

ENHANCING THERAPEUTICS: A COMPREHENSIVE REVIEW ON NASO-PULMONARY DRUG DELIVERY SYSTEMS FOR RESPIRATORY HEALTH MANAGEMENT

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ABSTRACT

Breathing health and wellness administration has actually experienced substantial improvements with the growth of ingenious medication distribution systems. This detailed testimonial discovers the Naso-Pulmonary Drug Delivery Systems (NPDDS) made to boost therapeutics for breathing problems. Attending to the detailed landscape of medication management to the breathing system the testimonial seriously analyzes numerous distribution systems concentrating on both nasal as well as lung paths. The testimonial explores aspects affecting nasal medicine absorption covering physicochemical residential or commercial properties, nasal results and also distribution results. A comprehensive examination of perfect nasal

medicine prospects highlights features such as suitable solubility, absorption residential properties, reduced dosage, and also security. The conversation reaches obstacles like ecological pH, mucociliary clearance, along with the effect of cold coupled with rhinitis on medicine absorption. The physicochemical homes of medicines, membrane layer leaks, as well as mucociliary clearance are taken apart in the context of aspects affecting nasal medicine absorption. The testimonial examines the duty of thickness in medicine absorption coupled with gives understandings right into approaches to enhance nasal absorption. Dosage forms, varying from fluid solutions to powder dose kinds, nasal gels, microspheres, plus numerous management devices are thoroughly checked out. Finally this evaluation settles varied point of views on NPDDS, providing a refined understanding of the difficulties as well as improvements in breathing wellness monitoring.

INTRODUCTION

The historic use of the nasal path in the Indian Ayurvedic clinical system referred to as "Nasya," laid the structure for modern intranasal medication distribution. Recognized as a useful as well as trusted option to parenteral as well as dental courses, intranasal management has actually been extensively utilized for dealing with leading nasal problems and also offering symptomatic alleviation.^[1] Nasal administration, accomplished through insufflations, serves as a versatile method for both topical and systemic drug delivery, with pharmacological targets often being a primary focus. Notably, intranasal administration proves advantageous for substances like peptides, proteins, and polar medications that face challenges in gastrointestinal fluids, intestinal absorption, and hepatic first-pass elimination. Its potential extends to bypassing the blood-brain barrier for direct drug delivery to the central nervous system, a particularly promising aspect for certain pharmacologically active substances.^[1]

Subsequent deposition in the lower airways, represents a significant facet of drug administration. With rapid absorption, especially for non-macromolecular medications, pulmonary-delivered drugs can enhance bioavailability. Formulations may incorporate permeation enhancers, stabilizers, and buffers to ensure protein stability and prevent aggregation. The pulmonary route boasts unique features, including a substantial absorptive area, thin mucosal membranes, and excellent blood supply, making it increasingly vital in contemporary drug delivery.^[1]

Breathing treatment, an age-old technique of medication management via the breathing system has actually confirmed reliable for regional therapy of lung problems such as bronchial asthma. Current years have actually observed the proceeded success of breathing treatment in resolving problems like persistent obstructive lung condition (COPD).^[2,3]

Presently, nasal management systems are utilized for varied objectives, varying from dealing with nocturnal enuresis, weakening of bones, together with migraine headache, to attending to vitamin B12 shortage. Continuous research study checks out the possible application of nasal distribution in locations like cancer cells therapy, epilepsy, rheumatoid joint inflammation, anti-emetics, as well as insulin-dependent diabetic issues.^[4,5] This advancing landscape underscores the adaptability together with increasing duty of intranasal as well as lung medication shipment systems in contemporary healing treatments.

Anatomy and Physiology of Nose and Pulmonary System^[6,7 12-18]

- **Nose:** - The nose, a multifunctional and intricate organ, serves as the primary entry point to the respiratory tract.
- **External Nose:** - Constituting a pyramidal framework in the mid-face the exterior nose includes nasal bones creating its exceptional element together with combined cartilage material forming its substandard area. The top side cartilages specify the center 3rd giving assistance for the underlying nasal shutoff. Raised nasal breathing sets off expansion muscular tissues, improving nasal respiratory tract patency throughout tasks like workout.
- **Vestibule:** - As the first sector experiencing the exterior atmosphere the vestibule is lined up with stratified squamous epithelium distinct from the breathing epithelium covering the remainder of the nasal tooth cavity. Transitions to pseudo stratified columnar epithelium take place coupled with the vestibule hosts thermo receptors essential for picking up nasal air movement.
- **Nasal Valve and Airflow:** - Located simply back to the nasal vestibule the nasal shutoff is delimited by the top side cartilage material, septum, plus the reduced edge of the pyriform aperture. The nasal septal inflame body an expansile vascular cells, adds functionally to this area, influencing the nasal respiratory tract's patency.
- **Nasal Septum:** - Dividing the nasal tooth cavity right into 2 areas the nasal septum enhances the mucosal surface. Making up an anterior cartilaginous part sustaining the nasal pointer as well as a back bony component the nasal septum displays variants with age together with sex.
- **Turbinates:** - Three or sometimes 4 scroll-like forecasts the turbinates prolong from the side nasal wall surface. Functionally substantial, the substandard turbinate plays a crucial duty in lung protection as well as nasal physiology. Cutting must be thought about cautiously, blog post detailed examination of prospective reasons for enhancement.
- **Histology:** - The nasal cellular lining consists of deadly epithelial as well as submucosal layers. Pseudo stratified columnar epithelium including digestive tract cells as well as ciliated as well as nonciliated columnar cells, develops the safety obstacle. Seromucous glands focused in the former nasal dental caries, produce either a filled with serum or mucous secretion.
- **Mucociliary Clearance:** - The nasal tooth cavity counts on mucociliary transport to get rid of secretions as well as particulates. The mucous covering as well as ciliated epithelial cells comprise the key parts of this clearance system.

- **Lungs:** - The lungs critical in the breathing system help with gas exchange by removing oxygen together with launching co₂. Cone-shaped fit with a slim peak getting to the origin of the neck the lungs encompass the foundation in the rib cage to the diaphragm. The left lung, sharing room with the heart, includes a heart notch. Both lungs show a hilum at their origin, acting as the entry factor for capillary together with respiratory tracts together with bronchopulmonary lymph nodes.
- **Lung regions:** - Categorizing the respiratory system system 3 areas consist of the nasopharyngeal (top respiratory system), tracheo-bronchial (main or performing air passages), and also alveolar (breathing airways or lung area).
 - **Right lung:** - The best lung, identified by a greater variety of wattles as well as sections than the left is elaborately split right into 3 wattle. These consist of the top center, as well as reduced wattles, delimited by 2 cracks-- one likely as well as one straight.
 - **Left lung:** - In comparison the left lung includes a department right into 2 wattles, specifically the top coupled with reduced wattles. This demarcation is helped with by the sloping split prolonging from the costal to the mediastinal surface area of the lung both over and also listed below the hilum.
- **Nasopharyngeal region:** - Termed the “top air passages” the nasopharyngeal area includes breathing airways expanding from the nose to the throat.
- **Tracheo-bronchial region:** - Referred to as the “main” or “carrying out respiratory tracts” the tracheo-bronchial area starts at the throat and also extends with the windpipe, bronchis together with bronchioles ending at the incurable bronchioles.
- **Alveolar region:** - Also acknowledged as the “breathing respiratory tracts”, “outer air passages” or “lung area” the alveolar area makes up the respiratory system bronchioles, alveolar ducts, coupled with alveoli.
- **Pulmonary epithelium:** - The lung includes varied cell kinds lining the air passages. From bronchi to bronchioles and also the alveolar area, different cell kinds, consisting of ciliated plus digestive tract cells, add to the epithelial framework.
- **The bronchial tubes:** - The bronchis display a cellular lining mainly made up of ciliated plus digestive tract cells. Moreover, one can discover the existence of filled with serum cells, brush cells along with Clara cells with a minimal variety of Kulchitsky cells.

- **The bronchioles:** - Characterized by mainly ciliated cuboidal cells, the bronchioles show a reduction in the regularity of digestive tract and also filled with serum cells as one progression along the air passages. Simultaneously, the variety of Clara cells boosts.
- **The alveolar region/The respiratory tracts:** - In plain comparison the respiratory tracts does not have mucous and also includes a significantly flatter epithelium, transitioning right into the basic squamous kind with a density varying from 0.1 to 0.5 μm .
- **Ciliated cells:** - In the tracheobronchial area, ciliated cells abundant in the main air passages, slowly reduce in the direction of the outer parts. The alveolar area does not have cilium, with a change to easy squamous epithelium. In the tracheobronchial area, a substantial percentage of epithelial cells brag ciliation leading to detailed insurance coverage of the main respiratory tracts by cilia. Relocating in the direction of the outer components of the tracheobronchial area, the wealth of cilia reduces eventually being lacking in the alveolar area.

Each cilium is furnished with roughly 200 cilia intermixed with various microvilli determining concerning 1-2 μm in size. These hair-like forecasts with a size of around 0.25 μm as well as a size of 5 μm add to the detailed systems promoting breathing features.

- **Major Functions of the Respiratory System**
- **Maintaining Hemostasis (Acid-Base Balance) of Arterial Blood:** - The respiratory system is critical in controlling the acid-base balance of arterial blood. It helps to maintain an ideal pH level of the blood through exhalation, which controls its carbon dioxide content.
- **Maintaining Heat Exchange:** - Another important role the respiratory system plays is in heat exchange. As air travels through the respiratory passages, it modifies its temperature by which makes it possible for the body to keep its internal temperature at an optimal level.
- **Removing Waste (Carbon Dioxide) from Body Tissues:** - The respiratory system forms part of an essential pathway through which waste products such as carbon dioxide, generated through metabolic activities mostly in cells, are expelled. Carbon dioxide is transported from various tissues of the body to lungs for removal using breaths during respiration.
- **Supplying Oxygen to the Body:** - A fundamental function performed by the respiratory system is oxygen delivery to body tissues. Oxygen is taken into lungs from environment

during breathe-in where it then enters into bloodstream and carried throughout body by circulatory system. These supports energy production and cellular activities with rich oxygenated blood supply.

- **Air Conditioning:** - The procedure of air conditioning is started by the nose, which warms up, humidifies as well as filters the inbound air so it can be traded for ideal respiration.
- **Organ of Sense - Smell:** - As an odor body organ the nose has nerves in its top component that create smells plus make it possible for feeling of odor.
- **Passage for Food and Air - Pharynx in Respiratory plus Digestive Systems:** - Pharynx in Respiratory plus Digestive Systems: The throat offers both as a breathing as well as gastrointestinal body organ. It permits flow of both air and also food with nasal/oral area permitting the flow of air together with oral/laryngeal area joining the flow of food.
- **Sense of Taste - Olfactory Nerve Endings in the Pharyngeal Epithelium:** - Within dental throat are discovered olfactory nerve ends that help in sampling. This combination in between preference buds and also olfactory light bulbs enhances total sensory experiences while consuming.
- **Hearing - Auditory Tube as well as Middle Ear:** - The center ear is attached to the exterior atmosphere by an auditory tube which plays a substantial function in controlling stress on both sides of the tympanic membrane layer therefore accomplishing balance required for appropriate hearing.
- **Protection - Lymphatic Tissue of Pharyngeal as well as Laryngeal Tonsils:** - The lymphatic cells in the pharyngeal and also laryngeal tonsils offers a safety feature by creating antibodies in action to antigens such as microbes. This adds to the body's body immune system and also protection versus possible infections.

Advantages of Pulmonary Drug Delivery

Sr. No.	Advantages	Description
1.	Needle-Free Administration	The requirement for needles can be eliminated by pulmonary drug delivery, thus providing a more convenient and patient-friendly approach
2.	Reduced Dose Requirement	This has the potential of reducing costs while at the same time making drug delivery efficient through the pulmonary route which often requires lower oral dosages.
3.	Lower Systemic Concentrations and Reduced Side Effects	Lower systemic concentrations cause a decrease in systemic side effects, thus improving the safety of the treatment.

4.	Rapid Onset of Action	Addressing acute medical conditions requires pulmonary drug delivery that leads to rapid action.
5.	Avoidance of Gastrointestinal Upset	By passing through the gastrointestinal tract, pulmonary drug delivery avoids causing stomach upset that often accompanies oral drugs.
6.	Prevention of Hepatic Degradation	Pulmonary administration prevents liver degradation thus safeguarding against deterioration and effectiveness of administered drugs.
7.	Alternative to Parenteral Route for Proteins and Peptides	A viable alternative to parenteral route for protein and peptide drugs may be through nasal route as some studies suggest.
8.	Convenience for Long-Term Therapy	For patients undergoing prolonged therapeutic regimens pulmonary drug delivery is particularly desirable since it offers an easier long-term therapy.
9.	Suitable for Drugs with Poor Gastrointestinal Stability	Nasal delivery is effective for drugs with poor stability in gastrointestinal fluids, providing a reliable administration route.
10.	Ideal for Polar Compounds with Poor Oral Absorption	Pulmonary drug delivery is well-suited for polar compounds that exhibit poor absorption through the oral route, providing an effective means of drug administration.

Table 1: Advantages of Pulmonary Drug Delivery.**Negative Aspects of Pulmonary Medication Distribution**

Sr. No.	Negative Aspect	Description
1.	Oropharyngeal Down Payment and Local Side Effects	May cause neighborhood adverse effects affecting the mouth as well as throat locations.
2.	Problem in Device Usage	Individuals might encounter troubles in effectively making use of lung medication tools possibly impacting medicine shipment
3.	Restricted Drug Absorption due to Mucus Layer	The existence of a mucus layer works as a physical obstacle restricting medicine absorption as well as impacting total efficiency
4.	Reproducibility Challenges	Physical as well as pharmaceutical obstacles present irregularity in the reproducibility of medicine shipment to the lungs.
5.	Requirements for Targeted Delivery Devices	Reliable medicine shipment to the lungs requires specialized shipment tools, including intricacy to management.
6.	Risk of Local Side Effects and Cilia Damage	Regional negative effects as well as possible damages to cilia on nasal mucosa can happen as a result of the make-up of the dose kind.
7.	Surfactant-Related Issues	Particular surfactants made use of as chemical boosters might position threats by a disturbance or liquifying membrane layers at high focus.

8.	Mechanical Loss into Other Respiratory Tract Parts	Inappropriate management methods might cause mechanical loss of the dose kind right into various other components of the breathing system especially the lungs impacting medicine efficiency.
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Table 2: Disadvantages of Pulmonary Drug Delivery.**Mechanism of Drug Absorption In Nasal Drug Delivery**

- **A General Overview**

The system of medicine absorption in nasal medicine distribution includes a number of essential procedures that assist in the uptake of the medicine with the nasal mucosa and also its succeeding access right into the systemic flow. The nasal mucosa which lines the nasal tooth cavity is abundant in capillary along with supplies a huge area for medicine absorption. Below is a summary of the major systems included::

Passive Diffusion: Many medications in nasal medication distribution rely upon passive diffusion for absorption. The medicine particles relocate from a location of greater focus (nasal solution) to a location of reduced focus (blood stream) throughout the mucosal membrane layers.

Transcellular Transport: Drug particles permeate the nasal epithelial cells to get to the blood stream. This procedure includes diffusion with the lipid-rich/containing cell membrane layers.

Paracellular Transport: Some medications might be taken in with the intercellular rooms in between epithelial cells. This route entails flow with limited joints in between surrounding cells.

Active/Energetic Transport: In specific instances certain providers on the nasal epithelial cells proactively assist in the activity of medicines right into the blood stream. This mechanism may be selective and involve carrier proteins.

Endocytosis/Exocytosis: Huge particles or fragments might be used up by the nasal epithelial cells via endocytosis creating vesicles. These vesicles can after that move the medicine throughout the cell plus launch it on the basolateral side with exocytosis.

Metabolic rate in the Nasal Mucosa: The nasal mucosa has enzymes that can metabolize specific medicines. Metabolic process in the mucosa can affect the bioavailability of the medicine getting to the systemic flow.

Mucociliary Clearance: The nasal mucosa is covered by a layer of mucus and also cilia aid in relocating this mucous. The mucociliary clearance device might influence the home time of medications in the nasal dental caries affecting absorption.

Permeability (Leaks of) Enhancement Strategies: Formulations might integrate leaks boosters to boost the absorption of medicines throughout the nasal mucosa. These boosters might momentarily interrupt limited joints or change the residential properties of the mucosal membrane layer.

Flow Charts/ Figure 1: Mechanism of Drug Absorption in Nasal Drug Delivery**OR**

The preliminary step in medication absorption from the nasal dental caries calls for nail down the mucous layer, functioning as a critical phase in the absorption procedure. Mucin the main healthy protein in mucous displays an inclination to bind to solutes, impeding their diffusion.

Additionally, changes in the ecological problems (e.g. pH, temperature level) can cause architectural adjustments in the mucous layer.^[10] While numerous absorption systems have actually been recognized, the primary use has actually been observed in 2 vital devices:

- a) **First Mechanism:-** This includes an aqueous course of transportation generally described as the paracellular course defined by its sluggish together with easy nature. Notably there exists an inverted log-log connection in between intranasal absorption as well as the molecular weight of water-soluble substances. Substances with a molecular weight surpassing 1000 Daltons display inadequate bioavailability.^[11]
- ❖ **Second Mechanism:-** This involves transport via a lipoidal course likewise referred to as the transcellular procedure. It helps with the transport of lipophilic medications, showing a price dependence on their lipophilicity. In addition medicines can go across cell membrane layers with an energetic transportation path promoted by carrier-mediated ways or by traversing the opening of limited joints.^[11]

How To Choose Potential Api To Deliver It Through Nasal Route^[19]

- An 'optimum' medication prospect for nasal shipment must have the adhering to attributes:
- a) Appropriate aqueous solubility to help with the management of the wanted dosage within a quantity varying from **25 to 150 ml per nostril** in the solution.
 - b) Ideal nasal absorption residential or commercial properties to make sure **reliable absorption** as well as restorative effectiveness.
 - c) **Absence of nasal inflammation** brought on by the medication, guaranteeing individual convenience throughout management.
 - d) A warranted professional basis for nasal dose types such as **a quick beginning of activity**, adding to the efficiency of the therapy.
 - e) Reduced dose need generally listed **below 25 mg per dosage**, boosting security as well as decreasing the danger of negative results.
 - f) No manufacturing of **poisonous nasal metabolites**, making sure the security of the nasal medicine shipment approach.
 - g) Absence of **undesirable smells or fragrance** connected with the medication, advertising a favorable person experience.
 - h) Showing appropriate security attributes to keep the honesty and also effectiveness of the medication throughout its life span as well as management.

❖ Barriers / Obstacles To Nasal Absorption

Nasal medication distribution systems are thought about a profitable opportunity for solution researchers as a result of their very easy and also simple solution techniques. The healing efficiency and also toxicities of medicine items provided intra-nasally are affected by a number of aspects.^[20] The complying with elements stand for obstacles to the absorption of medications with the nasal dental caries.

1. Low Bioavailability

Lipophilic medications usually experience reliable absorption from the nasal dental caries contrasted to polar medications. The pharmacokinetic accounts of lipophilic medicines commonly mirror those gotten after intravenous shot, with bioavailability coming close to 100%. As an example nasal management of Fentanyl showed quick Tmax (7 mins or much less) for both intravenous as well as nasal management with nasal bioavailability nearing 80% in the former component of the nasal dental caries.^[21]

The key restriction for nasal absorption of polar medications particularly big molecular weight polar medications like peptides as well as healthy proteins is their reduced membrane layer leaks. Medicines can go across the epithelial cell membrane layer via the transcellular path making use of focus inclinations, receptor-mediated or vesicular transportation devices, or the paracellular course with limited joints in between cells. Polar medicines with molecular weights listed below 1000 Da normally make use of the last path for membrane layer flow.^[22]

Larger peptides as well as healthy proteins have actually shown the capability to go across the nasal membrane layer via an endocytotic transportation procedure albeit in minimal quantities.^[23]

2. Reduced Membrane Layer Transportation

One more vital variable is the reduced membrane layer transportation, mostly credited to the quick clearance of the carried out solution from the nasal dental caries driven by the mucociliary clearance device. This sensation is especially substantial for medications that do not easily go across the nasal membrane layer. Research studies suggest that for both fluid plus powder solutions doing not have mucoadhesive homes the half-life of clearance varies from 15 to 20 mins^[24] It has actually been suggested that placing a solution in the former component of the nasal tooth cavity can decrease clearance prices plus improve absorption contrasted to down payment even more back in the nasal tooth cavity.^[25]

the nasal tooth cavity, vary from nasal declines which disperse the solution to a much more substantial location even more back in the nasal dental caries. The unification of bioadhesive excipients in solutions stands for a technique to neutralizing the rapid mucociliary clearance. Furthermore decreasing clearance can be accomplished by transferring the solution in the former much less ciliated component of the nasal tooth cavity consequently boosting absorption.^[26]

3. Enzymatic Destruction

An additional contributing variable albeit typically thought about much less substantial to the reduced transportation of peptides and also healthy proteins specifically throughout the nasal membrane layer is the capacity for enzymatic destruction. This destruction might take place either within the nasal tooth cavity lumen or throughout flow throughout the epithelial obstacle. Both of these websites have exopeptidases consisting of mono- plus di-amino-peptidases with the ability of cleaving peptides at their N as well as C termini together with endo-peptidases such as amino acid as well as cysteine which can strike inner peptide bonds.^[27]

Minimizing techniques for conquering this obstacle might include using enzyme preventions along with/or the saturation of enzymes functioning as possible techniques to boost the security together with transportation of peptide along with healthy protein particles.^[28]

❖ Elements Impacting Nasal Medication Absorption/ Factors Influencing Nasal Drug Absorption

• General Overview

The systemic bioavailability of medications provided with the nasal path is affected by different aspects including the physicochemical residential or commercial properties of the medications, the physiological and also physiological qualities of the nasal tooth cavity as well as the kind of picked nasal medication shipment system. The elements affecting nasal medication absorption are called complies with:

Physicochemical Properties of Drugs

The nature helpful consisting of their solubility, lipophilicity, molecular weight, coupled with fee dramatically affects their absorption with the nasal mucosa.

Physiological and also Anatomical Properties of the Nasal Cavity

The huge areas of the nasal tooth cavity, abundant blood supply as well as the existence of a slim epithelial obstacle add to medication absorption. The thickness of capillary and also the special framework of the nasal epithelium effect on the price and also degree of medication absorption.

Types of Nasal Drug Delivery System

The solution as well as distribution system selected for nasal medicine management play a

vital duty in medication absorption. Variables such as dose kind (spray, gel, powder), solution ingredients, together with medicine launch attributes can influence absorption.
Medication Concentration plus Dose
The focus of the medicine in the solution plus the carried out dosage can affect the price as well as degree of absorption. Greater focus might boost absorption however there might be limitations to this result.
Mucociliary Clearance
The fast elimination of materials from the nasal dental caries by mucociliary clearance can restrict the home time of medicines impacting absorption. Mucoadhesive solutions can counter this clearance system.
pH plus Environmental Factors
Nasal pH as well as ecological problems within the nasal tooth cavity can influence medicine security plus solubility, affecting absorption.
Enzymatic Degradation
Enzymatic task in the nasal tooth cavity resulting in the breakdown of medications can be a substantial obstacle specifically for peptides as well as healthy proteins.
Formulation Additives
The incorporation of particular excipients or ingredients in solutions, such as diffusion boosters or enzyme preventions, can customize medicine absorption features.
Patient Factors
Variants in specific nasal physiology wellness problems as well as person conformity can affect medicine absorption and also efficiency.
Bit Size as well as Shape
For particulate solutions such as powders the bit dimension plus form can influence deposition plus absorption features in the nasal tooth cavity.

Flow Charts/ Figure 2: General Overview of Elements Impacting Nasal Medication.

Absorption/ Factors Influencing Nasal Drug Absorption

1) Physiochemical properties of drug.

- a) Molecular size.
- b) Lipophilic-hydrophilic balance.
- c) Enzymatic degradation in nasal cavity.

2) Nasal Effect

- a) Membrane permeability.
- b) Environmental pH
- c) Mucociliary clearance
- d) Cold, rhinitis.

3) Delivery Effect

- a) Formulation (Concentration, pH, osmolarity)
- b) Delivery effects
- c) Drugs distribution and deposition.
- d) Viscosity

1) Physiochemical properties of drug

a) Molecular size

The dimension of the medication particle is an essential variable influencing medication absorption with the nasal course. There is a straight relationship in between the molecular weight (MW) as well as the permeation of lipophilic medicines, while soluble substances reveal a contrary connection. Particularly the price of permeation is dramatically affected by molecular dimension particularly for substances with a molecular weight equivalent to or higher than 300 Daltons.^[29]

b) Lipophilic-hydrophilic balance

The absorption procedure is likewise affected by the hydrophilic as well as lipophilic features of the medication. Normally, a rise in lipophilicity boosts the penetration of the substance via the nasal mucosa. Especially, medicines with high lipophilicity, such as naloxone, buprenorphine, testosterone as well as 17 α -ethinyl- oestradiol show almost full absorption when provided via the intranasal path.^[30,31]

c) Enzymatic degradation in nasal cavity

Peptides and also healthy proteins, with naturally reduced bioavailability throughout the nasal dental caries, are vulnerable to enzymatic destruction. There is a capacity for enzymatic destruction to happen either within the lumen of the nasal tooth cavity or throughout flow with the epithelial obstacle. Enzymes existing in these websites, consisting of exopeptidases like mono- as well as di-amino-peptidases with the ability of cutting peptides at their N as well as C termini along with endopeptidases such as amino acid together with cysteine have the capability to strike inner peptide bonds.^[32]

2) Nasal Effect

a) Membrane permeability (layer Leak)

The leak of the nasal membrane layer is a critical element affecting medication absorption with the nasal path. Water-soluble medicines, specifically those with big molecular weights such as peptides plus healthy proteins generally exhibit reduced membrane layer leaks. As a result, substances like peptides combined with healthy proteins are mostly taken in via an endocytotic transport procedure albeit in minimal amounts.^[23] On the various other hand water-soluble high molecular weight medications mainly go across the nasal mucous with easy diffusion making use of the aqueous pores, especially limited joints.

b) Ecological pH

The ecological pH dramatically affects the performance of nasal medication absorption. Tiny soluble substances, such as benzoic acid, salicylic acid plus alkaloid acid, display optimal nasal absorption in rats when they remain in the nonionized kind at details pH worths. Nevertheless significant absorption is still observed at pH worths where these substances are partly ionized. This recommends that the nonionized, lipophilic type goes across the nasal epithelial obstacle via the transcellular course while the extra lipophilic ionized type travels through the liquid paracellular course.

c) Mucociliary Clearance

Mucociliary allowance is a vital feature of the top breathing system targeted at stopping dangerous compounds such as irritants, germs, infections as well as contaminants from getting to the lungs. Products following or liquifying in the mucus cellular lining of the nasal dental caries are transferred in the direction of the nasopharynx inevitably being released right into the intestinal system. This procedure referred to as mucociliary clearance (MCC) affects the absorption procedure as liquified medications in the nasal tooth cavity are ousted by both the mucous and also the cilia- fundamental to the electric motor feature of MCC. The transportation price of mucus is roughly 6 mm/min. Protecting the efficiency of MCC is vital to avoid reduced breathing system infections.

d) Cold, Rhinitis

Rhinitis, a generally happening disorder, dramatically affects the bioavailability of medications. It is mainly classified right into allergic rhinitis plus typical rhinitis, both providing signs such as hypersecretion, irritating and also sneezing. These signs are generally activated by infections, microorganisms, or toxic irritants. Allergic rhinitis making up an allergic respiratory system condition impacting about 10% of the populace results from persistent or severe swelling of the mucous membrane layer of the nose. The visibility of such inflammatory problems can influence the absorption of medications with the mucous membrane layer because of the swelling.

3) Delivery effect factors / Shipment Impact Aspects

Elements affecting the distribution of medications throughout the nasal mucosa, consisting of surfactants, dosage pH, osmolarity, thickness, fragment dimension, nasal allowance, and also medication framework, can be purposefully leveraged to improve absorption. These aspects

play an important duty in maximizing the efficiency of medication shipment with the nasal path.

a) Formulation / Solution (Concentration, pH, Osmolarity)

The solution attributes, consisting of focus, pH, as well as osmolarity, are critical considerfluencing medication leaks with the nasal membrane layer.

I. pH Adjustment

The pH of the nasal solution plus nasal surface area plays a substantial duty in medicine leaks. To stop nasal inflammation it is a good idea to readjust the pH of the nasal solution within the variety of 4.5-- 6.5. This modification is important because of the existence of lysozyme in nasal secretions which works in damaging particular germs under acidic problems. Alkaline problems can bring about lysozyme lack of exercise as well as make the cells prone to microbial infection. Keeping the pH within the defined variety not just decreases inflammation however additionally helps with effective medication leaks while avoiding microbial development.^[14]

II. Concentration Gradient

The focus slope is a critical factor in the absorption/permeation procedure of medications with the nasal membrane layer. Significantly the absorption of L-Tyrosine with the nasal mucosa has actually been shown to boost with medication focus in nasal diffusion experiments. On the other hand, the absorption of salicylic acid was discovered to decrease with focus possibly as a result of damages to the nasal mucosa at greater focus.^[33]

III. Osmolarity

The osmolarity of the dose kind dramatically affects nasal medication absorption. Research studies carried out in rats making use of a design medication disclosed that the salt chloride focus in the solution affects nasal absorption. Ideal absorption was accomplished with a salt chloride focus of 0.462 M. Greater focus not just raised accessibility however likewise presented a danger of poisoning to the nasal epithelium.^[34]

b) Drugs distribution and deposition/ Medications Circulation and also Deposition

The circulation of a medication within the nasal tooth cavity is a crucial element affecting the performance of nasal absorption. The setting of medicine management can effect just how the medicine is dispersed in the nasal dental caries inevitably identifying the absorption

effectiveness. The absorption coupled with bioavailability of nasal dose types are dramatically affected by the website of personality.

I. Anterior Portion of the Nose

The former section of the nose supplies a prolonged nasal home time for the personality of the solution. This prolonged residence time improves the absorption of the medication, adding to boosted bioavailability.

II. Posterior / Back Chamber of Nasal Cavity

The back chamber of the nasal tooth cavity is used for the deposition of the dose kind. Nonetheless this area undergoes removal by the mucociliary clearance procedure bring about reduced bioavailability.

The site of disposition and distribution of dosage forms is heavily reliant on factors such as the delivery device, mode of administration, and physicochemical properties of the drug molecule. These factors to consider play an essential duty in establishing the general efficiency of nasal medication absorption.^[35]

c) Viscosity/ Thickness

The thickness of a solution plays a considerable function in nasal medication absorption. A greater thickness in the solution extends the call time in between the medication as well as the nasal mucosa therefore raising the period readily available for diffusion. Nevertheless, it's essential to keep in mind that very thick solutions can disrupt regular physical features such as ciliated whipping or mucociliary clearance. This disturbance might change the leaks of medicines recommending equilibrium is required to maximize contact time while keeping the stability of the nasal allowance systems.

Approaches To Boost Nasal Absorption

A number of techniques are used to improve the bioavailability of medicines in the nasal mucous membrane. These techniques consist of:

a) Enhancing Nasal Residence Time

Strategies to expand the moment the medicine resides in the nasal tooth cavity can be used. This consists of making use of mucoadhesive solutions, gels, or thixotropic systems that improve adherence to the nasal mucous membrane, hence lengthening the get in touch with time.

b) Boosting Nasal Absorption

Numerous techniques intend to boost the absorption of medicines via the nasal mucous membrane. This can entail using infiltration boosters, nanoparticles, or particular distribution systems created to enhance medicine absorption throughout the nasal epithelium.

c) Customizing Drug Structure to Change Physicochemical Properties

Altering the framework of the medicine to boost its physicochemical buildings can affect its absorption in the nasal dental caries. This could consist of adjustments to improve lipophilicity, solubility, or security inevitably boosting the medicine's general bioavailability.

These approaches are customized to deal with particular obstacles related to nasal medicine absorption wanting to enhance restorative end results.

Dosage Form In Naso-Pulmonary Drug Delivery System

Naso-pulmonary medicine distribution includes the management of medicines with the nasal path with the purpose of targeting the lung system. Different dose kinds are used in naso-pulmonary medication distribution systems to accomplish efficient together with targeted medicine distribution. Some typical dosage types in this context consist of:

Nasal Sprays

Metered-dose nasal sprays provide a regulated along with specific quantity of medicine. These sprays are developed to produce great bits that can get to the deep lung, helping with effective medication shipment to the lung system.

Nasal Inhalers

Completely dry powder nasal inhalers launch medication bits in powder kind. These inhalers work in supplying medications to the lungs as well as are typically utilized for the therapy of breathing problems.

Nasal Drops

Nasal decreases supply fluid solutions right into the nasal tooth cavity. They can be made to target certain areas of the nasal tooth cavity, affecting the absorption and also succeeding distribution of medications to the lung system.

Nasal Gels as well as Thixotropic Systems

Mucoadhesive gels or thixotropic systems comply with the nasal mucous prolonging the residence time of the medication. This extensive call time improves absorption as well as adds to the naso-pulmonary medicine shipment.

Nasal Powders

Completely dry powder solutions can be made for nasal distribution. These powders might boost medicine absorption and also give targeted shipment to the lung system.

Nasal Aerosols

Aerosolized solutions create great droplets or bits that can get to the reduced breathing system. Nasal aerosols are made for efficient as well as targeted medication shipment to the lungs.

Nasal Microspheres plus Nanoparticles

Microspheres plus nanoparticles are service providers for medication distribution supplying regulated launch along with boosted absorption. These particulate systems can be developed

for certain targeting of the lung system.

Nasal Patches

Transdermal spots made for nasal application can give continual launch of medications. These spots comply with the nasal mucous permitting regulated medication shipment.

Flow Charts/ Figure 3: General Overview of Dosage Form in Naso-Pulmonary Drug Delivery System

The selection of dosage form relies on aspects such as the physicochemical buildings of the medicine the preferred site of activity in the lung system, coupled with the healing objectives of the therapy. Naso-pulmonary medication distribution intends to enhance medicine absorption plus restorative effectiveness in breathing problems.

Selection of Dosage Form

The option of a Dosage Form (dose kind) is a vital choice that depends upon a number of variables to make certain the general success as well as efficiency of medicine distribution. These variables consist of:

Drug (Medicine) Characteristics

The physicochemical residential or commercial properties of the medicine, such as solubility, security and also molecular weight, affect the option of dose kind. For instance a lipophilic medicine could be ideal for a nasal spray while a water-soluble medication could be much better supplied as an option or nasal decrease.

Recommended Indication

The meant use the medication whether it's for a breathing problem, allergic reaction, or an additional clinical objective can direct the option of the ideal dose kind. Some problems might profit even more from a certain formula or shipment technique.

Individual Population

Consideration of the target person populace is vital. Aspects such as age capacity to utilize the shipment gadget as well as person choices contribute in selecting a dose kind. Pediatric or senior clients, for example, might have particular demands that affect the choice.

Therapeutic Goals

The restorative objectives of the therapy such as the preferred beginning of activity, period of result as well as organized absorption, effect the option of dosage kind. Various solutions provide differing launch accounts coupled with absorption features.

Advertising Preferences

Business factors to consider plus advertising choices likewise contribute. Some dose kinds might be easier for individuals while others might be favored for branding or market placing factors.

Regulative Considerations

Regulative needs and also standards might affect the option of dose type. The authorization procedure as well as regulative criteria for various solutions can differ, affecting the general growth timeline.

Flow Charts/ Fig.: - 4, General Overview of Selection of Dosage Form

Inevitably the option of a dose kind is a multi-dimensional choice that calls for an equilibrium in between clinical factors to consider, person requirements, and also useful

elements of substance abuse plus advertising. It entails a detailed understanding of the medication's residential properties, the meant healing end result, and also the attributes of the target individual populace.

A. Liquid Nasal Formulations

Fluid solutions especially aqueous state solutions are the key option for nasal medicine management. The hydrating effect of these prep works shows useful particularly in problems related to mucus membrane layer dry skin and also crust development in sensitive and also persistent conditions. Nevertheless obstacles associated with microbiological security, inflammation, as well as sensitive rhinitis existing significant negative aspects for water-based dose kinds mainly associated with the endangering impacts of essential conservatives on mucociliary feature.^[36]

1) Instillation & Rhinyle Catheter

Catheters function as a way to supply goes down to details areas of the nasal tooth cavity easily. The approach entails positioning the formula in a tube placing one end of the tube in the nose, together with providing the remedy right into the nasal tooth cavity by blowing via the contrary end utilizing the mouth^[37,25] Catheter application is identified by the dental filling before management plus the system's precision is mostly used for speculative researches.

2) Pressed Air Nebulizers

Nebulizers are tools made to provide medicine through a haze breathed in right into the lungs. Pushed air nebulizers utilize pressed air to separate clinical remedies/suspensions right into little aerosol beads for straight breathing.^[38] Corticosteroids as well as bronchodilators like salbutamol are frequently utilized with nebulizers. This technique targets the breathing system, quickening the beginning of activity as well as minimizing negative effects. Nevertheless it is not ideal for self-administration by the person.

3) Squeezed Bottle

Squeezed nasal containers function as shipment tools frequently utilized for decongestants. These containers have a straightforward jet electrical outlet as well as aerosolize a specific quantity when pushed launching the stress attracts air as well as occasionally impurities right into the container.^[39] Dose precision coupled with down payment depend upon the setting of

management, making dosage control testing. Squeezed containers with vasoconstrictors are not suggested for usage by kids.

4) Metered-Dose Pump Sprays

A lot of pharmaceutical nasal prep works on the marketplace consisting of services, solutions, or suspensions are provided by metered-dose pump sprays. These sprays infuse a penalty haze right into the nostril with a hand-operated pump device. Nasal sprays are made use of for regional or wide spread results, such as soothing chilly or allergy symptoms.^[40] The primary kinds consist of antihistamines, corticosteroids and also topical decongestants. Parts consist of the container, pump with the shutoff as well as the actuator.

B. Powder Dose Kinds

Dry powders are much less generally made use of in nasal medicine shipment. The vital benefits of this dose type consist of the lack of chemicals along with improved formulation security. Contrasted to remedies the management of powders might lead to extended call with the nasal mucosa.

1) Insufflators

Insufflators are tools developed to supply a medication compound for breathing. These gadgets can be built making use of a straw or tube consisting of the medicine compound in some cases with the incorporation of a syringe. The accomplished bit dimension in these systems is frequently raised contrasted to the initial powder bits as a result of poor deaggregation, leading to a high difference for first down payment locations. Lots of insufflator systems run with pre-dosed powder dosages in pills.^[37]

2) Dry Powder Inhaler (DPI)

Dry powder inhalers (DPIs) are tools made use of to supply a completely dry powder formula of an energetic medication for neighborhood or organized results through the lung path. DPIs are bolus medicine distribution tools which contain strong medication, either put on hold or liquified in a non-polar unpredictable propellant or in a completely dry powder that fluidizes upon breathing by the person.^[40] These inhalers are frequently used in the therapy of breathing conditions such as bronchial asthma, respiratory disease, emphysema, and also COPD. In addition they have actually been made use of in the therapy of diabetic issues.

The medicine is generally kept in a pill for hand-operated packing or in a proprietary type within the inhaler. After filling or actuation, the client positions the inhaler's mouth piece right into their mouth coupled with takes a deep inhalation, holding their breath for 5-10 secs. Different tools of this nature exist, as well as the supplied dosage is typically restricted to a couple of 10s of milligrams in a solitary breath to stay clear of coughing induction.

C. Pressurized Metered-Dose Inhalers (MDIs)

A pressurized metered-dose inhaler (MDI) is a tool created to provide a particular amount of drug to the lungs with a brief ruptured of aerosolized medication that the individual breathes in. This shipment system is commonly made use of in dealing with bronchial asthma, persistent obstructive lung illness (COPD) coupled with various other breathing problems. Usual medicines provided through MDIs consist of bronchodilators corticosteroids, or a mix of both for taking care of bronchial asthma as well as COPD. In addition much less frequently utilized drugs, such as mast cell preventions (e.g., cromoglicate or nedocromil) can likewise be provided with MDIs.

The benefits of MDIs consist of their mobility, small dimension, schedule over a wide dose variety per actuation, dosage uniformity, dose precision, material defense plus fast preparedness for usage.^[41]

In MDIs, gas usually makes up greater than 99% of the supplied dosage. When the gadget is actuated a solitary metered dosage of the formula including the drug either liquified or put on hold in the propellant is launched. The unpredictable gas breaks up right into beads together with the quick dissipation of these beads produces an aerosol including micrometer-sized medicine bits which are after that breathed in by the individual.

D. Nasal Gels

Nasal gels describe high-viscosity thickened remedies or suspensions. This system got minimal rate of interest up until the growth of specific application gadgets. Nasal gels provide numerous benefits consisting of:

- Decrease of post-nasal drip because of high thickness.
- Reduced preference influence with minimized ingesting.
- Decreased former leak of the solution.
- Minimized inflammation by including soothing/emollient excipients.
- Targeted shipment to the mucous for improved absorption.^[42]

The down payment of the gel in the nasal dental caries is affected by the setting of management. The high thickness of the solution restricts its dispersing capacity. Without certain application strategies the gel inhabits a slim circulation location in the nasal tooth cavity where it is straight positioned. Especially, the market has actually lately seen the introduction of the very first nasal gel consisting of Vitamin B12 for organized medicine.

E. Novel as well same other approaches

a) Microspheres

Microspheres play a crucial role in nasal drug delivery by enhancing absorption, providing sustained release, and offering protection against enzymatic degradation.

b) Liposomes

Liposomes are phospholipid vesicles composed of a bilayer enclosing one or more aqueous compartments. These compartments allow for the entrapment or adsorption of drugs.

c) Nasal Powder

Nasal powder may be formulated when solution and suspension dosage forms are impractical due to issues like drug stability. The advantages of the nasal powder dosage form include the absence of preservatives and superior stability in the formulation. However, the suitability of the powder formulation depends on factors such as solubility, particle size, aerodynamic properties, and nasal irritancy of the active drug and excipients. Another advantage of this system is the local application of the drug.^[43]

d) Nasal Drops

Nasal drops represent a convenient and simple system for nasal drug delivery. They can be administered with a squeeze bottle or a pipette. These formulations are commonly recommended for treating local conditions, despite facing challenges such as microbial growth, mucosal dysfunction, and non-specific loss to the nose or lower back. A notable disadvantage is the lack of dose precision, making nasal drops less suitable for prescription products. Studies have reported that nasal drops deposit human serum albumin more efficiently in the nostrils compared to nasal sprays.^[43-45]

e) Nasal Sprays

Nasal sprays are formulated with solutions and suspensions. With the availability of metered dose pumps and actuators, a nasal spray can deliver a precise dose ranging from 25 to 200

µm. The choice of pump and actuator assembly is determined by the morphology particle size (for suspensions) of the drug and the viscosity of the formulation.^[43,46]

Recent formulations of pulmonary drug delivery^[47,48]

Table 3: Recent Formulations of Pulmonary Drug Delivery.

Sr. No.	Formulation	Description	Advantage
1.	Insulin by Aerosol	Supplies non-invasive insulin shipment an option to shots.	Non-invasive technique possible renovation (improvement) in individual conformity.
2.	Nicotine Aerosol for Smoking Cessation	Helps smoking cigarettes cessation by providing regulated dosages of pure nicotine without cigarette smoke.	Assists lower withdrawal signs sustains people in giving up cigarette smoking.
3.	Alpha 1 Antitrypsin	Supplied through aerosol to deal with problems like COPD and also emphysema.	Local anti-inflammatory impacts targeting particular lung problems.
4.	Aerosols for Angina	Aerosol solutions for the therapy of angina, supplying rapid as well as targeted medicine distribution.	Fast as well as targeted alleviation of angina signs.
5.	Gene Therapy via Aerosol	Includes supplying restorative genetics straight to the lungs for hereditary condition or lung condition therapy.	Possible development in dealing with hereditary lung conditions.
6.	In Cancer Chromatography	Chromatography-based aerosols for providing anticancer representatives straight to lung growths.	Targeted cancer cells therapy to the lungs decreasing systemic negative effects.
7.	Pentamidine Aerosol	Utilized to avoid as well as deal with Pneumocystis jiroveci pneumonia in immunocompromised people.	Targeted avoidance of opportunistic infections in immunocompromised people.
8.	Gentamycin Aerosol	Aerosolized gentamicin for dealing with breathing infections, specifically in cystic fibrosis individuals.	Localized antibiotic delivery to combat respiratory infections.
9.	Ribavirin Aerosol	Utilized in the therapy of breathing viral infections, such as breathing syncytial infection (RSV).	Efficient antiviral therapy with regional distribution to the breathing system.
10.	Pulmonary Delivery of Lower Molecular Weight Heparin	Shipment of heparin for anticoagulant treatment especially for lung blood clot.	Localized delivery of anticoagulant therapy to the lungs.
11.	Controlled Delivery of Drugs to Lungs	Different solutions for regulated (controlled)	Maintained launch (Sustained release) of

		medication distribution to the lungs enhancing restorative efficiency.	medicine for boosted therapy end results.
12.	Pulmonary Delivery of Drugs for Bone Disorders	Checking out aerosol solutions for supplying medicines to attend to bone problems like weakening of bones.	Localized drug delivery to the lungs with potential systemic effects on bone health.

Future Direction/Scope

The naso-pulmonary drug delivery systems assessed below existing an appealing opportunity for future growths in breathing wellness monitoring. The intranasal course as a sensible choice for medicine management holds substantial capacity for the innovation of risk-free efficient solutions, allowing easy, pain-free and also lasting treatment. While difficulties continue in lung medication shipment (pulmonary drug delivery), recurring examinations right into peptide plus healthy protein medicines for systemic absorption by means of the lung system consisting of insulin calcitonin, LHRH analogs, rhG-CSF along with hGH highlight the progressing landscape. The future extent includes dealing with present restrictions plus broadening the collection of medicines amenable to naso-pulmonary delivery. Discovering ingenious solutions that improve medication safety enhance bioavailability along with ameliorate prospective negative effects will certainly be important. The proceeded examination right into aerosolized macromolecules, paired with the lack of severe security concerns and also very little issues pertaining to throat irritability or cough, leads the way for the expedition of a wider range of restorative representatives.

In the world of nasal medication shipment (drug delivery) systems the current developments stand for a beginning factor instead of an orgasm. Future study ventures ought to dive much deeper right into comprehending the devices controlling medicine absorption via the nasal tooth cavity. Furthermore checking out unique techniques to get rid of enzymatic deterioration, enhancing membrane layer transportation coupled with resolving mucociliary clearance obstacles will certainly be important. Joint initiatives in between scientists, pharmaceutical experts and also medical professionals are prepared for to foster advancements in NPDDS. As innovation progresses, the growth of targeted coupled with tailored medication shipment systems customized to specific client accounts holds remarkable possibility. Arising innovations, such as nanomedicine plus controlled-release solutions, existing interesting possibilities for expedition using boosted accuracy as well as healing end results. To conclude the future of naso-pulmonary drug delivery (medication

distribution) systems hinges on a vibrant landscape of technology plus partnership. As research study proceeds the translation of searching for right into medical applications holds the assurance of reinventing breathing wellness administration supplying individuals with even more effective, practical, as well as patient-friendly restorative choices. The trip towards unlocking the complete capacity of NPDDS is recurring, with many opportunities yet to be discovered for the development of breathing treatment.

CONCLUSION

Finally, the nasal tooth cavity arises as an appealing frontier for drug delivery (medication shipment), defined by its extensive location plus very vascularized mucosa. The abundant network of capillary within the nasal tooth cavity helps with straight absorption of medicines right into the systemic flow, preventing the difficulties postured by first-pass metabolic process. The substantial body of proof bordering nasal medicine shipment highlights its prospective energy, specifically for difficult medicines, offering possibilities to resolve pharmaceutical production together with medication shipment obstacles. The distinct characteristics of the nasal course such as access, simpleness plus capacity for lasting treatment placement it as an appealing option for medication management. In spite of difficulties fundamental in lung medication distribution systems recurring examinations right into a varied range of healing representatives highlight the developing landscape and also the continual search of options to improve medication security, bioavailability together with client conformity. As developments in modern technology and also formulation (solution) techniques remain to unravel, the future of naso-pulmonary drug delivery systems holds excellent pledge. The possibility for individualized and also targeted medicine shipment combined with the expedition of cutting-edge solutions plus arising modern technologies, foretells well for the area. Basically, the nasal tooth cavity with its one-of-a-kind physiological and also physical attributes provides a channel for transformative improvements in drug delivery (medication shipment). The trip in advance includes browsing obstacles, utilizing cutting-edge methods, plus converting research study searchings for right into substantial professional applications. The possibility of leveraging the nasal course for medication distribution stands for not just a clinical undertaking however a possible game-changer in pharmaceutical scientific researches with extensive ramifications for individual treatment as well as restorative results.

REFERENCES

1. CHIEN, Y.W., SU, K.S.E., & CHANG, S.F., (1989), Anatomy and physiology of the nose, in Y. W. Chen, K. S. E. Su, and S.-F. Chang, eds., Nasal systemic drug delivery: Drugs and the Pharmaceutical Sciences, v. 39: New York, Marcel Dekker Inc, 1989; 1-19.
2. Niven R. W. Delivery of biotherapeutics by inhalation aerosol. Critical reviews in therapeutic drug carrier systems, 1995; 12(2-3): 151–231. <https://doi.org/10.1615/critrevtherdrugcarriersyst.v12.i2-3.20>
3. Patton, J. S. Mechanisms of macromolecule absorption by the lungs. Advanced drug delivery reviews, 1996; 19(1): 3-36.
4. Pires, A., Fortuna, A., Alves, G., & Falcão, A. Intranasal drug delivery: how, why and what for?. Journal of pharmacy & pharmaceutical sciences: a publication of the Canadian Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques, 2009; 12(3): 288–311. <https://doi.org/10.18433/j3nc79>.
5. Illum L. Nasal drug delivery: new developments and strategies. Drug discovery today, 2002; 7(23): 1184–1189. [https://doi.org/10.1016/s1359-6446\(02\)02529-1](https://doi.org/10.1016/s1359-6446(02)02529-1).
6. <https://en.m.wikipedia.org/wiki/Lung>.
7. Moussavi, Z. Anatomy and Physiology of Respiratory System. In Fundamentals of Respiratory System and Sounds Analysis Cham: Springer International Publishing, 2006; 1-8.
8. Robinson, N. E., & Furlow, P. W. Anatomy of the respiratory system. Equine respiratory medicine and surgery, 2007; 3-17.
9. Broussard, A. J., Hall, S. M., & Levitzky, M. G. Respiratory system: anatomy and physiology. Essentials of Pediatric Anesthesiology, 2014; 38.
10. Illum, L. Bioadhesive formulations for nasal peptide delivery. Drugs and the pharmaceutical sciences, 1999; 98: 507-539.
11. Aurora, J. Development of nasal delivery systems: a review. Drug Deliv Technol, 2002; 2(7): 1-8.
12. Parvathi, M. Intranasal drug delivery to brain: an overview. Int J Res Pharm Chem, 2012; 2(3): 889â.
13. Sarkar, M. A. Drug metabolism in the nasal mucosa. Pharmaceutical research, 1992; 9: 1-9.
14. Arora, P., Sharma, S., & Garg, S. Permeability issues in nasal drug delivery. Drug discovery today, 2002; 7(18): 967-975.

15. Martin, E., Schipper, N. G., Verhoef, J. C., & Merkus, F. W. Nasal mucociliary clearance as a factor in nasal drug delivery. *Advanced drug delivery reviews*, 1998; 29(1-2): 13-38.
16. Charlton, S., Jones, N. S., Davis, S. S., & Illum, L. Distribution and clearance of bioadhesive formulations from the olfactory region in man: Effect of polymer type and nasal delivery device. *European journal of pharmaceutical sciences*, 2007; 30(3-4): 295-302.
17. Graff, C. L., & Pollack, G. M. Nasal drug administration: potential for targeted central nervous system delivery. *Journal of pharmaceutical sciences*, 2005; 94(6): 1187-1195.
18. Dondeti, P., Zia, H., & Needham, T. E. Bioadhesive and formulation parameters affecting nasal absorption. *International journal of pharmaceutics*, 1996; 127(2): 115-133.
19. Behl, C. R., Pimplaskar, H. K., Sileno, A. P., Demeireles, J., & Romeo, V. D. Effects of physicochemical properties and other factors on systemic nasal drug delivery. *Advanced drug delivery Reviews*, 1998; 29(1-2): 89-116.
20. Behl, C. R., Pimplaskar, H. K., Sileno, A. P., Xia, W. J., Gries, W. J., Demeireles, J. C., & Romeo, V. D. Optimization of systemic nasal drug delivery with pharmaceutical excipients. *Advanced drug delivery reviews*, 1998; 29(1-2): 117-133.
21. Striebel, H. W., Krämer, J., Luhmann, I., Rohierse-Hohler, I., & Rieger, A. Pharmacokinetics of intranasal fentanyl. *Der Schmerz*, 1993; 7: 122-125.
22. McMartin, C., Hutchinson, L. E., Hyde, R., & Peters, G. E. Analysis of structural requirements for the absorption of drugs and macromolecules from the nasal cavity. *Journal of pharmaceutical sciences*, 1987; 76(7): 535-540.
23. Inagaki, M., Sakakura, Y., Itoh, H., Ukai, K., & Miyoshi, Y. Macromolecular permeability of the tight junction of the human nasal mucosa. *Rhinology*, 1985; 23(3): 213-221.
24. Soane, R. J., Frier, M., Perkins, A. C., Jones, N. S., Davis, S. S., & Illum, L. Evaluation of the clearance characteristics of bioadhesive systems in humans. *International journal of pharmaceutics*, 1999; 178(1): 55-65.
25. Harris, A. S., Nilsson, I. M., & Alkner, U. Intranasal administration of peptides: nasal deposition, biological response, and absorption of desmopressin. *Journal of pharmaceutical sciences*, 1986; 75(11): 1085-1088.
26. Kublik, H., & Vidgren, M. T. Nasal delivery systems and their effect on deposition and absorption. *Advanced drug delivery reviews*, 1998; 29(1-2): 157-177.
27. Lee, V. H. Enzymatic barriers to peptide and protein absorption. *Critical reviews in therapeutic drug carrier systems*, 1988; 5(2): 69-97.

28. Morimoto, K., Miyazaki, M., & Kakemi, M. Effects of proteolytic enzyme inhibitors on nasal absorption of salmon calcitonin in rats. *International journal of pharmaceutics*, 1995; 113(1): 1-8.
29. Corbo, D. C., Liu, J. C., & Chien, Y. W. Characterization of the barrier properties of mucosal membranes. *Journal of pharmaceutical sciences*, 1990; 79(3): 202-206.
30. BAWARSHI-NASSAR, R. N., Hussain, A., & Crooks, P. A. Nasal absorption of 17 α -ethinyloestradiol in the rat. *Journal of pharmacy and pharmacology*, 1989; 41(3): 214-215.
31. Hussain, A., Hamadi, S., Kagashima, M., Iseki, K., & Dittert, L. Does increasing the lipophilicity of peptides enhance their nasal absorption? *Journal of pharmaceutical sciences*, 1991; 80(12): 1180-1181.
32. Lee, V. H. Enzymatic barriers to peptide and protein absorption. *Critical reviews in therapeutic drug carrier systems*, 1988; 5(2): 69-97.
33. Bhise, S. B., Yadav, A. V., Avachat, A. M., & Malayandi, R. Bioavailability of intranasal drug delivery system. *Asian Journal of Pharmaceutics (AJP)*, 2008; 2(4).
34. Ohwaki, T., Ando, H., Watanabe, S., & Miyake, Y. Effects of dose, pH, and osmolarity on nasal absorption of secretin in rats. *Journal of pharmaceutical sciences*, 1985; 74(5): 550-552.
35. Gizurarson, S., & Bechgaard, E. Intranasal administration of insulin to humans. *Diabetes research and clinical practice*, 1991; 12(2): 71-84.
36. Zia, H., Dondeti, P., & Needham, T. E. Intranasal drug delivery. *Clinical Research and Regulatory Affairs*, 1993; 10(2): 99-135.
37. Hughes, B. L., Allen, D. L., Dorato, M. A., & Wolff, R. K. Effect of delivery devices on nasal deposition and mucociliary clearance in rhesus monkeys. *Aerosol science and technology*, 1993; 18(3): 241-249.
38. Rathbone, M. J., Hadgraft, J., & Roberts, M. S. (Eds.). *Modified-release drug delivery technology*. CRC Press., 2002
39. Mygind, N., & Vesterhauge, S. Aerosol distribution in the nose. *Rhinology*, 1978; 16(2): 79-88.
40. Alagusundaram, M., Deepthi, N., Ramkanth, S., Angalaparameswari, S., Saleem, T. M., Gnanaprakash, K., & Chetty, C. M. Dry powder inhalers-an overview. *Int. J. Res. Pharm. Sci.*, 2010; 1(1): 34-42.
41. Newhouse, M. Advantages of pressurized canister metered dose inhalers. *Journal of Aerosol Medicine*, 1991; 4(3): 139-150.

42. Junginger, H. E. Mucoadhesive hydrogels. *Pharmazeutische Industrie*, 1991; 53(11): 1056-1065.
43. Rudman, K. L., O'Brien, E. K., & Leopold, D. A. Radiographic distribution of drops and sprays within the sinonasal cavities. *American journal of rhinology & allergy*, 2011; 25(2): 94-97.
44. Dhuria, S. V., Hanson, L. R., & Frey II, W. H. Intranasal delivery to the central nervous system: mechanisms and experimental considerations. *Journal of pharmaceutical sciences*, 2010; 99(4): 1654-1673.
45. Merkus, F. W., & van den Berg, M. P. Can nasal drug delivery bypass the blood-brain barrier? Questioning the direct transport theory. *Drugs in R & D*, 2007; 8: 133-144.
46. Surber, Christian & Elsner, Peter & Farage, Miranda. (2011). *Topical Applications and the Mucosa*. 10.1159/isbn., 978-3-8055-9616-9.
47. Bhavane, R., Karathanasis, E., & Annapragada, A. V. Agglomerated vesicle technology: a new class of particles for controlled and modulated pulmonary drug delivery. *Journal of Controlled Release*, 2003; 93(1): 15-28.
48. Le Brun, P. P. H., De Boer, A. H., Frijlink, H. W., & Heijerman, H. G. M. A review of the technical aspects of drug nebulization. *Pharmacy World & Science*, 2000; 22: 75-81.