharmacokinetics of nasal preparations.

Advantages of Nasal Drug Delivery System[2]

Intranasal administration offers several practical advantages from the viewpoint of patients (non-invasiveness, essentially painless, ease drug delivery and favorable tolerability profile)

Rapid drug absorption.

Quick onset of action.

Hepatic first – pass metabolism is absent.

The bioavailability can be improved by means of absorption enhancer or other approach.

Better nasal bioavailability for smaller drug molecules.

Limitations

Dose quantity is limited because of relatively small area available for the absorption of drug.

Time available for drug absorption is limited.

Diseased condition of nose impairs drug absorption.

The absorption enhancers used to improve nasal drug delivery system may have histological toxicity which is not yet clearly established.

Absorption surface area is less when compared to GIT.

Nasal irritation

Certain surfactants used as chemical enhancers may disrupt and even dissolve Membrane in high concentration.

Anatomy of Nose

The nose is the primary entrance to the respiratory tract, allowing air to enter into the body for respiration[3]. The deepness of nasal cavity is 120-140 mm deep, runs from the nasal vestibule to the nasopharynx and is divided into two by a cartilaginous wall called nasal septum. The nose has a surface area of around 160 cm^2 and a total volume of ~16-19 ml[4]. The nose serves as the mean of bringing warm humidified air into the lungs. Nose is a primary organ for filtering out particles in the inspired air, and it also serves to provide a first-line immunologic defence as it brings the inspired air into contact with the mucous-coated membrane. The nose has three main regions: vestibular, turbinate and olfactory region.

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The external nose having a pyramidal shape, which may differ greatly depending on race. Although this structure may not have an obvious relevance for intranasal administration of drugs and vaccines, it is important for the design of devices and for understanding the administration techniques.

Although there are several types of external noses in world population, there are mainly 3 types of nostrils; leptorrhine, described as long and narrow nostrils; plalyrrhine which are broad and flat; and mesorrhine which are between. The nose having central position in the face, outlined by the sharp contours of the forehead, cheeks, and jaws, is widely believed to influence decisively the observer's visual impression of the face[5]. The irregularities of nose size and shape often influence our opinion how we see the person, compared to our subjective judgment of how an ideal nose should look like.

The external nose anatomy can be separated into bony, cartilaginous, and soft tissue components. The soft tissue part of the nose is composed of skin, fibroadipose tissue and muscles of facial expression, controlled by the facial nerve. The skin is thickest over the nasofrontal angle. Reconstructive and plastic surgeons have analyzed the nose and face using linear and angular measurements of the nose and its surroundings in order to determine the major three-dimensional facial landmarks. These may be obtained into x, y and z coordinates of the nose[6-7]. Around 50 facial landmarks, 12 are related to the nose as shown in (Fig. 1). These landmarks may be used to estimate facial volumes and areas by the mean of several tetrahedral and triangles[8-10].

The nose has two large irregular cavities formed by 14 bones connected to each other by a tough fibrous membrane, which structure a roof, a floor, an inner and an outer wall. Each cavity extends from the base of the cranium to the roof of the mouth and opens to the face through the nostril and extends to oval opening into the upper part of the pharynx (throat), is known as nasopharynx. The nose passage is about 12-14 cm long and about 5 cm high. The total surface area of both nasal cavities is about 160 cm^2 (96.000 cm^2 if the nasal epithelial microvilli are included), the total volume is about 15 mL.The nasal cavity is much narrower above than below, where the olfactory region is located which is about 2.5 cm^2 in each cavity (about 3000 cm^2 in both cavities if the microvilli are included in the calculations) or about 3% of the nasal surface area. summarizes the anatomical facts of the nose. The horizontal bone separating the nasal cavity and the brain is called the cribriform plate of the ethmoid[11], a highly perforated bone by small vascular apertures that provides easy way for the nerve endings to enter the outer surface. The perforations is called foramina and are 20 on each side of the nose. This is the only site in the body in which central nervous system is in direct contact with the outer surface (mucosal membrane). The nasal floor is much wider than the upper (olfactory) region, concave in structure and wider in the middle than at either opening. The nasal septum, also called the inner wall, separates the two nasal cavities. This wall is thick in the superior border and has deep grooves, marked by numerous vascular and nervous canals providing pathway for e.g. the nasopalatine nerve. Septum is thinner in the middle than at the circumference and is generally bent to one or the other side. The posterior border of the nasal septum is free and separates the nasal cavities from behind[11-16]. It has been shown that the septum cartilage increases rapidly in size during the first years of life and remain constant after the age of two years[17]. However, ossification of the cartilaginous septum begins after the first six months of life and continues until the age of 36[18]. These deviations have been shown to prevent successful delivery of drugs into the nasal cavity. On other side of the anterior nasal septum, there is a small bar of cartilage, the vomeronasal cartilage. This is connected with a small opening which leads into the rudimentary vomeronasal organ.

The outer wall is convoluted into the folds of conchae or turbinate, which engender increased resistance to the airflow, producing intimate contact between inspired air and the mucosa. There are three (or four) conchaes in each cavity: the superior, middle and inferior conchae producing three irregular passages inside the nasal cavity called superior, middle and inferior meatuses[19]. The opening into the sphenoidal sinuses is located above and behind the superior conchae[20-22].

The posterior ethmoidal sinus, occasionally communicates with the sphenoidal sinuses, opens into the superior meatus. The maxillary sinuses are two large pyramidal cavities which enter into the nasal cavity through a large opening anteriorly into each of the middle meatuses[23-25].

The paranasal sinuses is pair of air filled cavities covered with a thin layer of respiratory mucosa and named after the skull bones: frontal, ethmoid, maxillary and sphenoid. The frontal sinuses grows in size until the late teens. The functions of the sinuses are not understood. They formed a collapsible framework to protect the brain from trauma, where other theories describe their ability to provide thermal insulation for the brain, imparting in voice resonance, humidifying and warming inspired air and provide moist to the nose. The nasal cavity is linked with arteries, veins, lymphs and neurons. Superior coronary supplied the upper lip and provides two vessels into the nose: inferior artery of the septum, which supplies blood to the anterior part or the nasal septum which supplies the ala of the nose. The veins of the nose are valve less and began in a venous plexus on the inferior nasal conchae, inferior meatus and the back part of the septum and drain into the pterygoid plexus. The lymphatic system includes lymphatic vessels and glands through which they pass. The lymphatics have the property of absorbing materials from the tissues and conveying them into the circulation. The largest cranial nerve, so-called fifth nerve or trifacial nerve (nervous trigeminus) the head and face supports the nasal cavity. This nerve is mainly a sensory nerve in addition to a number of other functions. The first division of this fifth nerve is called the ophthalmic nerve (nervous ophthalmicus), it supplies the eyeball, the lachrymal gland, the frontal sinuses, the nasal cavity and the integument of the nose[26-28].

Different factors affecting nasal drug absorption[29,30]

Various factors affect bioavailability of nasally administered drugs as follows;

Biological factors

Structural features: There are five different parts of nasal cavity: nasal vestibule, atrium, respiratory area, olfactory region and the nasopharnyx. This structure and the type of cells, density and number of cells present in that region influence the permeability. Absorption enhancers used in combination with drugs increases the permeation of compounds.

Biochemical changes: Enzymatic barrier to the delivery of drugs is nasal mucosa because of the presence of a large number of enzymes, which include oxidative and conjugative enzymes, peptidases and proteases. Protease and peptidase enzymes were responsible for the presystemic degradation and subsequent lower permeation of various peptide drugs, such as calcitonin, insulin, LHRH and desmopressin. To overcome these degradations use of protease and peptidase inhibitors such as bacitracin, amastatin, boroleucin and puromycin can be used.

Physiological factors

Nasal mucosa is highly permeable site. More blood supply due to parasympathetic stimulation gives congestion and low blood supply due to sympathetic stimulation gives relaxation, regulate the rise and fall in the amounts of drug permeated, respectively.

Nasal secretions Nasal secretions are produced by anterior serous and seromucus glands. permeability of drug is affected by:

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

Solubility of drug in nasal secretions: For permeation of drug solublisation is necessary. A drug should have appropriate physicochemical characteristics for dissolution in nasal secretions.

Alteration in pH of nasal cavity is observed between 5.5–6.5 in adults and 5.0–7.0 in infants. Permeation of drug would be greater if the nasal pH is lower than pKa of drug because under such conditions the penetrant molecules exist as unionized species.

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

Physicochemical properties of drug:

Molecular weight and size: Drug permeation is determined by molecular weight, molecular size, hydrophilicity and lipophilicity of the compound. In general, the bioavailability of these large molecules ranges from 0.5% to 5%. Physicochemical properties of the drug don't significantly affect permeation of drug LT 300 Da, which will mostly permeate through aqueous channels of the membrane.

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

Lipophilicity: The permeation of the excipients normally increases through nasal mucosa with increase in lipophilicity. It shows that nasal mucosa is primarily lipophilic in nature and the lipid domain plays an important role in the barrier function of these membranes although they have some hydrophilic characteristics.

pKa and partition coefficient: As per the pH partition theory, unionized species are absorbed better comparedwith ionized species and the same fact is true in the case of nasal absorption. There is constant relationship between pKa and nasal absorption of these drugs.

Polymorphism: Polymorphism is the important parameter in the nasal drug product development which is administered in particulate form. Polymorphism is responsible to affect dissolution of drugs and their absorption through biological membranes is affected by polymorphism. This factor should be used carefully considered in the dosage form development for the nasal delivery.

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

Physicochemical properties of formulation:

Physical form of formulation: Liquid formulations are less effective than powder form in delivering insulin in rabbits. Viscous formulations may help in minimizing nasal drip.

pH: extent of drug ionization is determined by pH partition hypothesis hence it is related to formulation pH. Nasal dosage form should be adjusted to appropriate pH to avoid irritation, to obtain efficient absorption and to prevent growth of pathogenic bacteria. Ideal pH should be adjusted between 4.5 and 6.5.

Osmolarity: Formulation tonicity substantially affect the nasal mucosa generally, an isotonic formulation is preferred.

Mechanism of Drug Absorption

The mechanism in the absorption of a drug from the nasal cavity is the passage through the mucus. Small or fine particles may easily pass through the mucus layer; however, large particles may find some difficulties. Mucus contains mucin, a protein with the potential to bind with solutes and thus affect the diffusion process. Structural changes done in the mucus layer as a result of environmental or physiological changes. Simantaneously to a drug's passage through the mucus, there are numerous mechanisms for absorption through the mucosa. These include simple diffusion across the

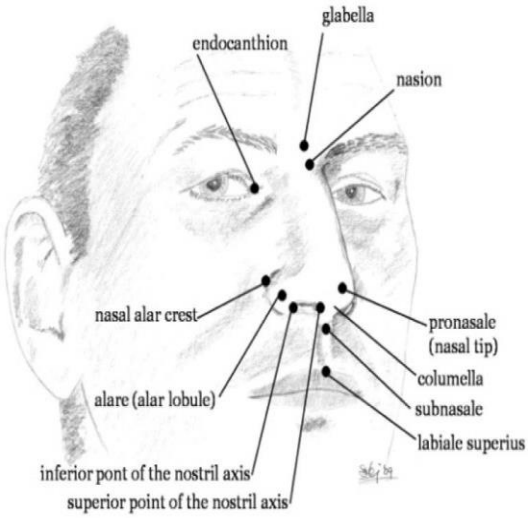

Figure 1: Anatomy of nose.

membrane, paracellular transport via movement between cell and pinocytosis by vesicle carriers. There are several mechanisms have been proposed, but paracellular and transcellular routes are mainly used. Paracellular transport is a slow process and passive dffusion. There is an correlation between intranasal absorption and the molecular weight of water-soluble compounds inversily. Poor bioavailable drugs are with a molecular weight greater than 1000 Daltons. The second absorption process involves transport through a lipoidal route that is also known as the transcellular process and is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drugs can also cross cell membranes by an active transport route via carrier-mediater or transport through the opening of tight junctions. Obstacles to drug absorption are potential metabolism before reaching the systemic circulation and inadequate residence time in the nasal cavity[31-33].

Different Nasal Drug Delivery System

Nasal Drops and Sprays

Nasal drops are simple, cost effective and most convenient delivery systems among all formulations. The limitation is the lack of precision in the administered dosage and the risk of contamination during use. Nasal drops can be delivered with a pipette or by a squeezy bottle. These formulations are usually recommended for the treatment of local conditions, but challenges include microbial growth, mucociliary dysfunction and non-specific loss from the nose or down back the throat[34,35].

Nasal spray consist of a chamber, a piston and an operating actuator. Nasal sprays are more accurate than drops and generate precise doses (25 - 200 µl) per spray like metered dose spray.This is a type of aerosols. Formulation properties such as thixotropy, surface tension and viscosity can potentially influence droplet size and dose accuracy[36-38].

Nasal Gels

A gel is a soft, solid or semi-solid-like material consisting of two or more components, one of which is a liquid, present in substantial quantity. The semi-solid behaviour of gels can be defined in terms of two dynamic mechanical properties: elastic modulus G' and viscous modulus G"[39]. The rheological properties of gels depend on the polymer type, concentration and physical state of the gel. They can range from viscous solutions (e.g.methylcellulose, xanthan gum and chitosan) to very hard, brittle gels (e.g gum, pectin and alginate). Bioadhesive polymers have shown good potential for nasal formulations and can control the rate and extent of drug release resulting in decreased frequency of drug administration and improved patient compliance[40,41]. Mucoadhesion mechanism in the nasal cavity can be explained by a number of theories, but it is generally accepted that the mechanism is based on two key stages, the contact and consolidation stages. So, when formulations containing bioadhesive polymers are instilled in the nasal cavity, they can spread over the nasal epithelium. Due to the improved surface contact, the polymer chains can diffuse within the mucus. This creates sufficient contact for entanglement. Secondary chemical bonds are then formed between the polymer chains and mucin molecules[44]. Many biocompatible and biodegradable polymers have been used to formulate mucoadhesive systems. These include poly-vinyl alcohol, chitosan, carbopol, alginate, hydroxypropyl methylcellulose, hydroxypropyl cellulose, starch and gellan gum. Nasal administration using mucoadhesive gels has been studied for different drugs: antibiotics such as roxithromycin and ciprofloxacin, insulin scopolamine hydrochloride, mometasone furoate carvedilol sumatriptan succinate, vaccines and proteins .

In spite of most gels exhibiting shear-thinning behaviour (pseudoplasticity), some gel formulations with suitable rheological properties cannot be easily delivered using a normal nasal spray device. *In situ*gelation can be used to overcome this problem, and has been investigated for the nasal delivery of mometasone furoate, carvedilol and influenza vaccine[45].

Nasal Suspensions and Emulsions

Suspensions are less used or investigated as nasal drug delivery systems. Analogous to marketed aqueous ophthalmic suspensions of the soft corticosteroid, a nasal aqueous suspension of same drug containing microcrystalline sodium carboxymethylcellulose for stabilisation and retention in the nasal cavity was used for the local treatment of allergic rhinitis. Absorption improvement has been attributed to solubilisation of the drug and the lipophilic absorption enhancers in the composition. Like wise, other low solubility compounds have been formulated in emulsions to increase the drug solubility, e.g. diazepam and testosterone[46].

Nasal Micellar and Liposomal Formulations

Different types of excipients can affect the drug absorption and are often required to reach therapeutic plasma levels when hydrophilic macromolecular drugs such as peptides and proteins are delivered by the nasal route.Among other surfactants used, bile salts are often used as enhancers, e.g. as micellar solutions Liposomes have also been investigated as nasal drug delivery systems and absorption enhancing effects were found for

Nose as a novel drug delivery system.

Table 1: Different dosage form for nasal.

Indication	Active pharmaceutical ingredient	Formulation
Analgesia	Diamorphine hydrochloride Fentanyl citrate	Powder and diluent for reconstitution-aqueous spray Nasal spray, solution
Acute treatment of migraine	Sumatriptan Zolmitriptan	Nasal spray, solution Nasal spray, solution
Endometriosis Ovarian stimulation	Nafarelin acetate	Nasal spray, solution
Nasal congestion (associated with sinusitis, common cold, rhinitis and other UTIs) Symptomatic relief of rhinorrhoea	Xylometazoline hydrochloride Oxymetazoline hydrochloride Azelastine Hydrochloride Ephedrine Ipatropium bromide	Nasal spray, solution, nasal drops Nasal spray, solution Nasal spray, solution Nasal drops Nasal spray, solution
Prophylaxis and treatment of perennial and seasonal allergic rhinitis	Budesonide, beclometasone dipropionate (and monohydrate (micronized), Mometasone furoate Triamcinolone acetonide Fluticasone propionate Fluticasone furoate Fluticasone with azelastine HCl Sodium cromoglicate	Nasal spray suspension Nasal spray suspension Nasal spray suspension Nasal spray suspension Nasal spray suspension Nasal spray suspension Nasal spray suspension, spray solution
Prostatic carcinoma (hormone -dependent)	Buserelin acetate	Nasal spray, solution
Nasal congestion	Levomenthol	Nasal ointment
Nasal infection	Neomycin sulfate and Chlorhexidine dihydrochoride	Nasal cream
Nicotine withdrawal symptoms	Nicotine	Nasal Spray Solution
Nocturia associated with multiple sclerosis The diagnosis and treatment of vasopressin-sensitive cranial diabetes insipidus. Establishing renal concentration capacity.	Desmopressin acetate	Nasal Spray Solution
Vaccinations	Influenza vaccine	Nasal spray suspension

insulin and calcitonin *in vitro* permeability studies[47].

Nasal Powders

Particulate nasal dosage forms are usually prepared by simply mixing the drug substance and the excipients by spray-drying or freeze- drying of drug .Dry-powder formulations containing bioadhesive polymers for the nasal delivery of peptides and proteins Water-insoluble cellulose derivatives and Carbopol® 934P were mixed with insulin and the powder mixture was administered nasally. The powder took up water, swelled, and established a gel with a prolonged residence time in the nasal cavity. Powder formulations for nasal drug delivery have been used e.g. for a somatostatin analogue using cross-linked dextran and microcrystalline cellulose for glucagon using microcrystalline cellulose for leuprolide and calcitonin using microcrystalline cellulose in combination with hydroxypropyl cellulose and for gentamicin sulfate using hydroxypropyl methylcellulose A bioadhesive powder containing beclomethasone dipropionate for local treatment of allergic rhinitis and hydroxypropyl cellulose as the carrier had a significantly enhanced nasal residence time compared with administration of a solution as drops[48-49].

Nasal Microparticle

microparticles may prolong the residence time in the nasal cavity . It was proposed that microspheres of albumin, starch, and DEAE-dextran (diethyl aminoethyl-dextran) absorbed water and formed a gel-like layer which was cleared slowly from the nasal cavity. After three hours of administration, 50% of the delivered amount of albumin and starch microspheres and 60% of the dextran microspheres were still present at the site of deposition. An increased contact time could increase the absorption efficiency of drugs[50].

CONCLUSION

The nasal route has become one of the most promising and versatile route for delivering drugs. Its unique process of extending the drug release, by passing the hepatic first-pass metabolism and direct delivery of drugs to brain holds great promise in the field of drug delivery. Many pharmaceutical dosage forms and their potential to be utilised for local or systemic drug administration has been discussed in their review article. It is expected that this review will help to understand and further to develop the intra-nasal formulations to achieve specific therapeutic objectives. However, a number of technical and practical issues, which are also highlighted in this review article, remain a hurdle to be overcome in order for the full potential to be realised.

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