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A comprehensive review on nasal drug delivery system

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ABSTRACT

Nasal drug delivery has developed as a promising alternative route for the administration of both systemic and local medications, due to its non-invasive nature, rapid onset of action, and potential to bypass first-pass metabolism. Drug absorption is made easier by a mucosal surface that is highly vascularized in the nasal cavity. The nasal cavity offers a highly vascularized mucosal surface, facilitating drug absorption through various mechanisms, including transcellular, paracellular, and receptor-mediated transport. To improve bioavailability and extend drug retention in the nasal mucosa, numerous dosage forms, including solutions, suspensions, gels, emulsions, nanoparticles, and microparticles, have been developed. To enhance drug absorption and stability, excipients like mucoadhesive polymers, permeation enhancers, and enzyme inhibitors are included. However, advanced formulation strategies, such as lipid-based carriers, nano formulations, and in situ gelling systems, are required to address issues like mucociliary clearance, enzymatic degradation, and limited drug permeability. Pain management, hormone therapy, vaccine administration, and the treatment of respiratory and central nervous system (CNS) disorders are just a few examples of the many therapeutic applications of nasal drug delivery. Due to the possibility of enhanced systemic absorption, intranasal delivery of biologics like proteins and peptides has also received attention. Nasal drug delivery has some drawbacks, including the possibility of mucosal damage with long-term use, nasal irritation, and variability in drug absorption due to physiological conditions. Further research is needed to overcome these challenges through innovative formulations and delivery technologies. Overall, nasal drug delivery remains a highly promising and evolving field with significant potential for improved patient outcomes and therapeutic efficacy.

Keywords: Nasal drug delivery; Intranasal route; Nanoparticles; Mucoadhesive systems; Bioavailability.

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INTRODUCTION

Systemic circulation, avoiding the hepatic first pass elimination. In addition, intranasal drug delivery enables the history of nasal drug delivery dates back to earlier topical applications of drugs intended for local effects. Nasal therapy also called 'Nasya karma' has been recognized form of treatment in the Ayurvedic system of Indian medicines [1]. The early 1980s saw the introduction of nasal route as a promising systemic delivery alternative to other conventional drug delivery routes [2]. Nasal route is easily accessible, convenient, and a reliable with a porous endothelial membrane and a highly vascularized epithelium that provides a rapid absorption of compounds into the dose reduction, rapid attainment of therapeutic invasiveness, self-administration, patient comfort, and patient compliance, which are the hurdles in intravenous drug therapy [3]. It was reported that lipophilic drugs are generally well absorbed from the nasal cavity with pharmacokinetic profiles, which are often identical to those obtained after an intravenous injection with a bioavailability approaching 100% [4], on the other hand absorption of hydrophilic drugs can be increased by means of absorption enhancers [5].

Drugs ranging from small chemicals to large macromolecules peptide/protein therapeutics, hormones, and vaccines, are being delivered through the nasal cavity [6]. The nasal delivery seems to be a favourable way to circumvent blood levels, quicker

onset of pharmacological activity, and fewer side effects [7,8]. 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 micro molecules 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. Large absorption surface area and high vascularization lead to fast absorption. In emergency, nasal route can be used as a substitute route of parenteral administration [9,10]. It was reported that lipophilic drugs are generally well absorbed from the nasal cavity with pharmacokinetic profiles, which are often identical to those obtained after an intravenous injection with a bioavailability approaching 100%. On the other hand, absorption of hydrophilic drugs can be increased by means of absorption enhancers. Drugs ranging from small chemicals to large macromolecules including peptide/protein therapeutics, hormones, and vaccines, are being delivered through the nasal cavity.

Advantages

- Rapid on set of action. It passes the Blood Brain
- Alternative to parenteral route especially for proteins and peptides.
- Improved bioavailability.
- Direct transport into systemic circulation and CNS is possible.
- Doesn't have any complex formulation requirement.
- Low risk of over dose.
- A self-administration is possible.
- Patient compliances and convenience is enhanced.
- Synergistic effects are reduced to low dose.
- Conducive route for the patient on long term therapy.
- Incompatible drug candidates for oral route can be successfully given via nasal route.
- Bioavailability of larger drug molecules can be enhanced by means of absorption.
- Hepatic first pass metabolism is absent.
- Nasal bioavailability of small drug molecules is good.
- Degradation of drug absorbed in GIT is avoided.
- Non-invasive and easy for administration.
- Availability of large nasal mucosal surface area for dose absorption.
- Absorption of drug is rapid via highly vascularised mucosa.
- Minimal after space.
- It is potential for sustain release.
- When a drug is rapidly metabolised orally. Ex-Isoprenaline [11,12,13]

Limitations

- Adversely affected by pathological condition.
- Systemic toxicity occurring due to absorption enhancers is not yet established.
- Smaller absorption surface compared with GIT.
- Enzymatic barrier to permeability of drug.
- Possibility of nasal drug irritation hence inconvenient with oral route.
- Some of the surfactants are used as chemical catalyst or even dissolved the membrane at higher concentration.
- There is a risk of both irreversible damage of the cilia of the nasal mucosa and local side effects from both constituents and substances additional to the dosage form.
- Irritation of nasal mucosa by some drugs like Budesonide, Azilactine.
- Delivery volume in nasal cavity is restricted to 25 -200 microlitre.
- Normal defence mechanism like mucociliary clearance and ciliary beating affects the permeability of drug.
- High molecular weight compounds cannot be delivered through this route.
- There can be a mechanical loss of the dosage form in other parts of the respiratory system. Ex; lungs due to the inappropriate. [14,15,16]

Ideal properties of drug candidates for Nasal drug delivery

- No nasal irritation from the drug.
- Appropriate nasal absorption properties.
- Low dose, Generally, below 25 mg per dose.
- Suitable stability characteristics.
- No aroma associated with the drug.
- A suitable clinical rationale for nasal dosage form. Ex; rapid onset of action, ability to deliver a wide range of drug types, including peptides and proteins.
- Reduced degradation of the drug before it reaches systemic circulation.
- Nontoxic. [17,18,19,20]

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 150cm^2 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

Table 1: Polymers used in Nasal drug delivery system [29, 30, 31]

S.No	Polymer	Characteristics
1.	Cellulose derivatives Soluble: hydroxypropyl methyl cellulose, Hydroxy propyl cellulose (HPC), methylcellulose (MC), Carboxymethyl cellulose (CMC) Insoluble: ethyl cellulose (EC), microcrystalline cellulose (MCC)	Prolong the residence time of drug in Sustain the release of drug due to high viscosity Act as absorption enhancer Effective increases intranasal bioavailability.
2.	-Polyacrylates -Carbomers -Polycarbophils	Excellent mucoadhesive and gel forming capability Capable of attaching to mucosal surfaces hence ensure intimate contact between the formulation and membrane surface
3.	-Starch -Maize starch -Degradable starch microspheres (DSM)	Effectively improve absorption of both small hydrophobic and hydrophilic macromolecular drugs. Mostly used in mucoadhesive microparticulate nasal delivery system
4.	Chitosan	Insoluble at neutral and alkaline pH It can form water soluble salts with inorganic and organic acids Low cost, Biodegradable and Biocompatible.
5.	Fibrin	A natural protein involved in blood Clotting, Fibrin forms a gel like structure that can Used as scaffold for cell delivery, it provides a temporary support structure for cell growth and promotes tissue repair.
6.	Hyaluronic acid	This natural polymer is present in the extracellular matrix and has excellent biocompatibility and Mucoadhesion properties it can be used to create hydrogels for nasale drug delivery, providing sustained release of the drug.
7.	Synthetic polymer (poly lactic co- glycolic acid) PLGA	This biodegradable and biocompatible polymer is widely used in drug delivery systems including nasal formulations it.
8.	Polyethylene glycol (PEG)	This is non-toxic and hydrophilic polymer is often used to modify the surface properties of nano particles, improving their stability and cellular uptake.
9.	Polyvinyl pyrrolidine (PVP)	This water-soluble polymer is used as a film forming agent in nasal spray, helping to improve drug deposition in the nasal cavity.
10.	Other polymers Carbopol	This polymer is used as film forming agent and viscosity modifier in nasal spray.

folded structure consists of three turbinate: the superior, the median and the inferior. 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 nonolfactory 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. In this way the mucus layer is propelled in a direction from the anterior towards 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. The mucus secretion is composed of about 95% water, 2 % mucin, 1% salts, 1% of other proteins such as albumin, immunoglobulins, lysozyme and lactoferrin, and b 1% lipids.[21] The mucus secretion gives immune protection against inhaled bacteria and viruses. Schematic figure of a sagittal section of nasal cavity is shown in Figure 1.

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

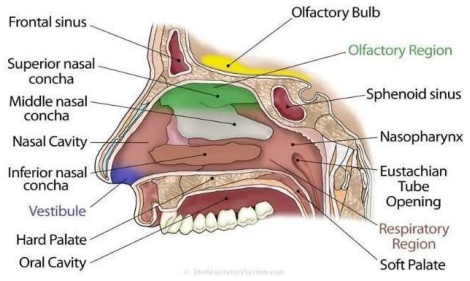

Figure 1: Schematic figure of a sagittal section of nasal cavity

Mechanism of Nasal absorption

The absorbed drugs from the nasal cavity must pass through the mucus layer; it is the first step in absorption. Small, unchanged drugs easily pass through this layer but large, charged drugs are difficult to cross it. The principle protein of the mucus is mucin, it has the tendency to bind to the solutes, hindering diffusion. Cell type of the nasal epithelium and drug transport was shown in Figure 2.

Additionally, structural changes in the mucus layer are possible as a result of environmental changes (i.e. pH, temperature, etc.) So many ab sorption mechanisms were established earlier but only two mechanisms have been predominantly used, such as [11,15,21,22,23]

First mechanism- It involves an aqueous route of transport, which is also known as the paracellular route but slow and passive. There is an inverse log correlation between intranasal absorption and the molecular weight of water-soluble com pounds. The molecular weight greater than 1000 Daltons having drugs shows poor bioavailability.

Second mechanism- It involves transport through a lipoidal route and it is also known as the transcellular.

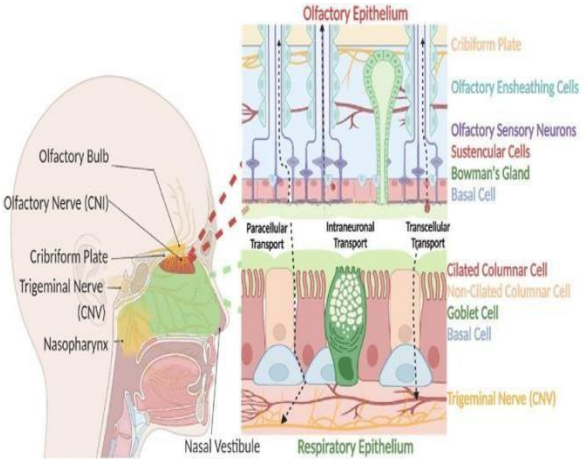

Figure 2: Cell type of the nasal epithelium and drug transport

Barriers to nasal absorption

Nasal drug delivery system is considered has a profitable route for the formulation scientist because it has easy and simple formulation strategies. Intra-nasally administered drug products therapeutic efficacy and toxicities are influenced by number of factors. Following are the barriers to the absorption of drugs through nasal cavity are shown in **Figure 3**.

Low bioavailability: Lipophilic drugs are generally well absorbed from the nasal cavity compared to polar drugs. The pharmacokinetic profiles of lipophilic drugs are often identical to those obtained after an intravenous injection and bioavailability approaching 100%. A good example of this is the nasal administration of Fentanyl where the t_{max} for both intravenous and nasal administration have been shown to be very rapid (7 min or less) and the bioavailability for nasal anterior part of the nasal cavity can decrease clear- administration was near 80%. The most important factor limiting the nasal absorption of polar drugs and especially large molecular weight polar drugs such as peptides and proteins is the low membrane permeability. [24,25]

Drugs can cross the epithelial cell mem brane either by the transcellular route exploiting simple concentration gradients, by receptor mediated or vesicular transport mechanisms, or by the paracellular route through the tight junctions between the cells. Polar drugs with molecular weights below 1000 Da will generally pass the membrane using the latter route.

Low membrane transport: Another importance factor is low membrane transport is the general rapid clearance of the administered formulation from the nasal cavity due to the mucociliary clearance mechanism. This is especially the case for drugs that are not easily absorbed across the nasal membrane. It has been shown that for both liquid and powder formulations, that are not mucoadhesive, the half- life of clearance is in the order of 15–20 min. It has further been suggested that the deposition of a formulation in the anterior part of the nasal cavity can decrease clearance and promote ab sorption as compared to deposition further back in the nasal cavity. Most nasal sprays of various makes have been shown to deliver the formulation to a limited area in the anterior part of the nasal cavity as opposed to nasal drops which will be delivered to a larger area further back in the nasal cavity. The use of bioadhesive excipients in the formulations is an approach to overcome the rapid mucociliary clearance. The clearance may also be reduced by depositing the formulation in the anterior, less ciliated part of the nasal cavity thus leading to improved absorption.[26, 27, 28] List of polymers used in nasal drug delivery is given in Table 1.

Metered Dose Inhalers: 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), [31]. Table 2 gives the list of Metered dose inhalers and techniques used. The advantages of MDIs are their portability and small size, availability over a wide do sage range per actuation, dose consistency, dose accuracy,

Table 2: List of Metered dose inhalers and techniques used [39-41]

Formulations	Excipients	API	Disease	Marketed Name	Techniques used
Meter dose inhalers	Suspending agents Co-solvent Drug stabilizer	Budesonide Glycopyrrolate Formoterol fumarate	COPD	AstraZeneca	Sub optimal Inhalation technique
Pressurised metered dose inhalers	Propellants Surfactants Buffering agents	Termeterol	COPD	Ventoline, Galaxo SmithKline	Different inhalational techniques
Metred dose inhalers	Preservatives Chelating agents Lecithin Sorbitol	Salbutamol	Obstructive pulmonary disease	Asthaline	Optimal inhaler technique
Metered dose inhalers	Binding agents, Fillers	Salbutamol, Antibiotics	Asthma COPD	Novartis Pharma	Metered Dose Technique
Metered Dose Inhalers	Film formers, Glidants	Glycopyrrolate	Uncontrolled Asthma	AstraZeneca	Randomised controlled technique
Pressurised Meter dose inhalers	Propellants Surfactants Buffering agents	Budesonide Fluticasone Beclomethasone	Respiratory disease	Galaxo SmithKline	Different Inhalational Techniques
MDI, Nebuliser	Diluents, Lubricants Cosolvent	Ipratropium bromide Oxymetazoline HCl Fentanyl citrate	Asthma	Pharmacia	Optimal Dose Inhalers
Metered Dose Inhalers, Nebulisers, Spacres	Solubilizing agents, surfactants, propellants	salmeterol Silicoxib Risperidone	Acute asthma for paediatrics	Proventil HFA	Randomised controlled Technique
Metered Dose Inhalers	Binding agents, propellants	Salbutamol Salmeterol, Dimorphine HCl Azelastine HCl	Asthma	Xopenex HFA	Inhaler technique
Metered Dose Inhalers	Diluents, Surfactants Humectant	Bambuterol Albuterol	Asthma Respiratory disorder	Azmacort	Metered dose Inhaler Technique
Meter dose inhalers	Suspending agents Co-solvent Drug stabilizer	Budesonide Glycopyrrolate Formoterol fumarate	COPD	AstraZeneca	Sub optimal Inhalation technique

protection of the contents and that they are quickly ready for use [32-35]. Figure 4 shows the Usage of Metered Dose Inhalers.

Metered-dose inhalers (MDIs) deliver a specific amount of aerosolized medication to the lungs for treating respiratory diseases.

Comparative dose charts help understand the low, medium, and high daily doses based on the medication strength and number of puffs.

Inhalers are a primary delivery method for medications used to treat asthma and chronic obstructive pulmonary disease (COPD).

Proper inhaler technique is crucial for ensuring the full dose of medication reaches the lungs.

Spacers can be used with MDIs to improve medication delivery and reduce side effects.

Besides MDIs, other types of inhalers include dry powder inhalers (DPIs) and soft mist inhalers. [36-38].

Nasal Powders: Nasal powder typically refers to powdered medications or supplements that are intended for nasal administration. These formulations can be used for various purposes, including treating nasal congestion, delivering medications for conditions like allergies, or even for drug delivery in certain therapies. It is important to use nasal powders as directed and consult with a healthcare professional for specific applications. [42, 43]. Nasal Powders example is given in Figure 5.

Nasal powders are powdered medications that are inhaled through the nose. They can be used to deliver drugs for various purposes, such as:

Decongestants: To relieve nasal congestion caused by colds or allergies.

Pain relief: Some pain medications can be administered nasally for rapid absorption.

Hormone replacement: Certain hormones can be delivered nasally for absorption into the bloodstream.

Table 3: List of Metered dose inhalers and techniques used [39-41]

Formulation	Excipients used	API	Disease	Marketed name	Techniques used
Nasal powders	Lactose, talc, magnesium stearate	Budesonide	Asthma	Pulmicort, Rhinocort, Turbuhaler	Purification, crystallization
	Magnesium stearate, Microcrystalline cellulose, sodium bicarbonate	Sumatriptan succinate	Migraine headache	Onzetra xsail	Direct compression
	Hydroxyl propyl cellulose, magnesium stearate, stearic acid	Beclomethasone dipropionate	Asthma, Allergy, Rhinitis	Teijin rhinocort, Qvar-redihaler, Beconase AQ, QNASL	Rapid expansion of supercritical solution
	Lactose	Dexamethason ecipecilate	Asthma, Arthritis,	Erizas	Solvent extraction
	Hyaluronic acid, chitosan glutamate	Gentamicin	Serious bacterial infections, UT infections	Garamycin, Gentak, genoptic	Solvent evaporation
	Sodium carboxy methyl cellulose, lactose monohydrate, magnesium stearate	Granisetron	Nausea & vomiting	Sancuso, Kytril, Granilet	Freeze drying
	Hydroxypropyl cyclodextrin, mucoadhesive polymer	Lorazepam	Anxiety, Insomnia, Amnesia, epilepsy	Ativan, Lorivan, L-zepam	Spray drying
	Sodium alginate, Chitosan hydrochloride	Metoclopromide	Nausea, vomiting	Reglan, metozolv ODT	Spray drying
	Chitosan propylene glycol	Verapamil	Angina, hypertension	Calan, verap, verelan	Spray drying, precipitation
	Chitosan/ Pectin poly electrolyte	Tacrine	Alzheimer's	Cognex	Spray drying

Table 4: List of Metered dose inhalers and techniques used [39-41]

Formulations	Excipients	API	Disease	Marketed name	Techniques used
Nasal sprays	Buffers	Salmon calcitonin	Osteoporosis	Karil 200 I.E	Nasal pump technique
	Solubilizers	Desmopressin	Antidiuretic	Minirin nasal spray	Nasal drops
	Preservatives	Buserelin	Buserelin	Profact nasal	Squeezed bottle Technique
	Antioxidants	Nafarelin	Endometriosis	Synarela	MDI technique
	Humectants	Oxytocin Zolmitriptan	Migraine	Syntocinon	Nasal spray aerosol technique
	Surfactants	Sumatriptan imigran	Migraine	Ascotop	Nasal pump technique
	Bio adhesive polymer	Dihydrofroergotamin	Migraine	Astrazenic	Nasal pump technique
	Penetration enhancer	Estradiol	Hormone replacement	Acrediol	Squeezed bottle technique
Nasal drops	Emulsifier	Bambuterol	Respiratory disorders	Asthalin	Nasal drop technique
Nasal sprays	Surfactants	Phenylephrine, chlorpheniramine	Cold	Artreven	Nasal pump droplets technique
	Buffers	Salmon calcitonin	Osteoporosis	Karil 200 I.E	Nasal pump technique

Vaccines: Nasal powder vaccines are being developed for diseases like influenza.[44, 45]

List of Marketed Nasal Powders and techniques used are given in Table 3.

Nasal Sprays: Nasal sprays are liquid medications delivered into the nasal passages to treat a variety of conditions. They offer a convenient and targeted way to deliver drugs, providing relief from congestion, allergies, and other nasal ailments. List of Marketed Nasal sprays and techniques used are given in Table 4. The active ingredients in nasal sprays can help to reduce inflammation, open up nasal passages, or deliver medication directly into the bloodstream. [48,49] Example of nasal sprays is given in Figure 6.

Nasal sprays are liquid medications administered into the nose. They're used for a variety of reasons, including:

Decongestants: Reduce nasal congestion from colds, allergies, or sinus infections.

Allergy Relief: Antihistamine or steroid nasal sprays can alleviate allergy symptoms.

Steroid Nasal Sprays: Reduce inflammation in the nasal passages, often for chronic sinusitis or nasal polyps.

Saline Nasal Sprays: Used to moisturize nasal passages and relieve dryness.

Other Medications: Some nasal sprays deliver medications for migraines or hormone replacement [50,51]

Nasal Liquids: "Nasal liquids" is a broad term, but generally, it refers to liquid formulations designed for administration into the nasal passages. These can include nasal sprays, drops, or washes. They're used to deliver medication, moisturize the nasal passages, or cleanse them.

List of Marketed Nasal sprays and techniques used are given in Table 5. The advantage of liquid formulations is that they can be easily dispersed within the nasal cavity, providing targeted relief or treatment. Nasal liquids are a method of delivering medication directly into the nasal passages. Example of Nasal Liquids is given in Figure 7.

This can be advantageous for several reasons:

Targeted Delivery: The medication goes directly to the source of the problem, like inflammation or congestion in the nasal passages.

Faster Absorption: Some medications can be absorbed quickly into the bloodstream through the nasal lining, leading to faster relief.

Bypass the Digestive System: This is helpful for medications that might be broken down in the stomach or liver before they can take effect.

Congestion: Decongestant nasal sprays.

Sinus Infections: Antibiotic or steroid nasal sprays.

Pain Relief: Some pain medications can be administered nasally.

Hormone Replacement: Certain hormones can be delivered nasally.[55, 56]

Nasal Gels: Nasal gels are a type of medication that is administered through the nose. They are often used to treat conditions that affect the nose or sinuses, such as allergies, sinus infections, and congestion. [59, 60]. List of Marketed Nasal gels and techniques used are presented in table 6. Nasal gels can also be used to deliver medication for other conditions, such as migraines and pain. Example of nasal gel is shown in Figure 8. There are two main types of nasal gels:

- In situ gels
- Mucoadhesive gels

Evaluation studies: *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 mucosal 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-coloured ampoules. The samples withdrawn are suitably replaced. The samples are estimated for drug content by suitable analytical technique. The temperature is maintained at 37^{o}C throughout the experiment.[64-66]

In Vivo* Nasal Absorption studies:* The animal models employed for nasal absorption studies can be of two types, viz., whole animal or in vivo model and an isolated organ perfusion or ex vivo model. These models are discussed in detail below: 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

Table 5: List of Marketed Nasal sprays and techniques used [57, 58]

Formulations	Excipients	API	Diseases	Marketed name	Techniques used
Nasal drops	Propylene glycol, sodium benzoate, Sorbitol	OxymetazolineXylometazoline	Erythema, allergic rhinitis	Nostrilla, Rhofade, Otrivin	Lyophilization, micro encapsulation
Nasal saline spray	Preservatives, EDTA, benzyl alcohol, antioxidants	Phenyl ephrine, NaCl, oxymetazoline	Sinus allergy, Nasal blockage, cold	Nazofed-5	Spray drying, freeze drying, blending
Nasal vaccines	Stabilizers, adjuvants, Preservatives, Surfactants	SARS-CoV-2 spike protein, SARS-CoV-2 nucleocapsid protein, antigens	COVID -19	Incovacc	Recombinant technology
Nasal aerosol spray	Solvents, preservatives, surfactants, stabilizers, Humectants	Phenyl ephrine, mupirocin, azelastine	Nasal inflammation Sinusitis, nasal congestion	Afrin, Dristan, Zetonna	Pressure spray method, Jet nebulization, freeze drying
Nasal decongestants	Chitosan, antioxidants, penetration enhancers surfactants	Pseudo ephedrine, oxymetazoline	Asthma	Sudafed, afrin, Zincam, claritin-D	Lyophilization, compound techniques, micronization, spray drying
Nebulizer aerosol	Polymercuric nitrate, Polysorbates, EDTA	Salbutamol, corticosteroids, Aztreonam	Asthma, COPD, cystic fibrosis	Atrovent, duoneb, Xopenex	Vibrating mesh technology, jet nebulization
Aerosols	Preservatives Polysorbates 80 Sorbitan, oleic acid, Trioleate	Bronchodilators	Asthma, COPD, bronchitis, tuberculosis	I-Rinse	Super critical fluid technology, high pressure homogenization, spray drying
Nasal spray	Phenyl ethyl alcohol, Benzalkonium chloride, antioxidants	Decongestants, Salmon calcitonin, Mucolytics	Cold, rhinitis, nasal polyps	Well air -FZ, asuflu -AZ	Nasal pump technology
Nasal drops	Sorbitol, preservatives, sodium benzoate	Calcitonin	Allergy, Erythema	Otrivin	Lyophilization
Nasal spray suspension	Solubilizers, surfactants, preservatives, tonicity agents	Decongestants Diphenhydramine	Sinusitis, hay fever, allergies	Nasonex	Mechanical dispersion, emulsification

drug solution is not drained from the nasal cavity through the mouth.[67-69]

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.

Rabbit model: The rabbit offers several advantages as an animal model for nasal absorption studies:

- It permits pharmacokinetic studies as with large animals (like monkey)
- It is relatively cheap, readily available and easily maintained in laboratory settings.
- The blood volume is large enough (approx. 300ml)
- To allow frequent blood sampling (l-2ml).

Thus, it permits full characterization of the absorption and determination of the pharmacokinetic profile of a drug. Rabbits (approx. 3 kg) are either anaesthetized or maintained in the conscious state depending on the purpose of study. In the anaesthetized model, intramuscular injection of a combination of ketamine and xylazine is given to anaesthetized rabbit. The rabbit's head is held in an upright position and nasal spray of drug solution is administered into each nostril. The body temperature of the rabbit is maintained at 37°C during experiment with the help of a heating pad. The blood samples are collected by an indwelling catheter in the marginal ear vein or artery. [70-74]

(C) *Ex vivo* Nasal Perfusion Models: Surgical preparation is the same as that is for in vivo rat model. During the perfusion studies, to minimize the

loss of drug solution a funnel is placed between the nose and reservoir. The drug solution is placed in a reservoir maintained at 37°C and is circulated through the nasal cavity of the rat with a peristaltic pump. The perfusion solution passes out from the nostrils (through the funnel) and runs again into the reservoir. The drug solution in the reservoir is continuously stirred. The amount of drug absorbed is estimated by measuring the residual drug concentration in the perfusing solution. Rabbit can also be used as the animal model for ex vivo nasal perfusion studies. The rabbit is anaesthetized with parenteral uretliane-acepromazine. A midline incision is made in the neck and the trachea is cannulated with a polyethylene neonatal endotracheal tube. The oesophagus is isolated and ligated.[75]

The distal end of the oesophagus is closed with suture and flexible tygon tubing is inserted into the proximal end and advanced to the posterior part of the nasal cavity. To avoid drainage of drug solution from the nasal cavity the nasopalatine tract (that connects nasal cavity to the mouth) is closed with an adhesive. The drug in isotonic buffer solution is recirculated using a peristaltic pump.

(D) *In-vivo* bioavailability study: It 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 × 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 analyse using the HPLC system. [76-77]

Applications

Delivery of non-peptide pharmaceuticals: Low molecular weight (below 1000 Daltons) small non-peptide lipophilic drugs are well absorbed through the nasal mucosa even though absence of permeation enhancer. Nasal membrane containing epithelium is highly vascularized and it contains large surface area it is readily accessible for drug absorption because presence of nasal turbinate. Drugs with extensive pre-systemic metabolism, such as progesterone, Estradiol, propranolol, nitro-glycerine, sodium cromoglycate can be rapidly absorbed through the nasal mucosa with a systemic bioavailability of ap proximately 100%. These drugs can reach widespread circulation within few minutes after dosing, as the venous blood passes from the nose directly into the systemic circulation. In fact, many drugs that are administered intranasally are often absorbed faster and more efficiently than those from oral administration translating into a quick uptake Some of non-peptide drugs being studied for nasal delivery and have shown good bioavailability by this route includes: [78]

- Adrenal corticosteroids
- Sex hormones: 17ß-estradiol, progesterone, norethindrone, and testosterone.
- Vitamins: vitamin B
- Cardiovascular drugs: hydralazine, Angiotensin II antagonist, nitro-glycerine, isosorbide dinitrate, propranolol, and colifiliumtosylate.
- Autonomic nervous system:
- Sympathomimetics: Ephedrine, epinephrine, phenylephrine,
- Xylometazoline, dopamine and dobutamine.
- Para sympathomimetics: nicotine, methacholine
- Para sympatholytic: scopolamine, atropine, ipratropium
- Prostaglandins
- Central nervous systems stimulants: cocaine, lidocaine
- Narcotics and antagonists: buprenorphine, naloxone.
- Histamine and antihistamines: disodium cromoglycate, meclizine
- Antimigraine drugs: dierogotamine, ergotamine tartrate
- Penicillin, cephalosporins, gentamycin.
- Antivirals: Phenyl-p-guanidine benzoate, enviroxime.
- Inorganic compounds: Inorganic salts, colloidal gold, colloidal carbon, colloidal silver.

Delivery of peptide-based pharmaceuticals: Peptides & proteins have a generally low oral bioavailability because of their physico-chemical instability and susceptibility to hepato-gastrointestinal first-pass elimination. Examples are insulin, calcitonin, pituitary hormones etc. These peptides and proteins are hydrophilic polar molecules of relatively high molecular weight, are poorly absorbed across biological membranes with bioavailabilities obtained in the region of 1–2% concentrations when ad ministered as simple solutions. To overcome this problem mainly we are using the absorption enhancers like surfactants, glycosides, cyclodextrin and glycols to increase the bioavailability. Nasal route is proving to be the best route for such biotechnological products [79].

Delivery of Drugs to Brain through Nasal Cavity: This delivery system is beneficial in conditions like Parkinson's disease, Alzheimer's disease or pain because it requires rapid and/or specific targeting of drugs to the brain. The development of nasal delivery system to brain will increase the fraction of drug that reach the CNS after nasal delivery. The olfactory region located at the upper remote parts of the nasal passages offers the potential for certain compounds

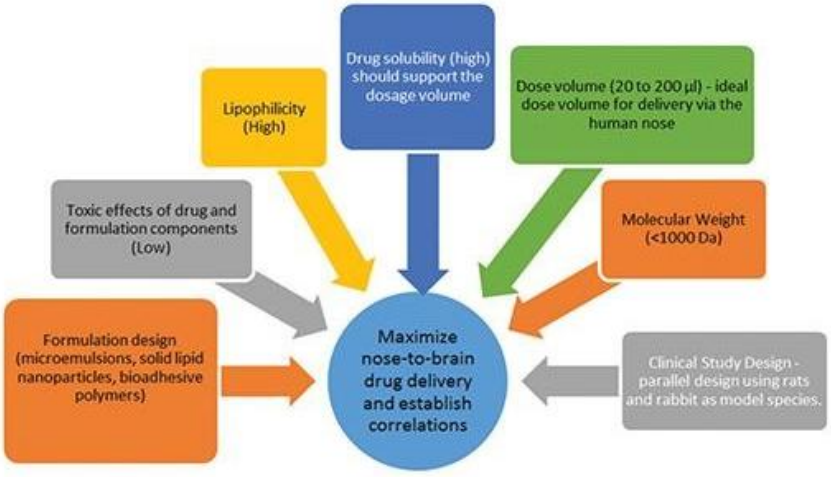

Figure 3: Barriers to the absorption of drugs through nasal cavity

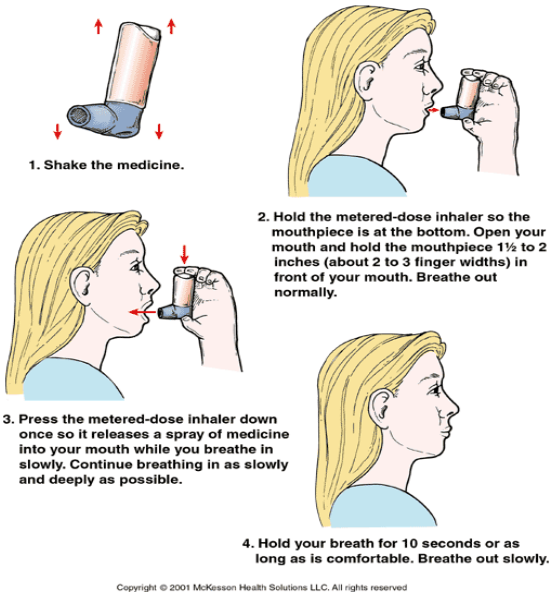

Figure 4: Usage of Metered Dose Inhalers

Figure 5: Nasal Powders

Figure 6: Nasal Sprays

Figure 7: Nasal Liquids

Figure 8: Nasal Gels

to circumvent the blood-brain barrier and enter into the brain.

The recent studies express neurotrophic factors such as NGF, IGF I, FGF and ADNF have been intranasally delivered to the CNS shows good results to increase the bioavailability of drug in the brain. Studies in humans, with proteins such as AVP, CCK analog, MSH/ACTH and insulin have revealed that they are delivered directly to the brain from the nasal cavity [80].

Delivery of Vaccines through Nasal Route: Mucosal sites give first line of defence against the microorganisms entered into the body, nasal mucosa act by filtering the pathogens from the inspired air by compaction and mucociliary clearance. Nose with nose- associated lymphoid tissue (NALT) acts as an effective site of immune system, it is called Waldeyer´s Ring in human beings and nasal secretions mainly contains immunoglobulins (IgA, IgG, IgM, IgE), protective proteins such as complement as well as neutrophils and lymphocytes in the mucosa. Main reasons for exploiting the nasal route for vaccine delivery are

- The nasal mucosa is the first site of contacts with inhaled pathogens,
- The nasal passages are rich in lymphoid tissue,
- Creation of both mucosal and systemic immune responses,
- Low cost, patient friendly, non-injectable, safe. Nasal delivery of vaccines has been reported to not only produce systemic immune response, but also local immune response in the nasal lining, providing additional barrier of protection.

Delivering the vaccine to the nasal cavity itself stimulates the production of local secretory IgA antibodies as well as IgG, providing an additional first line of defense, which helps to eliminate the pathogen before it becomes established. Recently, for the diseases like anthrax and influenza are treated by using the nasal vaccines prepared by using the recombinant Bacillus anthracis protective antigen (rPA) and chitosan respectively. The common diseases like measles, pertussis, meningitis and influenza causing pathogens are mainly enter into the body through the nasal mucosal surfaces and hence good candidates for nasal vaccines. Nasally administered vaccines, especially if based on attenuated live cells or adjuvanted by means of an immunostimulatory or a delivery system, can induce both mucosal and systemic (i.e. humoral and cell-mediated) immune responses [81-84].

CONCLUSION

Nasal drug delivery is a promising non-invasive approach for both systemic and localized drug administration, providing benefits such as fast drug absorption, bypassing first-pass metabolism, and enhanced patient compliance. The use of polymers—both natural and synthetic—plays a crucial role in optimizing drug release, Mucoadhesion, and stability. Applications of nasal drug delivery span across multiple therapeutic areas, including central nervous system disorders, infectious diseases, and vaccine delivery, demonstrating its versatility and potential for innovation. However, despite its advantages, nasal drug delivery faces limitations such as mucociliary clearance, enzymatic degradation, and inter-individual variability in nasal anatomy and physiology. Comprehensive evaluation techniques, including *in vitro*, *ex vivo*, and *in vivo* studies, are essential to assess drug permeability, safety, and efficacy. While significant progress has been made in nasal drug delivery systems, further research is needed to overcome existing challenges and optimize formulations for improved bioavailability and patient outcomes. Advances in nanotechnology, bioadhesive polymers, and targeted delivery strategies will continue to shape the future of this field, paving the way for more effective and patient-friendly therapeutic options.

REFERENCES

1. Hickey, A. J. (2004). Pharmaceutical inhalation aerosol technology (2nd ed.). Marcel Dekker.
2. Illum, L. (2003). Nasal drug delivery—Possibilities, problems and solutions. Journal of Controlled Release, 87(1–3), 187–198. https://doi.org/10.1016/S0168-3659(02)00368-6
3. Ugwoke, M. I., Verbeke, N., & Kinget, R. (2001). The biopharmaceutical aspects of nasal mucoadhesive drug delivery. Journal of Pharmacy and Pharmacology, 53(1), 3–21. https://doi.org/10.1211/0022357011775230
4. Arora, P., Sharma, S., & Garg, S. (2002). Permeability issues in nasal drug delivery. Drug Discovery Today, 7(18), 967–975. https://doi.org/10.1016/S1359-6446(02)02452-2
5. Singh, A. K., Singh, A., & Madhav, N. V. S. (2012). Nasal cavity: A promising transmucosal platform for drug delivery and research approach from nasal to brain targeting. Journal of Drug Delivery and Therapeutics, 2(3), 22–33.
6. Chirag, P., Tyagi, S., Mangukia, D., Ishita, S., Shreya, P., & Pinkesh, P. (2013). A recent review on alternative system of parenteral delivery: Nasal drug delivery system. Journal of Drug Discovery and Therapeutics, 1, 12–18.
7. Dale, O., Nilsen, T., Loftsson, T., Tønnesen, H. H., Klepstad, P., Kaasa, S., Holand, T., & Djupesland, P. G. (2006). Intranasal midazolam: A comparison of two delivery devices in human volunteers. Journal of Pharmacy and Pharmacology, 58(10), 1311–1318. https://doi.org/10.1211/jpp.58.10.0005
8. Ozer, Y. A. (1990). The importance of intranasal route for application of drugs and nasal drug delivery systems. Turkish Journal of Pharmaceutical Sciences, 30(3), 136–147.

9. Chajed, S., Sangle, S., & Barhate, S. (2011). Advantageous nasal drug delivery system: A review. International Journal of Pharmaceutical Sciences and Research, 2(6), 1322–1336.
10. Zaheer, A., Sachin, & Swamy, N. G. N. (2012). Mucoadhesive polymers: Drug carriers for improved nasal drug delivery. Indian Journal of Novel Drug Delivery, 4(1), 2–16.
11. Illum, L. (1996). Nasal delivery: The use of animal models to predict performance in man. Journal of Drug Targeting, 3, 427–442.
12. Ravikumar, R., Balan, R., Ganesan, N., & Thiruvengadam, D. (2015). Recent modalities in drug delivery via inhalation therapy – An advanced treatment strategy for pulmonary carcinoma. International Journal of Pharmacy and Pharmaceutical Sciences, 7, 8–21.
13. Behl, C., Pimplaskar, N. K., Sileno, A. P., Demeireles, J., & Romeo, V. D. (1998). Effect of physicochemical properties and other factors on nasal drug delivery. Advanced Drug Delivery Reviews, 29, 89–116.
14. Hickey, J. (2004). Pharmaceutical inhalation aerosol technology (2nd ed.). Marcel Dekker.
15. Alagusundaram, M., Deepthi, N., Ramkanth, S., Angalaparameswari, S., Saleem, T. S. M., Gnanaprakash, K., Thiruvengadarajan, V. S., & Chetty, C. M. (2010). Dry powder inhalers—An overview. International Journal of Research in Pharmaceutical Sciences, 1(1), 34–42.
16. Sharma, P. K., Chaudhari, P., Kolsure, P., Ajab, A., & Varia, N. (2006). Recent trends in nasal drug delivery system—An overview. Advance Research in Pharmaceuticals and Biologicals, 5, 1–4.
17. Arora, P., Sharma, S., & Garg, S. (2002). Permeability issues in nasal drug delivery. Drug Discovery Today, 7(18), 967–975.
18. Aulton, M. E. (2002). Pharmaceutics: The science of dosage form design (2nd ed.). Churchill Livingstone.
19. Aurora, J. (2002). Development of nasal delivery systems: A review. Drug Delivery and Technology, 2(7), 1–8.
20. Bawarshi, R. N., Hussain, A., & Crooks, P. A. (1989). Nasal absorption of 17α-ethinyloestradiol in the rat. Journal of Pharmacy and Pharmacology, 41, 214–215.
21. Bernstein, J. M., Reddy, M. S., Scannapieco, F. A., Faden, H. S., & Ballow, M. (1997). The microbial ecology and immunology of the adenoid: Implications for otitis media. Annals of the New York Academy of Sciences, 830, 19–31.
22. Buri, P. (1966). Hydrogels destinés à la muqueuse nasale. Pharmaceutica Acta Helvetiae, 41, 88–101.
23. Chien, Y. W., Su, K. S. E., & Chang, S. F. (1989). Nasal systemic drug delivery. In Marcel Dekker series on drug delivery (pp. 1–77). Marcel Dekker.
24. Chien, Y. W., & Chang, S. F. (1987). Intranasal drug delivery for systemic medications. Critical Reviews in Therapeutic Drug Carrier Systems, 4, 67–194.
25. Corbo, D. C., Liu, J. C., & Chien, Y. W. (1990). Characterization of the barrier properties of mucosal membranes. Journal of Pharmaceutical Sciences, 79, 202–206.
26. Dodane, V., Khan, M. A., & Merwin, J. R. (1999). Effect of chitosan on epithelial permeability and structure. International Journal of Pharmaceutics, 182, 21–32.
27. Donnelly, A., Kellaway, I. W., Taylor, G., & Gibson, M. (1998). Absorption enhancers as tools to determine the route of nasal absorption of peptides. Journal of Drug Targeting, 5, 121–127.
28. Durrani, Z., McInerney, T. L., McLain, L., Jones, T., Bellaby, T., Brennan, F. R., & Dimmock, N. J. (1998). Intranasal immunisation with a plant virus expressing a peptide from HIV-1 gp41. Journal of Immunological Methods, 220, 93–103.
29. Edman, P., Björk, E., & Ryden, L. (1992). Microspheres as a nasal delivery system for peptide drugs. Journal of Controlled Release, 21, 165–172.
30. Finlay, W. H. (2001). The mechanics of inhaled pharmaceutical aerosols. Academic Press.
31. Upadhyay, S., Parikh, A., Joshi, P., Upadhyay, U. M., & Chotai, N. P. (2011). Intranasal drug delivery system—A glimpse to become maestro. Journal of Applied Pharmaceutical Science, 1(3), 34–44.
32. Gizurarson, S., & Bechgaard, E. (1991). Intranasal administration of insulin to humans. Diabetes Research and Clinical Practice, 12, 71–84.
33. Hardy, J. C., Lee, S. W., & Wilson, C. G. (1985). Intranasal drug delivery by spray and drops. Journal of Pharmacy and Pharmacology, 37, 294–297.
34. Harris, A. S., Nilsson, I. M., Wagner, Z. G., & Alkner, U. (1986). Intranasal administration of peptides. Journal of Pharmaceutical Sciences, 75, 1085–1088.
35. Hirai, S., Yashiki, T., & Mima, H. (1981). Effect of surfactants on nasal absorption of insulin in rats. International Journal of Pharmaceutics, 9, 165–171.
36. Hofstee, B. H. (1952). Specificity of esterase II. Journal of Biological Chemistry, 199, 365–371.
37. Hughes, B. L., Allen, D. L., Dorato, M. A., & Wolff, R. K. (1993). Effect of devices on nasal deposition and mucociliary clearance in rhesus monkeys. Aerosol Science and Technology, 18, 241–249.
38. Hussain, A., Hamadi, S., Kagoshima, M., Iseki, K., & Dittert, L. (1991). Does increasing the lipophilicity of peptides enhance their nasal absorption? Journal of Pharmaceutical Sciences, 80, 1180–1181.
39. Hussain, A. A., Hirai, S., & Bawarshi, R. (1981). Nasal absorption of progesterone in rats. Journal of Pharmaceutical Sciences, 70, 466–467.

40. Hussain, A. A., Hirai, S., & Bawarshi, R. (1979). Nasal absorption of propranolol in rats. Journal of Pharmaceutical Sciences, 68, 1196–1199.
41. Hussain, A. A., Foster, T., Hirai, S., Kashihara, T., Batenhorst, R., & Jones, M. (1980). Nasal absorption of propranolol in humans. Journal of Pharmaceutical Sciences, 69, 1240–1243.
42. Hussain, M. A., Koval, C. A., Shenvi, A. B., & Aungst, B. J. (1990). Recovery of rat nasal mucosa from the effects of aminopeptidase inhibitors. Journal of Pharmaceutical Sciences, 79, 398–400.
43. Illum, L., Mathiowitz, E., Chickering, D. E., & Lehr, C. M. (2011). Advantageous nasal drug delivery system: A review. International Journal of Pharmaceutical Sciences and Research, 2(6), 1322–1336.
44. Parvathi, M. (2012). Intranasal drug delivery to brain: An overview. International Journal of Research in Pharmacy and Chemistry, 2(3), 889–895.
45. Hardy, J. G., Lee, S. W., & Wilson, C. G. (1985). Intranasal drug delivery by spray and drops. Journal of Pharmacy and Pharmacology, 37, 294–297.
46. Rudman, K. L., O'Brien, E. K., & Leopold, D. A. (2011). Radiographic distribution of drops and sprays within the sinonasal cavities. American Journal of Rhinology & Allergy, 25, 94–97.
47. Mahalaxmi, R., Kumar, D. S., & Shirwaikar, A. (2007). Preparation of mucoadhesive microspheres for nasal delivery by spray drying. Indian Journal of Pharmaceutical Sciences, 69, 651–657.
48. Mosab, A. (2025). Approaches to achieve an oral controlled release drug delivery system using polymers: A recent review. International Journal of Pharmaceutical Sciences, 7, 16–21.
49. Giuliani, A., Balducci, A. G., Zironi, E., Colombo, G., Bortolotti, F., & Lorenzini, L. (2018). In vivo nose-to-brain delivery of ribavirin. Drug Delivery, 25, 376–387.
50. Dinanath, G., Padmini, K., Dipak, M., & Namdeo, J. (2017). Development of particulate mucoadhesive gel for intranasal delivery. Asian Journal of Pharmaceutical and Clinical Research, 10, 222.
51. Kritika, S., Bhupen, K., & Banasmita, K. (2016). Development of mucoadhesive microsphere-loaded intranasal gel. Asian Journal of Pharmaceutical and Clinical Research, 9, 139–144.
52. Balducci, A. G., Nastruzzi, C., Colombo, P., & Sonvico, F. (2013). Antidiuretic effect of desmopressin chimera agglomerates. International Journal of Pharmaceutics, 440, 154–160.
53. Pringels, E., Callens, C., Vervaet, C., Dumont, F., Slegers, F., Foreman, P., & Remon, J. P. (2006). Influence of deposition and spray pattern of nasal powders on insulin bioavailability. International Journal of Pharmaceutics, 310, 1–7.
54. Martignoni, I., Trotta, V., Lee, W. H., Loo, C. Y., Pozzoli, M., Young, P. M., Scalia, S., & Traini, D. (2016). Resveratrol solid lipid microparticles for nasal delivery. Journal of Microencapsulation, 33, 735–742.
55. Mosab, A. (2025). Approaches to achieve an oral controlled release drug delivery system using polymers: A recent review. International Journal of Pharmaceutical Sciences, 7, 16–21.
56. Charlton, S. T., Davis, S. S., & Illum, L. (2007). Evaluation of bioadhesive polymers for nose-to-brain delivery. Journal of Controlled Release, 118, 225–234.
57. Giuliani, A., Balducci, A. G., Zironi, E., Colombo, G., Bortolotti, F., & Lorenzini, L. (2018). In vivo nose-to-brain delivery of ribavirin. Drug Delivery, 25, 376–387.
58. Deleu, D., & Hanssens, Y. (2000). Second-generation triptans in acute migraine therapy. Journal of Clinical Pharmacology, 40, 687–700.
59. Rudman, K. L., O'Brien, E. K., & Leopold, D. A. (2011). Radiographic distribution of drops and sprays. American Journal of Rhinology & Allergy, 25, 94–97.
60. Mustafa, E., Shaimaa, N. M., & Al, A. (2016). Design of zolmitriptan liquisolid orodispersible tablets. International Journal of Pharmaceutical Sciences, 9, 297–303.
61. Pelgrim, G. J., Das, M., Haberland, U., Slump, C., Handayani, A., & Van Tuij, S. (2015). Development of an ex vivo beating heart model. Biomedical Research International, 2015, 1–8.
62. Kozlovskaya, L., Abou-Kaoud, M., & Stepensky, D. (2014). Quantitative analysis of drug delivery to the brain via nasal route. Journal of Controlled Release, 189, 133–140.
63. Thornton-Manning, J. R., & Dahl, A. R. (1997). Metabolic capacity of nasal tissue. Mutation Research, 380, 43–59.
64. Stevens, J., Ploeger, B. A., van der Graaf, P. H., Danhof, M., & de Lange, E. C. (2011). Nose-to-brain transport pharmacokinetic model. Drug Metabolism and Disposition, 39, 2275–2282.
65. Giuliani, A., Balducci, A. G., Zironi, E., Colombo, G., Bortolotti, F., Lorenzini, L., Galligioni, V., Pagliuca, G., Scagliarini, A., Calzà, L., & Sonvico, F. (2018). In vivo nose-to-brain delivery of ribavirin. Drug Delivery, 25, 376–387.
66. Hammarlund-Udenaes, M., de Lange, E., & Thorne, R. G. (2014). Pharmacokinetic concepts in brain drug delivery. In Drug delivery to the brain (pp. 127–161). Springer.
67. Lee, V. H. L. (1988). Enzymatic barriers to peptide and protein absorption. Critical Reviews in Therapeutic Drug Carrier Systems, 5, 69–97.
68. Rathananand, M., Kumar, D. S., Shirwaikar, A., Kumar, R., & Kumar, D. S. (2007). Preparation of mucoadhesive microspheres for nasal delivery. Indian Journal of Pharmaceutical Sciences, 69, 652–657.

69. Martin, E., Nicolaas, G. M., Schipper, J., Coos, V., & Frans, W. H. (1997). Nasal mucociliary clearance. Advanced Drug Delivery Reviews, 29, 13–38.
70. McMartin, C., Hutchinson, L. E., Hyde, R., & Peters, G. E. (1987). Structural requirements for nasal absorption. Journal of Pharmaceutical Sciences, 76, 535–540.
71. Mestecky, J., Moldoveanu, Z., Michalek, S. M., Morrow, C. D., Compans, R. W., Schafer, D. P., & Russell, M. W. (1997). Vaccine delivery by mucosal routes. Journal of Controlled Release, 48, 243–257.
72. Ugwoke, M. I., Agu, R. U., Verbeke, N., & Kinget, R. (2005). Nasal mucoadhesive drug delivery. Advanced Drug Delivery Reviews, 57, 1640–1665.
73. Morimoto, K., Miyazaki, M., & Kakemi, M. (1995). Effects of proteolytic enzyme inhibition. International Journal of Pharmaceutics, 133, 1–8.
74. Mygind, N., & Vesterhauge, S. (1978). Aerosol distribution in the nose. Rhinology, 16, 79–88.
75. Newhouse, M. T. (1991). Advantages of pressurized metered-dose inhalers. Journal of Aerosol Medicine, 4, 139–150.
76. O'Hagan, D. T., & Illum, L. (1990). Absorption of peptides and proteins from the respiratory tract. Critical Reviews in Therapeutic Drug Carrier Systems, 7(1), 35–97.
77. Ohwaki, K., Ando, H., Watanabe, S., & Miyake, Y. (1985). Effects of dose, pH and osmolarity. Journal of Pharmaceutical Sciences, 74, 550–552.
78. Ramaprasad, Y. V. (1996). Intranasal drug delivery systems. Indian Journal of Pharmaceutical Sciences, 58, 1–8.
79. Sarkar, M. A. (1992). Drug metabolism in the nasal mucosa. Pharmaceutical Research, 9, 1–9.
80. Satish, B. B., Adhikrao, V. Y., Amelia, M. A., & Rajkumar, M. (2008). Bioavailability of intranasal drug delivery system. Asian Journal of Pharmaceutics, 201–215.
81. Soane, R. J., Frier, M., Perkins, A. C., Jones, N. S., Davis, S. S., & Illum, L. (1999). Evaluation of clearance characteristics of bioadhesive systems. International Journal of Pharmaceutics, 178, 55–65.
82. Soane, R. J., Hinchcliffe, M., Davis, S. S., & Illum, L. (2001). Clearance characteristics of chitosan-based formulations. International Journal of Pharmaceutics, 217, 183–191.
83. Striebel, H. W., Kramer, J., Luhmann, I., Rohierse-Hohler, I., & Rieger, A. (1993). Pharmacokinetics of intranasal fentanyl. Der Schmerz, 7, 122–125.