WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

A REVIEW ON NASOPULMONARY DRUG DELIVERY SYSTEM

Mr. Verma Pankaj Sudama[1], Miss. Harshada Dhak[2], Dr Sonali Uppalwar[3]

IDEAL INTITUTE OF PHARMACY, POSHERI, WADA, MUMBAI UNIVERSITY

ABTRACT:

Non-invasive techniques called naso pulmonary drug delivery systems (NPDDS) transfer medication into the lungs through the nose. Compared to conventional oral and injectable techniques, this strategy has a number of benefits, such as focused distribution, quick absorption, and avoidance of first-pass metabolism. For those who struggle with other types of medication, NPDDS are a useful alternative because they are very simple to give. Usually, nasal sprays, inhalers, or nebulizers are used to give NPDDS. The drug and the intended location of action determine which particular gadget is utilized. Nasal decongestants, asthma meds, and hormone replacement and migraine treatments are a few typical examples of pharmaceuticals administered via NPDDS. A key factor in the efficacy of NPDDS is the nasopulmonary system's anatomy. Drugs enter the nose through its many structures, including the nasal septum, turbinates, and a mucosal lining that is highly vascularised. The main target for medication absorption into the bloodstream is the lungs, which have a complex network of airways and a vast absorptive area of up to 100m^2. The physicochemical qualities of the drug, the nasal cavity's anatomy and physiology, and the particular delivery method employed are some of the variables that might affect how well a drug is absorbed through the nasal route. The future of NPDDS is promising, with potential for advancements such as increased use of nanotechnology, the development of personalized systems, and the ability to deliver complex medications like vaccines and proteins.

KEYWORD: System for Nasopulmonary Drug Delivery (NPDDS),Delivery of Drugs Intranasally ,The Pulmonary Route ,First-pass metabolism ,Quick Absorption of Drugs ,Targeted Administration of Medicines ,Mucosa of the nose ,The lung's epithelium ,Nasal sprays, inhalers.

INTRODUCTION OF NASOPULMONARY DRUG DELIVERY SYSTEM (NPDDS) OVERVIEW

In the past, the Indian Ayurvedic medical system administered drugs via the nasal passage; this procedure is known as "Nasya." It is currently acknowledged that intranasal medication administration is a practical and dependable substitute for oral and parenteral methods. Without a doubt, the intranasal delivery of medications for the For a very long time, topical nasal problems have been utilised extensively for symptomatic relief, prophylaxis, and therapy.1,2 The pulmonary route has become more significant in recent years because of its special qualities, which include a huge absorptive area of up to 100m.2 The nasopulmonary medication delivery method has advanced in recent years. seen as a viable strategy for the effective nasal administration of medications. This thorough analysis seeks to investigate the prospective uses and advantages of this cutting-edge drug delivery method in the future. Noninvasive techniques for delivering medications through the nose and into the lungs are known as naso-pulmonary drug delivery systems (NPDDS).Compared to conventional oral and injectable drug administration methods, these systems have a number of benefits, such as quick absorption due to their high vascularity and vast surface area of the pulmonary and nasal mucosa enable quick drug absorption into the bloodstream; avoidance of first-pass metabolism since medications given via the NPDDS avoid the liver, preventing first-pass metabolism, which can lower the bioavailability of some medications; targeted delivery because the NPDDS can be used to deliver medications straight to the lungs, which is especially advantageous for the treatment of respiratory conditions; NPDDS are a suitable choice for people who are unable or unwilling to take oral or injectable drugs because they are very simple to administer.3,4 Usually, nebulisers, inhalers, or nasal sprays are used to give NPDDS. The medicine being delivered and the intended site of action determine the kind of device that is employed. The multiple Commonly prescribed medications that use NPDDS include nasal decongestants, which are nasal sprays that relieve congestion in the nose brought on by allergies or the common cold, and asthma medications, which include inhaled corticosteroids, bronchodilators, and leukotriene inhibitors; migraine drugs, such as the nasal spray form of Sumatriptan, which is a migraine treatment; Nasal sprays can be used to deliver oestrogen and testosterone as part of hormone replacement treatment.5-6 These days, nasal management systems are used for a variety of purposes, such as treating vitamin B12 deficiency, nocturnal enuresis, bone weakening, and migraine headaches. An ongoing investigation examines the potential use of nasal distribution in conditions such as insulin-dependent diabetes, rheumatoid joint inflammation, cancer cell treatment, epilepsy, and antiemetics 8,9

ANATOMY AND PHYSIOLOGY OF NASO PULMANARY SYSTEM

Nose: The nose is the main entrance to the respiratory system and is a complex, multipurpose organ.

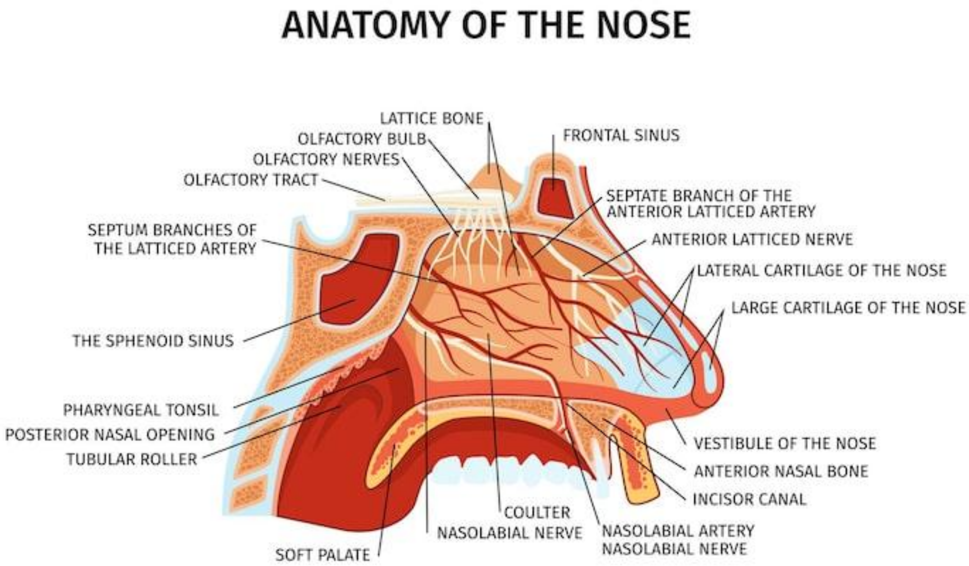


FIG : 1 ANATOMY OF NOSE 53

The external nose :The external nose forms a pyramidal structure in the middle of the face. comprises cartilage material that forms its substandard area and nasal bones that create its remarkable element. The centre third is specified by the top side cartilages, which support the underlying nasal shutoff. Increased nasal breathing causes muscle growth, enhancing nasal respiratory tract patency during exercises and other activities.

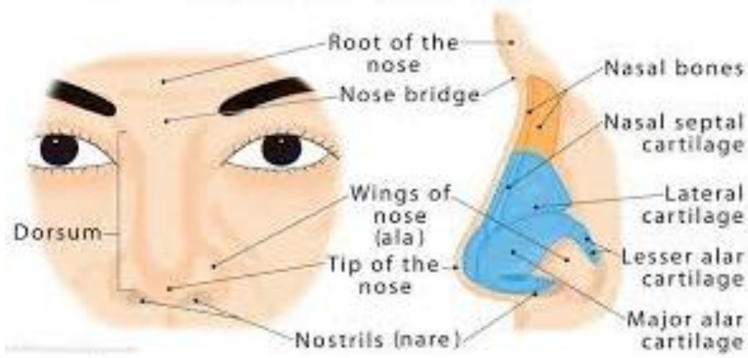


FIG : 2 THE EXTERNAL NOSE 54

Vestibule: The vestibule is coated with stratified squamous epithelium that is different from the breathing epithelium that covers the rest of the nasal tooth cavity because it is the first area to experience the outside atmosphere. Changes to columnar pseudo-stratified The vestibule's epithelium contains thermoreceptors that are necessary for detecting nasal air flow.

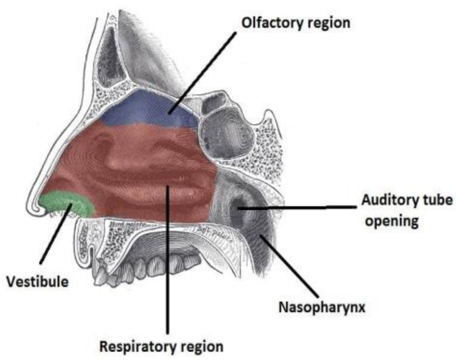


FIG :3 THE ANATOMY OF VESTIBULE 55

Nasal Valve and Airflow: The nasal cutoff is situated directly beyond the nasal vestibule and is bounded by the septum, top side cartilage, and the pyriform aperture's diminished margin. The nasal respiratory tract's patency is influenced by the functional addition of the nasal septal inflate body and expansile vascular cells.

The nasal septum, which divides the nasal tooth cavity into two sections, improves the mucosal surface.

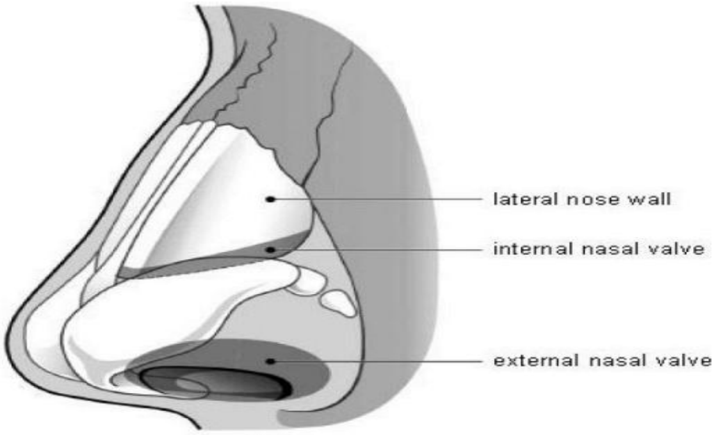


FIG : 4 NASAL VALVE 56

Nasal Septum: The nasal septum improves the mucosal surface by splitting the nasal tooth cavity in half. The nasal septum, which consists of a back bony component and an anterior cartilaginous portion supporting the nasal pointer, exhibits variations.

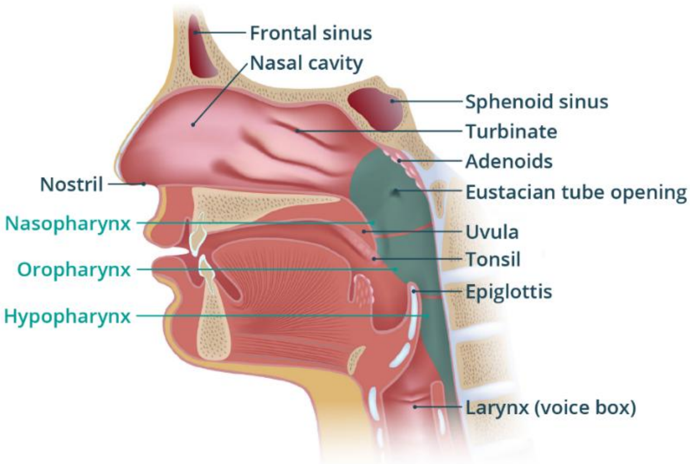


FIG: 5 NASAL SEPTUM 57

Turbinates: These extend from the lateral nasal wall surface in three or occasionally four scroll-like projections. carefully, a thorough analysis of potential justifications for improvement in a blog article.

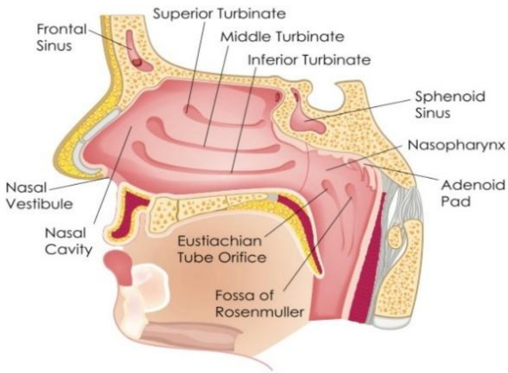


FIG : 6 TURBINATE 58

Histology: Deadly epithelial and submucosal layers make up the nasal cellular lining. The safety barrier is developed by pseudo stratified columnar epithelium, which includes ciliated and nonciliated columnar cells as well as digestive tract cells. Serum or mucous secretions are produced by seromucous glands located in the old nasal dental cavities.

Mucociliary Clearance: To eliminate secretions and particles, the nasal tooth cavity relies on mucociliary transport. The essential components of this clearing system are ciliated epithelial cells and the mucous coating.9-18

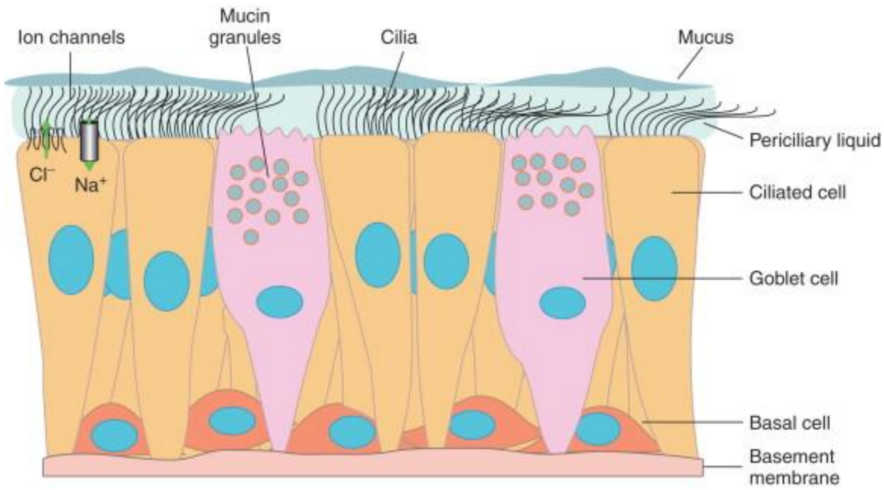


FIG: 7 MUCOCILIARY CLEARANCE 59

Lungs: The main components of the human respiratory system are the lungs. Two lungs are situated close to the heart in mammals and the majority of other animals.each side of the heart's backbone. In a process known as gas exchange, they work in the respiratory system to draw oxygen from the surrounding air and transport it into the bloodstream, as well as to expel carbon dioxide from the bloodstream into

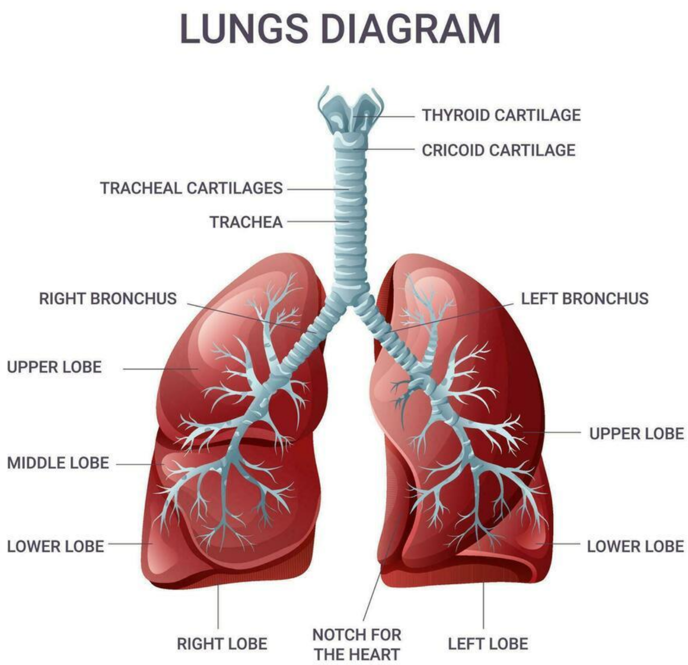


FIG: 8 THE HUMAN LUNGS 60

the atmosphere. Their shape is conical, with a broad concave base that rests on the diaphragm's convex surface and a thin, rounded apex at the top. The lung's apex reaches just above the sternal end of the first rib and extends into the root of the neck. The lungs extend downhill from the bottom portion of the body to the front of the chest and near the backbone in the rib cage.the diaphragm from the trachea. The cardiac notch of the left lung is an indentation in its border that allows the left lung to share space with the heart. An indentation created on the surfaces of the lungs where they rest against the heart is known as the cardiac impression.

The hilum, a central recession in both lungs, is where the airways and blood arteries enter the lungs at the root of the lung. The hilum also contains bronchopulmonary lymph nodes.

Lung regions: -The alveolar sac, located deep within the lung, is where the respiratory tract ends after beginning at the nose. There are several methods for classifying the different sections of the respiratory system.

Right lung: Compared to the left, the right lung has more lobes and segments. It is separated by two fissures, one horizontal and one oblique, into three lobes: an upper, middle, and lower lobe.

Left lung: The oblique fissure, which runs from the costal to the mediastinal surface of the lung both above and below the hilum, separates the left lung into an upper and a lower lobe.

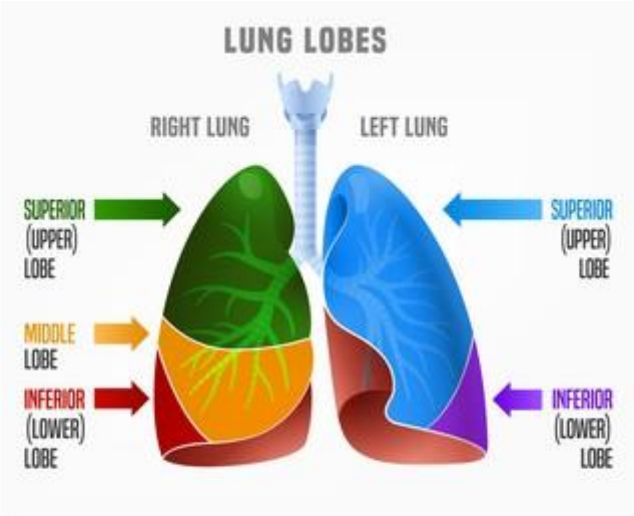


FIG : 9 RIGHT AND LEFT LUNGS 61

Nasopharyngeal region: Also known as the "upper airways," this area includes the respiratory airways that go from the nose to the larynx.
The tracheo-bronchial region, also known as the "central" or "conducting airways," begins in the larynx and travels through the trachea, bronchi, and bronchioles before terminating at the terminal bronchioles.

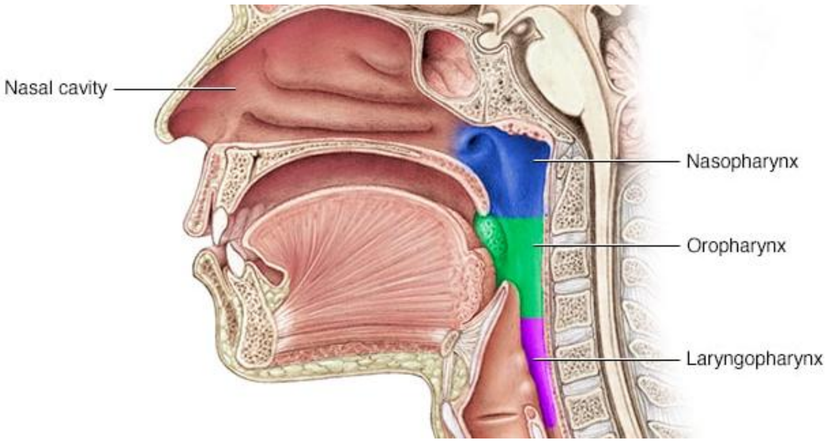


FIG : 10 NASOPHARYNGEAL REGION 62

Alveolar region: Also known as the "pulmonary region," "peripheral airways," or "respiratory airways," this area is made up of the alveolar ducts, alveoli, and respiratory bronchioles.

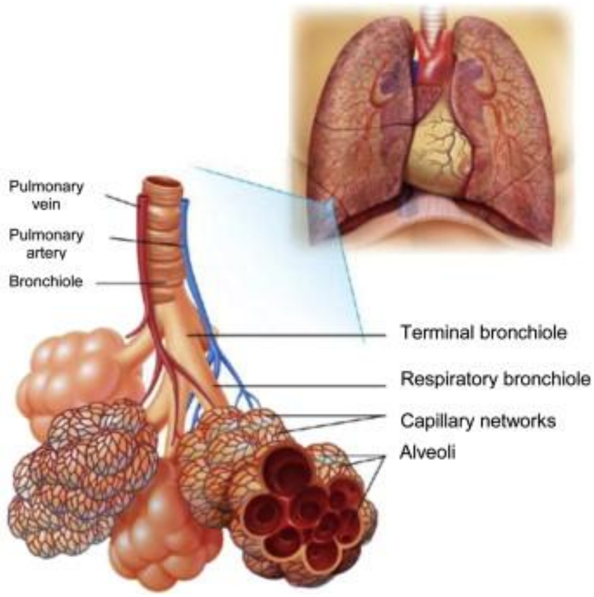


FIG:11 ALVEOLAR RGION 63

The epithelium of the lungs: More than six of the more than 40 distinct cell types that make up the lung line the airways. Pulmonary epithelia's variety can be demonstrated by looking at its three main levels of structure.

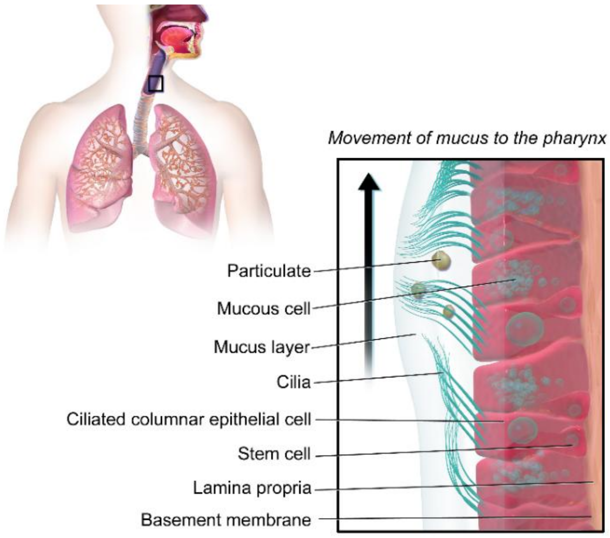


FIG : 12 THE EPITHELEUM OF LUNGS 64

The Bronchi: The bronchi are primarily lined by goblet and ciliated cells. There are also a few Kulchitsky cells along with some serous, brush, and Clara cells.

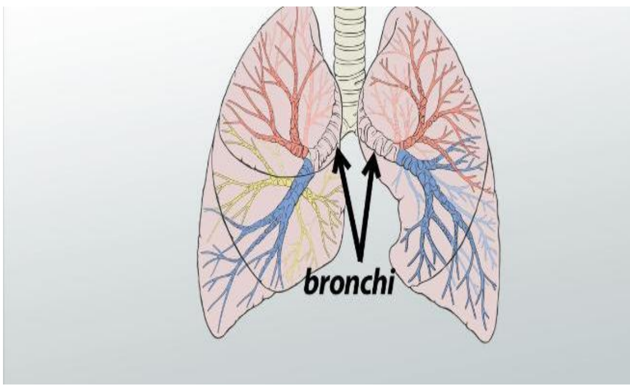


FIG : 13 THE BRONCHI 65

The Bronchioles: The ciliated cuboidal cells that line the bronchioles constitute the main component. As the airways advance, the frequency of goblet and serous cells declines while the number of Clara cells rises.

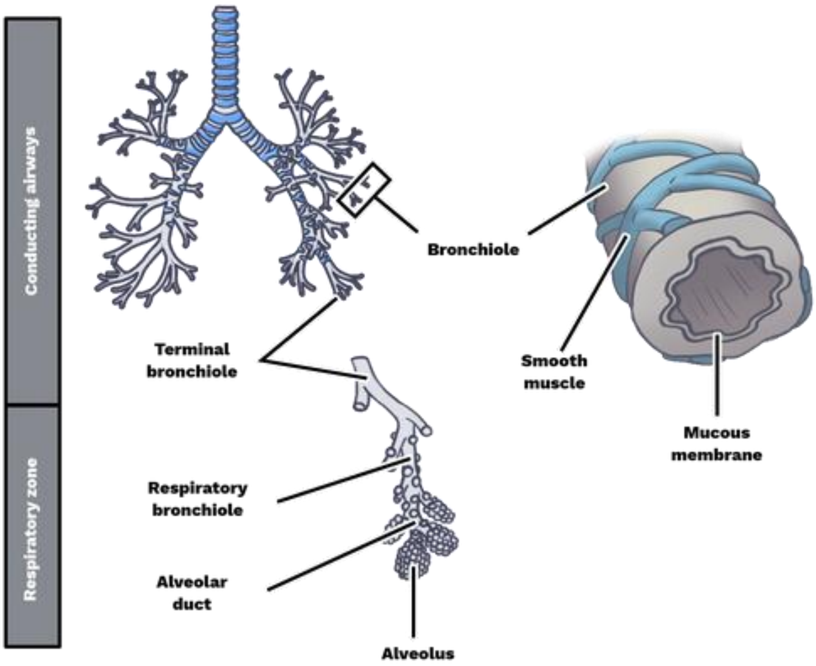


FIG: 14 THE BROCHIOLRS 66

Alveolar region: The alveolar region is mucus-free and has a significantly flatter epithelium that is 0.1–0.5 μm thick and of the simple squamous type.

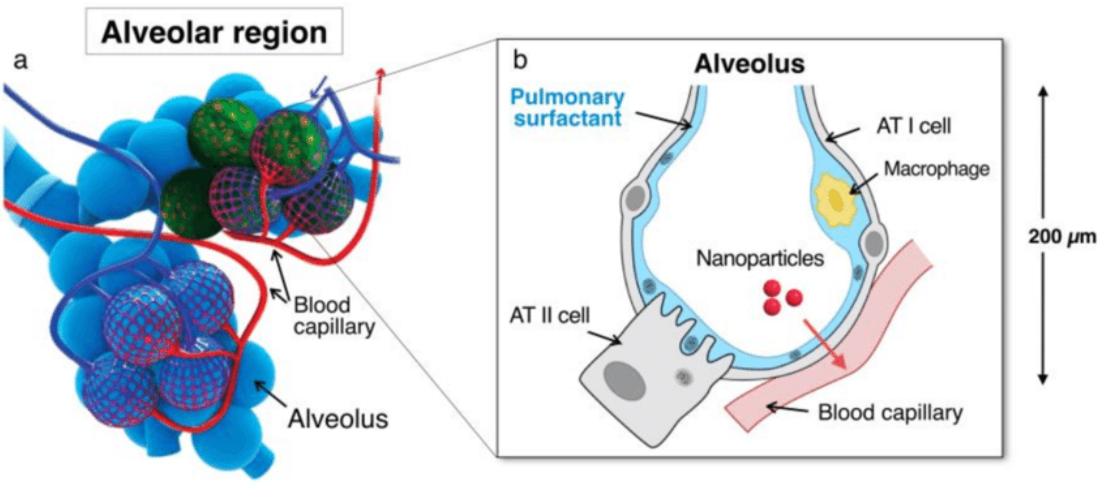


FIG : 15 ALVEOLAR REGION 67

Ciliated cells: A significant percentage of the epithelial cells in the trachea bronchial region are ciliated, resulting in a nearly total coverage of the central airways Cilia. The cilia are missing in the alveolar region and less numerous towards the tracheobronchial region's perimeter. Each ciliated cell contains 200 cilia and many microvilli, which are between 1 and 2 μm long. The cilia are hair-like projections that measure roughly 5 μm in length and 0.25 μm in diameter.19

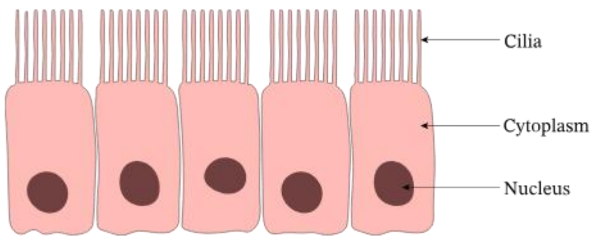


FIG: 16 CILIATED CELL 68

MAJOR FUNCTION OF THE RESPIRATORY

1. Preserving arterial blood haemostasis (acid-base balance)
2. Preserving heat exchange
3. Eliminating carbon dioxide waste from bodily tissues
4. Giving the body oxygen.

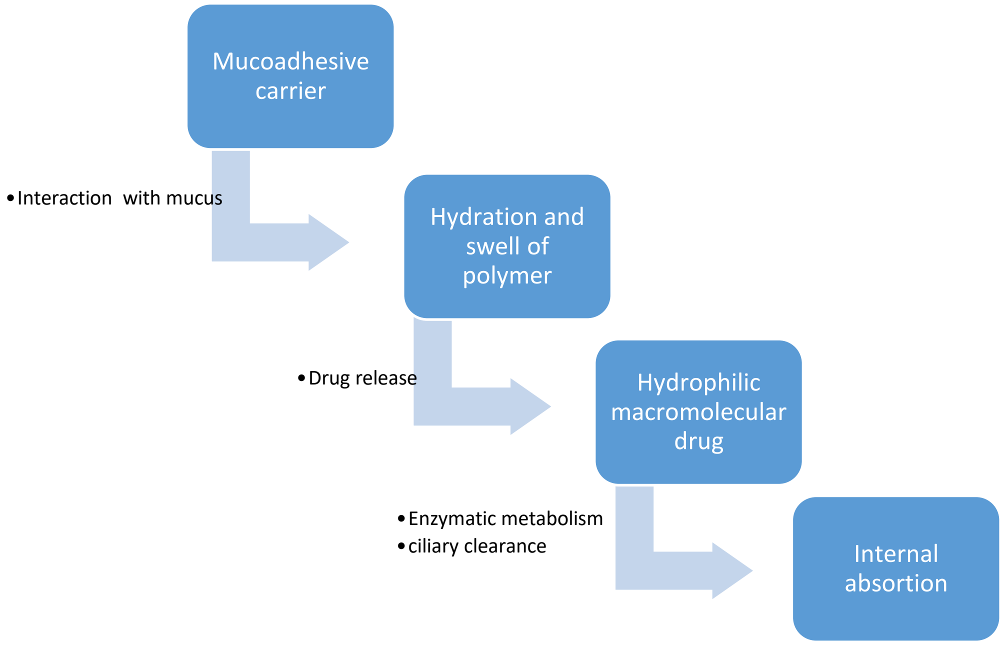
ADVANTAGES OF PULMANARY DRUG DELIVERY SYSYTEM

1. The pulmonary delivery is needle-free.
2. A tiny portion of an oral dose is needed.
3. Less systemic side effects are linked to low concentrations in the systemic circulation.
4. Quick Start of Action
5. Preventing gastric distress
6. In pulmonary drug administration, the liver does not break down the drug.
7. Research to date suggests that the nasal route is a substitute for the parenteral route, particularly for medications containing proteins and peptides.
8. Compared to parenteral medication, it is more convenient for patients, particularly those undergoing long-term therapy.
9. Nasal administration is used for medications that have low stability in GIT fluids.
10. Polar substances with little oral absorption might be especially well-suited for this administration method.

DISADVANTAGES PULMONARY DRUG DELIVERY

1. Local side effects are caused by oropharyngeal deposition.
2. The patient can have trouble appropriately utilizing the pulmonary medication devices.
3. The mucus layer's physical barrier may restrict drug absorption.
4. A number of variables, such as the pharmacological and physiological barriers, influence the repeatability of drug administration in the lungs.
5. Drug delivery devices are necessary to target drug delivery, in addition to the lungs being an accessible surface for drug delivery complexes.
6. Both the drug and ingredients added to the dosage form include the risk of causing local adverse effects and permanent harm to the cilia on the nasal mucosa.
7. At high concentrations, several surfactants utilized as chemical enhancers have the potential to destabilize and even dissolve membranes

MECHANISM OF DRUG ABSORBTION IN NASAL DELIVERY SYSTEM



Out of the several methods that have been put out, two have received the most attention.
In the first, an aqueous transportation method is used, which is sometimes referred to as the paracellular pathway.
This mechanism's main characteristic is that it is a passive, sluggish path.The molecular weight of water-soluble substances and intranasal absorption have an inverse log-log relationship.
A medication with a molecular weight more than 1000 Daltons showed poor bioavailability.
The second method, referred to as the transcellular process, entails transport via a lipoidal pathway and is in charge of carrying lipophilic medications whose rate is influenced by their lipophilicity.
For instance, the natural biopolymer chitosan, which comes from shellfish, helps to deliver drugs by creating tight connections between epithelial cells.

DOSAGE FORM OF NASO-PULMONARY DRUG DELIVERY SYSTEM

1. NASAL DROP

They are the most straightforward and practical nasal medication delivery method yet created. Nose drops can be administered by pipette or bottle or by squeezing. These drug formulations are frequently suggested for the treatment of local disorders, such as experiencing some difficulties including mucosal malfunction, microbial growth, and non-specific loss of the nose or lower back. Nasal drops might not be helpful for prescription medications because of this system's main drawback, which is its lack of dosage accuracy. According to reports, nasal drops are more effective than nasal sprays at depositing human serum albumin in the nostrils.21-25

2. Sprays for the nose

Nasal sprays are made from a solution and suspension. A nasal spray can precisely provide a dosage between 25 and 200 µm thanks to the availability of metered dose pumps and actuators. The morphology
The choice of pump and actuator assembly is determined by the formulation's viscosity and the drug's particle size (for suspensions).20,26,27,28

3. Gels for the nose

There wasn't much interest in this method until the introduction of a precise dosage device. Nasal gels are thickened liquids or suspensions with a high viscosity. A nasal gel's advantages include lowering post-nasal drip because of its high viscosity and reducing flavor. impact as a result of decreased swallowing, less anterior formulation leaks, decreased discomfort from the use of calming/emollient excipients, and increased absorption through mucosal targeting.22,27-30

4. NASAL POWDER

If solution and suspension dosage forms cannot be created, for instance because of poor drug stability, this dosage form may be created. The nasal powder's benefits dose form is the lack of the formulation's improved stability and preservative. The solubility, particle size, aerodynamic characteristics, and nasal irritancy of the active ingredient and excipients, however, determine whether the powder formulation is appropriate. Another benefit of this approach is that the medication may be applied locally.22,28,29,31,32,33.

5. Liposomes

These phospholipid vesicles are made up of a bilayer that encloses one or more aqueous compartments, where drugs can be adsorbed or trapped.

6. Microspheres

Microspheres are crucial for nasal drug administration because they improve absorption, provide prolonged release, and shield the medication from enzymatic breakdown.34

7. Rhinyle catheterization and instillation

Drops are simply delivered to a designated area of the nasal cavity using catheters. After placing the formulation in the tube and holding it with one end in the nose, the solution was blown through the other end using the mouth to enter the nasal cavity. The precision of the system and the filling before administration define the dosage of catheters, which are mostly utilized for experimental research only.35
8.Nebulizers: Nebulizers produce a thin mist of medication suspension or solution that is breathed for an extended amount of time. Usually, individuals with serious respiratory disorders are treated with them.
or those who are unable to successfully employ MDIs or DPIs 4,36,37

FORMULATION APPORACH IN NASO PULMANORY DRUG DELIVERY SYSTEM

these are the most widely used.
These are mentioned below.
The following
Liposomes
Microspheres
Nasal Gels
Nasal Drops
Nasal Sprays
Nasal Powders

By tackling the particular difficulties involved in delivering medications to both the nasal and pulmonary areas, formulation techniques in nasopulmonary drug delivery systems seek to maximize therapeutic efficacy and patient compliance. Creating multifunctional formulations that effectively target both delivery sites is one strategy. For example, formulations based on nanoparticles can be designed to encapsulate medications and make it easier for them to pass through nasal mucosal barriers while simultaneously allowing for deposition and absorption in the lungs during inhalation.38-41

Formulation	Application	Marketed example
1 nasal gels	prolonged drug release and Residence time in nasal Cavity	mucinex sinus- max full force nasal gel
2 nasal drop	simple and convient adminis -tration for small volume	otrivin nasal drop
3 nasal spray	widely used for various drug Due to ease of administration	flonase nasal spray

Table no. 1 : The many formulation techniques used in naso-pulmonary drug delivery systems, along with an example, drawbacks, and solutions 40

Theories of the Nasopulmonary Drug Delivery System

"Nasopulmonary drug delivery" refers to the act of administering drugs through the nose canal to the lungs and upper respiratory tract. This approach has several advantages, like as avoidance of first-pass metabolism, rapid onset of action, and non-invasive administration. There are five ideas about the mechanism of pulmonary drug administration. The following five theories are taken into account for the medicine distribution via the pulmonary drug delivery route: Electronics theory

Wetting Theory

Diffusion Theory

Adsorption Theory

Fracture Theory

Numerous ideas that maximize drug delivery, absorption, and efficacy in the nasal and pulmonary regions form the foundation of nasopulmonary drug delivery systems. One theory is mucociliary clearance, which regulates how mucus and other particles move through the respiratory epithelium. well-known hypothesis. In order to achieve optimal drug deposition and retention, pulmonary drug delivery systems must account for the lungs' clearance processes. However, nasal drug delivery systems must overcome these clearance mechanisms to guarantee adequate drug retention and absorption in the nasal cavity.Regarding the connection between particle size and aerodynamic performance, another hypothesis emphasizes the importance of optimizing particle size distribution and aerodynamic

characteristics to facilitate efficient drug administration to the pulmonary and nasal areas 23,42,43,44

Current pulmonary medication delivery formulations

Aerosolized insulin and aerosolized nicotine for quitting smoking
Alpha 1 Antitrypsin
Angina Aerosols
Aerosolized gene therapy
In cancer chromatography
Pentamicine aerosol
Gentamycin aerosol
Ribavirin aerosol
Lower molecular weight heparin pulmonary delivery
Controlled medication delivery to the lungs
Drugs for bone diseases pulmonary delivery 45,46

How to Pick a Possible API to Deliver It via Nasal Delivery

The following characteristics are necessary for a "optimal" pharmaceutical prospect for nasal shipment:
a) Sufficient aqueous solubility to aid in controlling the desired dose within a range of 25 to 150 ml per nostril in the solution.
b) The best nasal absorption qualities for homes or businesses to provide dependable absorption and restorative efficacy.
c) The medication-induced nasal irritation is absent, ensuring patient convenience during treatment.
d) A professional basis that is warranted for nasal dosage types, such as a rapid onset of action, which increases the therapy's effectiveness.
e) Lower dose requirements, often indicated below 25 mg per administration, increase security and lower the risk of adverse effects.
f) Preventing the production of toxic nasal metabolites, ensuring the nasal approaching the transportation of medications.
g) The absence of offensive fragrances or odors associated with the drug, promoting a positive patient experience.
h) Displaying the proper security features to maintain the medication's integrity and efficacy throughout time, as well as management.47

The evolution of nasopulmonary medication delivery system

Various evaluations were conducted for the dosage types of naso-pulmonary medications. To evaluate naso-pulmonary medication delivery systems, a thorough process is used to ascertain their efficacy, safety, and clinical application. The physicochemical properties of the formulation are first analyzed to ensure optimal drug aerosolization and deposition inside the respiratory system. Cascade impaction is one technique used to analyze particle size distribution and aerodynamic behavior, which are crucial elements in evaluating lung penetration and deposition efficiency.

Parameters
1 fine particle fraction
2 emitted dose
3 delivered dose
4 drug content uniformly
5 In vitro in vivo corelation 48-50

Factors affecting nasal drug absorption

A number of factors impact the overall bioavailability of drugs that are provided via the nasal route. The elements might be impactful on the medicine's physiochemical qualities, the cavum's physiological and anatomical characteristics, and, consequently, the kind and features of the selected nasal medication administration system. Many medications depend on these parameters to reach therapeutically effective blood levels after nasal delivery. The following represents the elements that affect medication absorption through the nose.

1. The medication's physiochemical characteristics;
Molecular size
lipophilic-hydrophilic equilibrium
enzymatic breakdown in cavum.

2. The nasal outcome,
mucociliary clearance
environmental ph
membrane porosity
Rhinitis and a cold.

3. Outcome of delivery:
Formulation (osmolality, pH, and concentration) Drug dispersion deposition consequences of delivery
Viscosity 51

FUTURE VIEWS AND DIFFICULTIES

NDDS is a promising drug delivery technology with several potential applications. NDDS has a promisinanng future, and significant developments in this field should be anticipated in the years to come. The subsequent are some significant themes that may have an impact on the future development of NDDS:
1 Increased use of nanotechnology Among other advantages for NDDS, omaterials can improve medication solubility, permeability, and targeting. We should expect to see more nanomaterials being utilized in the development of new NDDS systems in the future.
2 Development of specialized NDDS systems
It is possible to create NDDS systems that are specifically tailored to each patient's needs. This may be achieved by taking into account factors including the patient's age, sex, and condition. Prospective advancements of The market should be able to customize NDDS systems more.
3 Complex medication administration using NDDS systems
Complex medications that are difficult to distribute through traditional channels, such proteins and vaccinations, can be delivered using NDDS devices. We should expect to employ NDDS in the future to deliver an ever-increasing range of sophisticated drugs. These are only a few of the numerous opportunities for the nasal medication delivery method going forward.52

FINAL RESULTS

The mucosa of the nasal cavity is highly vascularized and has a vast surface area. Substances used by wealthy people network of blood arteries bypasses the firstpass metabolism by entering the systemic circulation directly. An increasing amount of data about nasal drug delivery points to its potential application for difficult medications that can ease the difficulties associated with pharmaceutical production and delivery.

REFFERANCES:

1.ChienY.W., Su K.S.E., Chang S.F., Nasal Systemic Drug Delivery, Ch. Marcel-Dekker, New York, 1: 1-77.

2. Illum.L, Jorgensen. H, Bisgard. Hand Rossing. N, Bioadhesivemicrospheres as a potential nasal drug delivery system. Int. J. of Pharmaceutics, 189-199

3. Ibrahim, A., Aziz, O. A. A., Dena, A. S. A., & El-Sherbiny, I. M. "Current

advancements in nasopulmonary drug delivery systems", In Advanced and Modern Approaches for Drug Delivery, 2023; (pp. 91-111). https://doi.org/10.1016/B978-0-323-91668-4.00027-7

4. Chaudhari, R., Deshmukh, A., Sahu, V., Pharm, B., & Pote, P. R, "NASO
Pulmonary Drug Delivery System-A Novel Approach" World J Pharmaceut Res. 2020;9;(15);542-558. DOI: 10.20959/wjpr202015-19255

5. Kumbhalkar, P.R., Mustafa, S.S.M., Ramchandani, T.K., Ramani, M.S.,
Kadak, S.A., Shaikh, A.S., Khan, T.J. and Zodape, P.M. "A REVIEW
ON INHALATION DRUG DELIVERY SYSTEM" Irjmets, 2023; 5(12);
1155-116. DOI : https://www.doi.org/10.56726/IRJMETS47347

6. Pal, R., Pandey, P., Nogai, L., Anand, A., Suthar, P., SahdevKeskar, M.,
& Kumar, V. "The future perspectives and novel approach on gastro retentive drug delivery system (GRDDS) with currrent state" Journal of Population Therapeutics and Clinical Pharma., 2023; 30(17), 594-613. https://doi.org/10.53555/jptcp.v30i17.2852

7. Appasaheb, P. S., Manohar, S. D., Bhanudas, S. R., & Anjaneri, N. "A review on intranasal drug delivery system", Journal of Advanced Pharmacy Education & Research, 2012; 3(4); 333-346.

8. 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.

9. 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.

10. https://en.m.wikipedia.org/wiki/Lung.

11. Moussavi, Z. Anatomy and Physiology of Respiratory System. In Fundamentals of Respiratory System and Sounds Analysis Cham: Springer International Publishing, 2006; 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. Marttin, 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. np, https://en.m.wikipedia.org/wiki/Lung)

20. Rudman KL, O'Brien EK, Leopold DA. Radiographic distribution of drops and sprays within the sinonasal cavities. Am J Rhinol Allergy, 2011; 25: 94-7.

21. Suber C, Elsner P, Farage MA: Topical Application and the Mocosa. Curr Probl Dermatol. Basal, Kerger, 2011; vol 40; pp 20-35.

22. Shyeilla VD, Leah RH, William HF 2nd: Intranasal delivery to the central nervous system: mechanisms and experimental considerations. J Pharma Sci,2010; 99: 1654-1673.

23. Merkis FW, Van den Berg MP: Can Nasal Drug Delivery Bypass the blood barrier? Questioning the direct transport theory Drug R D, 2007; 133-144.

24. Thulasiramarajun TV. Et al./Asian Journal of Research in Pharmaceutical Science and Biotechnology, 2013; 1(1); 16-34.

25. Critical Reviews in Therapeutic Drug Carrier System, 1997; 14(4): 395-453.

26. Hammarlund-Udenaes M, de Lange E, Thorne RG. Pharmacokinetic concepts in brain drug delivery in drug delivery to the brain. In: Physiological Concepts, Methodologies and Approaches. New York: Springer, 2014; 127-61.

27. Hardy JG, Lee SW, Wilson CG. Intranasal drug delivery by spray and drops. J Pharm Pharmacol, 1985; 37: 294-7.

28. Watson J, Wright S, Lucas A, Clarke KL, Viggers J, Cheetham S, et al. Receptor
occupancy and brain free fraction. Drug Metab Dispos, 2009; 37: 753-60.

29. Dinanath G, Padmini K, Dipak M, Namdeo J. Development of particulate mucoadhesive gel for intranasal delivery. Asian J Pharm Clin Res, 2017; 10: 222.

30. Kritika S, Bhupen K, Banasmita K. Development and characterizationof
mucoadhesive microsphere-loaded intranasal gel of venlafaxine hydrochloride. Asian J Pharm Clin Res, 2016; 9: 139-44.

31. Giuliani A, Balducci AG, Zironi E, Colombo G, Bortolotti F, Lorenzini L, et al. In vivo nose-to-brain delivery of the hydrophilic antiviral ribavirin by microparticle agglomerates. Drug Deliv, 2018; 25: 376-87.

32. Ravikumar R, Balan R, Ganesan N, Thiruvengadam D. Recent modalities in drug
delivery via inhalation therapy – An advanced treatment strategy for pulmonary

carcinoma. Int J Pharm Pharm Sci, 2015; 7: 8-21.

33. Mosab A. Approaches to achieve an oral controlled release drug delivery system using polymers: A recent review. Int J Pharm Pharm Sci, 2025; 7: 16-21.

34. Özer AY. The importance of intranasal route for application of drugs and nasal drug delivery systems. Pharm JTPA, 1990; 30: 136-47.

35. Hughes B.L., Allen D.L., Dorato M.A., Wolff R.K., Effect of devices on nasal deposition and mucociliary clear-ance in rhesus monkeys, Aerosol Sci. Technol, 1993; 18: 241–249.

36. Geller, D. E. "Comparing clinical features of the nebulizer, metereddose inhaler, and dry powder inhaler", Respiratory care, 2005;50(10); 1313-1322.

37. Pandey, P., Pal, R., Singh, S., & Gupta, H., "THE CURRENT STATUS IN MUCOSAL DRUG DELIVERY SYSTEM (MDDS) AND FUTURE PROSPECTUS IN DELIVERY: A SYSTEMATIC REVIEW", 2023; 8(10); 76-106. https://doi.org/10.47760/ijpsm.2023.v08i10.007

38. Pal, R., Pandey, P., Jha, D., Dutta, P., Sahoo, S., Gupta, R., ... & Chawra, H. S. "The Utilization of 32 Full Factorial Design (FFD) for Optimization of Lincomycin Hydrochloride (LNH) Loaded Nanogel Involving; Design of Experiments (DoE) an Advanced Approach", Advances in Research, 2023; 24(6), 272-281. https://doi.org/10.9734/air/2023/v24i61009

39. Hussein, N. R., Omer, H. K., Elhissi, A. M., & Ahmed, W. "Advances in nasal drug delivery systems. In Advances in medical and surgical engineering", 2020; 279-311). https://doi.org/10.1016/B978-0-12-819712-7.00015-2

40. Pal, R., Pandey, P., Thakur, S., Chanana, A., & Singh, R. P. "BIODEGRADABLE POLYMER'S ENHANCING DRUG DELIVERY ACTIVITY IN DIFFERENT NOVEL DRUG DELIVERY SYSTEM", 2022; 12(1); 2046-2069. DOI: 10.20959/wjpps2023

41. Rawat, S., Rai, A., Kaur, S., Goyal, A., & Singh, I. "NanotechnologyBased Drug Delivery Systems for the Treatment of Pulmonary Diseases", In Nanotechnology and Drug Delivery, 2024; (pp. 251-305). Jenny Stanford Publishing.https://doi.org/10.1201/9781003430407-7

42. Chhajed, S., Sangale, S., & Barhate, S. D. "Advantageous nasal drug delivery system: a review", International Journal of Pharmaceutical Sciences and Research, 2011; 2(6); 1322.

43. Smola M, Vandamme T, Sokolowski A. Nanocarriers as pulmonary drug delivery systems to treat and to diagnose respiratory and non respiratory diseases. Int J Nanomedicine. 2008;3(1):1-19. PMID: 18488412; PMCID: PMC2526354.

44. Smart, John D. "Theories of mucoadhesion." Mucoadhesive materials and drug delivery systems (2014): 159-174. https://doi.org/10.1002/9781118794203.ch07

45. Rohan Bhavane, Efstathios Karathanasis, Ananth V. Annapragada, "Agglomerated vesicle technology": a new class of particles for controlled and modulated pulmonary drug delivery, Journal of Controlled Release, 2003; 15– 28.

46. P.P.H. Le Brun, A.H. de Boer, H.G.M. Heinemann and H.W. frijlink "A review of the technical aspects of drug nebulization", Pharm World Sci, 2000; 22(3): 75-81

47. 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.

48. Deshkar Sanjeevani Shekhar, Vas Alisha Swizal "Recent updates on dry powder for inhalation for pulmonary drug Delivery systems" Int. J. Res. Pharm. Sci. 2019; 10(4):29 47-2948.

49. Rawat, S., Rai, A., Kaur, S., Goyal, A., & Singh, I. "NanotechnologyBased Drug Delivery Systems for the Treatment of Pulmonary Diseases", In Nanotechnology and Drug Delivery, 2024; (pp. 251- 305).Jenny Stanford Publishing. https://doi.org/10.1201/9781003430407-7

50. Alnasser, S. "A REVIEW ON NASAL DRUG DELIVERY SYSTEM AND ITS CONTRIBUTION IN THERAPEUTIC MANAGEMENT". Asian Journal of Pharmaceutical and Clinical Research, vol. 12, no. 1, Jan. 2019, pp. 40-45, doi:10.22159/ajpcr.2019.v12i1.29443.

51. Coro DC, Liu JC, Chien YW. Characterization of the barrier properties of mucosal membranes. J Pharm Sci, 1990; 79: 202-206.

52. Frank DO, Kimbell JS, Pawar S, Rhee JS. Effects of anatomy and particle size on nasal sprays and nebulizers. Otolaryngol Head Neck Surg 2012;146:313-9.

53. https://www.freepik.com/free-photos-vectors/human-nose-anatomy

54. https://www.pinterest.com/pin/anatomy-of-the-nose--1759287347801913/

55. https://teachmeanatomy.info/head/organs/the-nose/nasal-cavity/

56. https://norellehealth.org/conditions/nasal-valve-collapse/

57. https://www.healthdirect.gov.au/nose-and-throat

58. https://entkidsadults.com/turbinate-reduction/

59.https://www.sciencedirect.com/topics/immunology-and-microbiology/mucociliary-clearance

60.https://www.vecteezy.com/vector-art/35633943-lungs-medical-educational-diagram-vector-illustration

61. https://www.shutterstock.com/search/right-lung

62.https://www.mayoclinic.org/diseases-conditions/nasopharyngeal-carcinoma/symptoms-causes/syc-20375529

63. https://www.sciencedirect.com/topics/medicine-and-dentistry/alveolar-cell

64. https://en.wikipedia.org/wiki/Respiratory_epithelium

65https://study.com/learn/lesson/bronchi-function-anatomy.html

66. https://theory.labster.com/bronchioles_all/

67.https://www.researchgate.net/figure/a-Schematic-representation-of-the-alveolar-region-b-Sketch-of-a-human-pulmonary_fig1_359890312

68. https://afuncan.com/#