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Nasopulmonary Drug Delivery Systems: A Review of Formulation Strategies, Mechanisms, and Therapeutic Applications

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Abstract

The nasopulmonary drug delivery approach entails the administration of therapeutic agents through the nose or inhalation into the lungs. Such a mode of delivery provides a rapid effect, an efficient access to respiratory organs, minimal body exposure when delivering locally acting drugs, and a non-invasive method of medication administration to patients requiring certain selected medications. The efficiency of delivery depends on various physiological parameters including mucociliary clearance, epithelial permeability, aerosols properties, formulation composition, device specifications, and patient compliance. Nasal formulations are represented by drops, spray, powder, gel, and mucoadhesive formulations while inhalers usually represent pressurized metered-dose inhalers, dry-powder inhalers, nebulization solution and suspension, and innovative carrier systems. Clinical studies are being conducted with the involvement of liposomal, polymeric nanoparticle and nanoemulsion, in-situ gel formulations. This review highlights the area of interest and physiology of the nasopulmonary route, main strengths and weaknesses, deposition and absorption mechanisms, formulation and manufacturing technology, applications, advanced delivery systems, quality assessment and future directions. This area involves many challenges for the researchers since success depends on finding appropriate correlation between drug, formulation, device, and patient.

Keywords: Nasopulmonary delivery; nasal drug delivery; pulmonary drug delivery; inhalation; dry-powder inhaler; nebuliser; liposomes; nanoparticles; aerosol deposition; formulation evaluation.

1. INTRODUCTION

1.1 Background

The drug delivery route impacts the amount of the active compound reaching the target site, the speed of onset, systemic absorption, and the practicality of patient treatment. While oral delivery is convenient, it may be limited by GI breakdown, first pass effect, or delayed onset. While parenteral delivery can overcome some of

these limitations, it may require needles and skilled medical professionals in many cases. Nasal and pulmonary delivery routes offer another possibility as they deliver a drug formulation directly to the respiratory mucosa.

Nasal delivery involves the use of the nasal cavity for the purpose of local or systemic drug delivery. The pulmonary delivery route involves the inhalation of the drug in order to spread it throughout the airways or lungs. While both routes involve mucosal membranes, their anatomy, available surface, clearance, deposition, and devices used are different. Therefore, they should be considered related but not interchangeable drug delivery routes.

1.2 Reasons for Conducting the Review

Research into such delivery systems has grown increasingly popular as inhalation devices, particulate systems, biopharmaceutical formulation, and nanotechnology have advanced. Inhaled drugs have been used to treat asthma and COPD, whereas nasal delivery systems have been extensively used for rhinitis and certain acute illnesses. Nasal and pulmonary delivery of vaccines, peptides, proteins, and systemic drugs is also currently being investigated.

1.3 Objectives of the Review

The present review aims to: (i) explain the concept of nasal and pulmonary delivery; (ii) describe relevant anatomy and physiology; (iii) explain the pros and cons as well as the mechanisms of absorption; (iv) describe the various dosage forms, manufacturing methods, and advanced carriers; (v) list applications and evaluation criteria; and (vi) list the development challenges and future prospects.

2. CONCEPT, SCOPE AND ROUTE SELECTION

2.1 Nasal Delivery

In this method of drug delivery, a formulation is applied directly to the mucosal surface of the nasal cavity. Some of the types of formulations used are aqueous solutions, metered-dose aerosols, powders, gels, and delivery systems. The formulation can have local actions like nasal anti-inflammatory effects or systemic effects through absorption. This route is preferred in instances where quick effect is needed or bypassing the stomach process. However, inefficiency might result due to the low dose and limited contact because of the mucociliary clearance.

2.2 Pulmonary Delivery

Pulmonary delivery is defined as aerosol administration to the lungs. The deposition is dependent on the aerodynamic size of the particles and the mode of inhalation used. Deposition occurs either in the mouth, in the conducting airways or in the periphery of the lungs. Deposition within the pulmonary tract enables the formulation to get into the targeted site in the lungs in greater concentration than with the oral route despite the swallowed medication.

2.3 Determinants of Route Compatibility

Criteria such as the strength of a drug, solubility, stability, weight of the molecule, dosage to be administered, desired target site, and effective range are used in choosing an administration route. Other criteria include disease stage, presence of secretions, obstruction, congestion of the nose, patient's age, breath holding capacity, coordination, and patient's choice. Assessment of a formulation is inseparable from a means of administration.

2.4 Comparative Merits of Nasal vs Pulmonary Routes

The nasal route offers easily reachable membrane and fast absorption while the drawbacks include low volume, fast clearance of mucosa making higher dosage difficult to administer. The pulmonary route boasts large absorptive surface with a thin covering of alveolar epithelium facilitating permeation, although there are difficulties in its administration. Thus nasal administration and pulmonary delivery require their own quality control requirements.

3. ANATOMY AND PHYSIOLOGY OF THE NASAL CAVITY

3.1 Structural Regions

The nasal cavity consists of vestibular, respiratory, and olfactory regions. The vestibule consists of epithelium similar to skin tissue and hair that filters large particles. The respiratory region is notable for its prevalence of ciliated epithelium along with cells producing mucus and high vascularization. The olfactory region is located in the upper part of the cavity and includes sensory cells; it is especially important in studies related to nose-to-brain delivery, but it is hard to access reliably.

3.2 Mucus and Mucociliary Clearance

Mucus helps to capture the inhaled particles and pathogens. Ciliated mucosa helps to clear the mucus towards the nasopharynx, where it is either expelled or swallowed. It decreases the time needed for dissolution and absorption of the drug. Clearance is affected by mucus viscosity, functioning of cilia, hydration and presence of infections or inflammation. Mucoadhesive dosage forms help to increase the residence time; however, too high viscosity can affect spreading, comfort or functioning of cilia.

3.3 Nasal Epithelial Barrier and Absorption

The passage of drugs through nasal epithelium is done either transcellularly or paracellularly. Small-molecule drugs that are lipid soluble have good permeability across membranes while water-soluble or bigger molecules find it difficult to pass through the membranes. There are permeation enhancers that increase the transport of drugs, although there are safety issues associated with these since the destruction of the nasal membrane may result in inflammation or cell injury.

3.4 Considerations for Formulation

The nasal drug delivery systems need to have an appropriate pH, tonicity, viscosity, microbial quality, and spray ability. They must be dispersed properly at the targeted sites without causing pain, drainage, and bad taste.

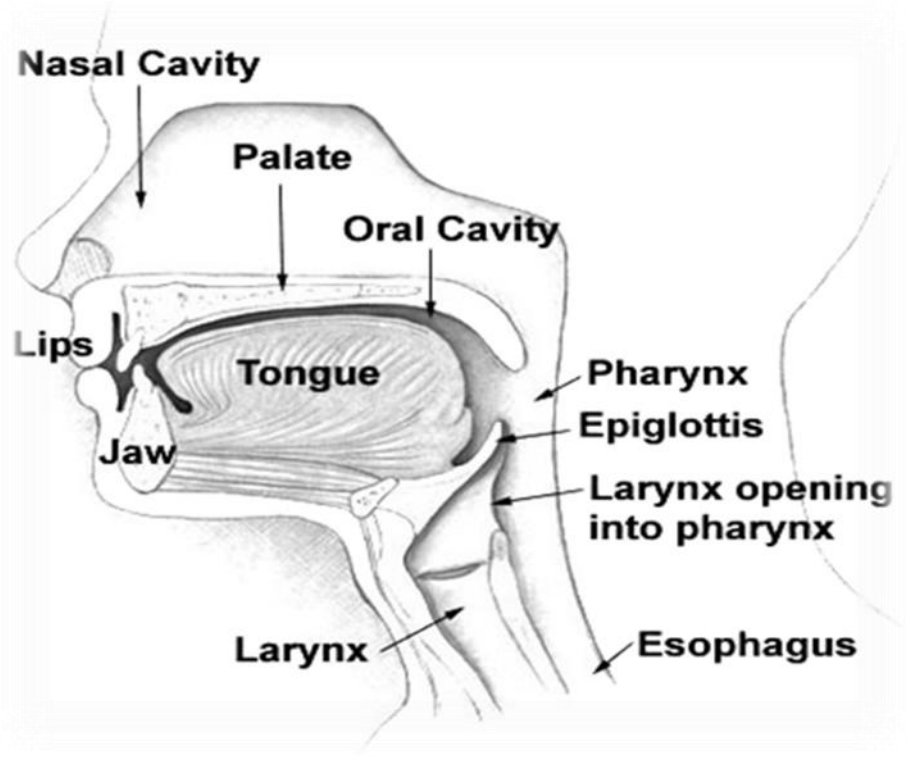


Diagram1: structure of nasal cavity

4. ANATOMY AND PHYSIOLOGY OF THE RESPIRATORY SYSTEM

4.1 Conducing Airways

Inhalation of air occurs through the nose and mouth and then passes through the pharynx, larynx, trachea, bronchi, and bronchioles. Air is heated, humidified, and filtered by the conducting airways. Mucus and cilia aid in the removal of deposited particles, and the shape of the branches and flow of air determine particle impaction and sedimentation. Obstructive diseases of the lungs will affect the deposition of particles due to constricted airways and high mucus production.

4.2 Gas Exchange Area

Alveoli, located in the distal regions of the respiratory tract, provide a surface area and air-blood barrier that facilitate the exchange of gases. This anatomical design allows some inhaled drugs to pass through the lungs. Defense systems like alveolar macrophages help remove foreign particulates from the respiratory system. Deposition and release are two important considerations in the design of deep-lung products.

4.3 Aerosol deposition

Aerosol deposition is affected by a variety of factors such as particle aerodynamic size and shape, density, hygroscopic swelling, inspiratory flow rate, breath-holding time, airway shape, and device performance. Big particles will deposit in the mouth and upper airways, medium-size particles deposit in the conducting airways, whereas ultra-fine particles will stay suspended in the airways and will be exhaled. There are no clear boundaries between them as all of these factors affect aerosol deposition.

4.4 Patient and disease-related factors

Patients with low inspiratory flow rates may not produce enough force to disperse dry powder from some inhalers. Patients with poor hand-breath coordination will not be able to deliver medicine from a pressurized metered-dose inhaler without a spacer or correct technique. It may be necessary to choose an appropriate device depending on patient's age and disease condition.

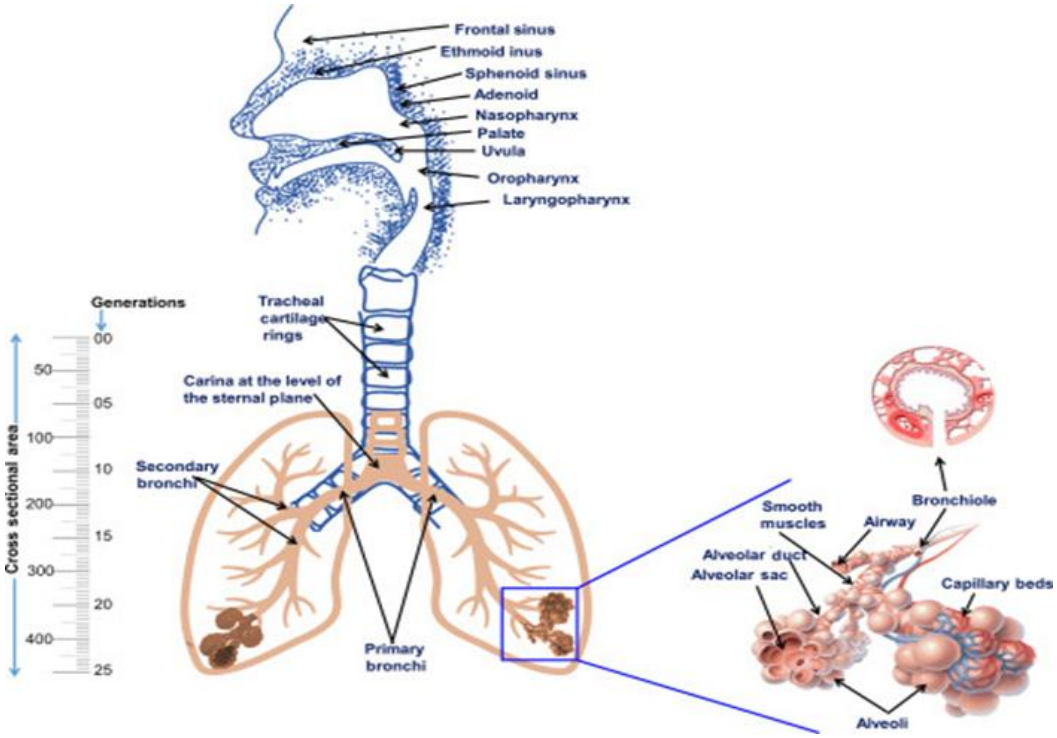
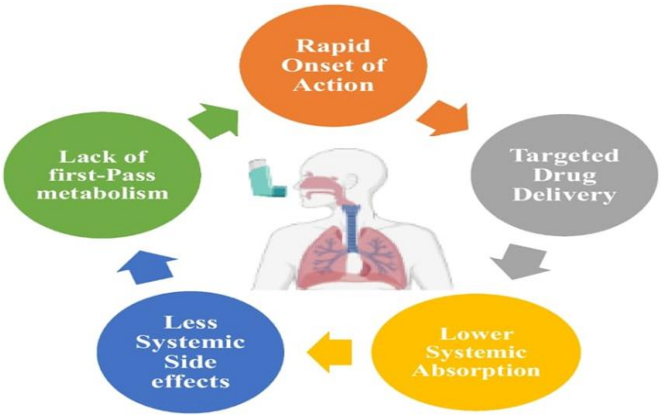


Diagram 2 : structure of respiratory system

5. ADVANTAGES AND LIMITATIONS

5.1 Potential benefits

Non-invasive modes of administration (nasal and pulmonary) may increase the acceptability of the treatment because of fear of injections. Local delivery systems allow direct application to the area of action, making it possible to use smaller amounts of the drug than with systemic administration. Nasal administration may provide fast onset in some cases for certain molecular targets. In the case of pulmonary administration, direct access to the conducting airways can be provided, which is applicable for bronchodilators, corticosteroids, antimicrobial agents, and some biologics. There may be pharmacokinetic benefits due to protection from gastrointestinal digestion and the first-pass effect for certain compounds.



5.2 Limitations

Limitations of such routes mainly concern dosing limitation, the mucosal barrier (mucociliary clearance, mucus, and enzyme activity), and related formulation issues. The dose limitation issue is especially relevant for the nasal administration. Effective use of the pulmonary route requires proper handling of the devices and adequate inhalation volume. Adherence may be impaired due to irritation of nasal mucosa, coughing, dysgeusia, or bronchospasm. Among other formulation issues there can be mentioned drug dissolution, chemical instability, and moisture sensitivity.

Disadvantage	Description
Limited drug absorption	The nasal mucosa provides a relatively small surface area for drug absorption.
Mucociliary clearance	Mucus and ciliary movement can rapidly remove the formulation from the nasal cavity.
Nasal irritation	Some drugs or formulations may cause irritation, dryness, or discomfort in the nasal mucosa.
Limited dose capacity	Only a small volume of formulation can be administered into the nasal cavity.
Enzymatic degradation	Some drugs, especially peptides and proteins, may be degraded by enzymes present in the nasal mucosa.
Variability in absorption	Absorption can vary with mucus thickness, nasal congestion, disease conditions, and individual differences.
Formulation challenges	Maintaining suitable pH, viscosity, particle size, and stability can be difficult.

5.3 Safety and patient factors

Drugs for long-term administration require assessment of local effects on tissues and systemic distribution. Appropriate excipients are needed in relation to the selected route of administration and concentration. The need for preservatives and permeation enhancers must be justified. Information about training in using the device, washing procedure, dose calculation, and proper labeling must be included. Inhalable drugs are not necessarily more unsafe than oral and parenteral drugs; their safety depends on the particular compound, dosage, and patient condition.

5.4 Benefits versus risks

Objectives of development go beyond just optimization of delivery or absorption. One should seek to provide reproducible drug exposure with good safety and convenience properties and economic efficiency. Systemic absorption is undesirable in local treatment, but important in systemic treatment

6. MECHANISM OF NASAL AND PULMONARY DELIVERY

6.1 Nasal drug deposition and absorption

The nasal administration device produces droplets/particles, which enter the nasal cavity and deposit on the nasal mucosa. Deposition of the drug is influenced by nozzle design, plume pattern, spray speed, head position and mode of administration. The drug needs to dissolve in the mucus, stay in contact with the mucosa for sufficient time and pass the epithelial barrier. Possible clearance paths may be drainage to the anterior nares, passing to the oropharynx, swallowing, or clearance through mucociliary clearance.

6.2 Pulmonary aerosol generation

Inhalers and nebulizers produce aerosols by different methods. Inhalers use a propellant in order to create an aerosol. Inhalers that use dry powder depend on air flow created by the patient. Nebulizers use jet, ultrasonic, or vibrating mesh technology to turn the liquid drug into inhalable droplets.

6.3 Drug release and absorption

After deposition, the drug molecule could be released and dissolved, transported through airway lining fluids, interact with the mucus layer, internalized by cells, and removed from the target site. The rate of dissolution of the drug is determined by particle size, solid state, solubility, and local fluid properties. Drugs that are hydrophobic have high rates of diffusion through biological membranes while large hydrophilic drugs require special delivery systems. The carrier could control the rate of drug release, protect the drug molecule from degradation, and interact with the cells but it does not guarantee the clinical effect.

6.4 Clearance mechanism

The particles that are present in the conducting airways could be cleared using mucociliary transport and then swallowed. The particles that are present in the distal portions of the airways could be phagocytosed by alveolar macrophages, dissolved and absorbed or retained depending on physicochemical characteristics of the drug molecule. Nasal formulations are subjected to drainage and mucociliary clearance.

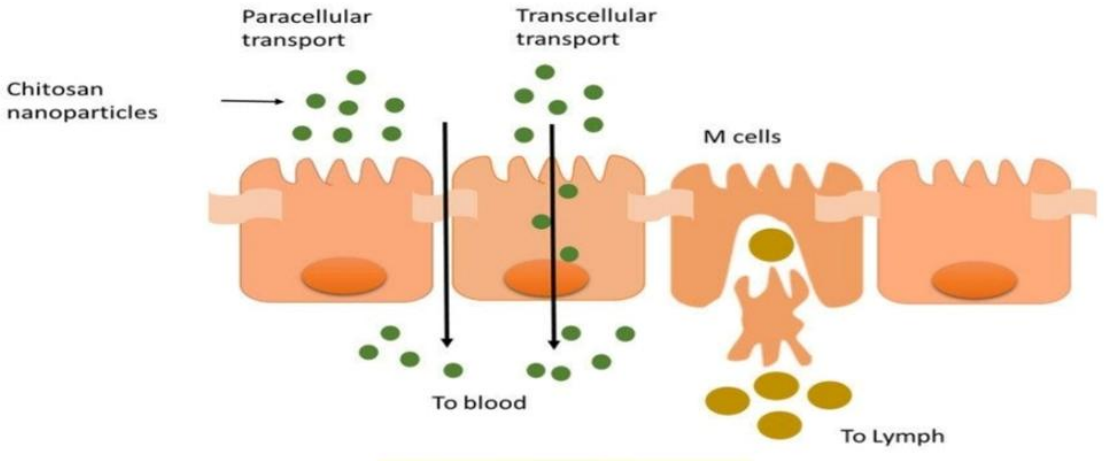


Diagram 3: structure of mechanism of action

7. FORMULATION TYPES AND PREPARATION METHODS

7.1 Nasal dosage forms

The nasal dosage forms include solutions and suspensions that are applied as drops or metered sprays. Although some powders provide increased stability to certain drugs, they require adequate dispersion and tolerable nasal sensation. The gels and mucoadhesive preparations increase the contact time of these drugs with the nasal mucosa. The in-situ gels are applied as liquids and transform into gels due to certain physiological processes. These preparations should not interfere with the process of mucociliary clearance or cause any discomfort.

7.2 Pulmonary dosage forms

The pressurized metered-dose inhalers consist of the drug, propellant, and selected excipients in a pressurized container with a metering valve. The dry-powder inhalers release the micronized drug or drug with a carrier (e.g., lactose) and depend on the airway flow for the drug dispersion. The nebulizer solutions or suspensions are used to deliver aerosols and can be beneficial for patients unable to use hand-held inhalers.

7.3 General Preparation Process

The preformulation assessment involving solubility, pKa, stability, particulate properties, and compatibility is normally carried out at the start of development. The preparations are then manufactured by an appropriate process, filled into the appropriate container or device, and tested for dose uniformity, aerosolization performance, microbial characteristics, and stability. It is important that process parameters are well controlled and correlated to the quality attributes.

7.4 Manufacture

In case of liquids, dissolution and dispersion, proper filtration, and aseptic manufacture with validated microbial controls are required. In the case of dry powders, control of the particle size, moisture content, flow properties, blend uniformity, and electrostatic charge is required. For spray devices, pump performance, drop size distribution, and delivered dose need to be assured. Scale-up is to maintain the attributes responsible for clinical performance.

8. ADVANCED DELIVERY SYSTEMS: LIPOSOMES AND NANOCARRIERS

8.1 Liposomes

A liposome consists of vesicles that have one or more phospholipid bilayer membranes surrounding an aqueous cavity. Hydrophilic substances are dissolved in the aqueous core, whereas hydrophobic drugs form part of the lipid membrane. Liposomes protect a drug from degradation, allow for controlled release and help regulate interaction with biomembranes. Performance of liposomes depends on lipid composition, size of particles, lamellarity, surface charge, loading efficiency, and storage conditions.

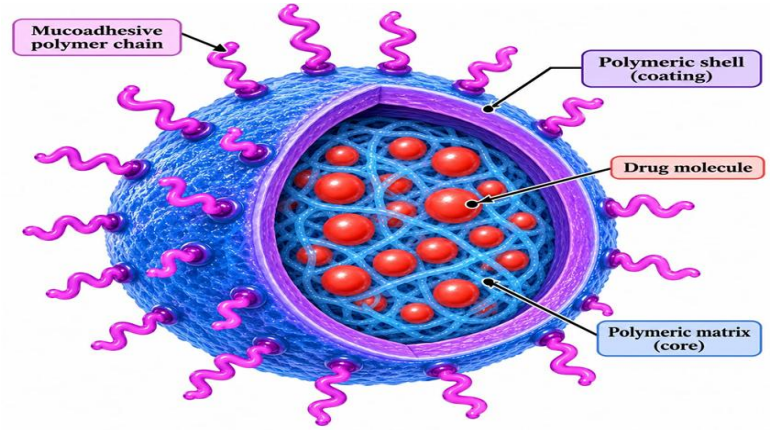


Diagram4: structure of liposomes

8.2 Liposome preparation and characterization

Methods of liposome preparation in laboratory include thin film hydration followed by size reduction; alternatively, preparation may use sonication, membrane extrusion, or filtration based on the required vesicle type. Problems involved in preparation relate to solvent residue, oxidative stress, agglomeration, and drug leakage. Characterization involves measurement of vesicle size, size distribution, morphology, surface charge, drug content, loading efficiency, release profile, and stability of the system.

8.3 Other Nanocarriers

Polymeric nanoparticles, lipid nanoparticles, nanoemulsions, and solid lipid carriers have been studied as vehicles for delivering via the respiratory tract. Such approaches seek to increase solubility, protect the cargo, control release, or improve interactions with target cells. Mucoadhesive polymers and in situ gels are used to prolong the time of action in the nasal cavity. There are special problems in production, safety, scale-up, and regulation associated with each of these methods.

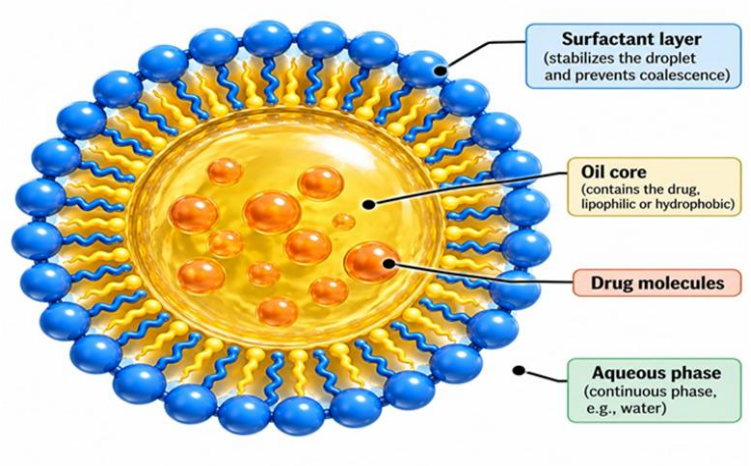


diagram 6: structure of niosomes

8.4 Translational Problems

The performance of a nanocarrier that appears to work well in vitro models can be different in mucosal fluids, lung lining fluids, or diseased airways. The problems of toxicity, inflammation, clearance, reproducibility, and

stability need to be investigated carefully. Claims about targeted delivery or controlled release must be proven by appropriate data. New formulations need to be compared to clinically relevant controls.

9. APPLICATIONS IN MEDICINE

9.1 Nasal applications

There are nasal formulations that have found application in the treatment of allergic rhinitis, nasal blockage and other similar local ailments. Some drugs use the nasal pathway for achieving quick results in systemic effect. There has been research conducted on the possibility of delivering vaccine and peptide/proteins using the nasal pathway and this depends on various factors including stability of antigens/molecules, immunity of the mucosa, proper dose and effectiveness.

9.2 Pulmonary applications

The bronchodilators and the inhaled corticosteroids form an essential part of the foundation of asthma and COPD therapy. Some of the drugs that are good candidates for inhalation include the antimicrobials used in the treatment of respiratory infections and specially designed drugs to work in the lungs. Inhalation of some drugs limits systemic exposure, but it does not prevent the systemic absorption and side effects.

9.3 Pulmonary administration

The large surface area and thin epithelium of the lungs have prompted research into systemic delivery of peptides, proteins, and other molecules. Successful products require reliable deposition, proper dissolution and absorption, acceptable local tolerability, and reliable delivery devices. This is not a suitable route for all drugs, and pulmonary safety must be carefully assessed.

9.4 Nose-to-brain delivery

Intranasal delivery has been explored as a possible route of delivery to the central nervous system through olfactory or trigeminal routes. This area faces difficulties in deposition in the right location, distinguishing transport from systemic distribution, and clinical efficacy. It should be considered an area of research rather than a validated delivery route to the brain.

9.5 Patient-centered administration

Clinical efficacy depends on proper administration and patient compliance. Patient education includes priming, breathing rate, breath-holding when necessary, cleaning of the device, storage of the device, dose counters, and replacement criteria. Health care practitioners need to regularly assess the technique because errors are common and may persist without demonstration and feedback.

10. EVALUATION AND QUALITY CONTROL

10.1 Evaluation of nasal products

Parameters may include appearance, pH, viscosity, osmolality, content of the drug, delivered dose uniformity, spray pattern, plume dimensions, droplet-size distribution, pump performance, microbiology, and efficacy of the preservatives. For dry powders and gels other parameters, such as flow characteristics, particle-size distribution, mucoadhesion, gelling capacity, and in vitro release can also be measured.

10.2 Evaluation of pulmonary products

Parameters needed for inhalation products include delivered dose, aerodynamic particle-size distribution, fine-particle dose or fine particle fraction, emitted dose, device resistance, and performance at clinically relevant flow rates. Cascade impaction is used to measure the aerodynamic particle-size distribution. Output rate and residual volume for nebulization are also parameters that may need to be determined.

10.3 Carrier-specific tests

Tests that can be applied to liposomes and nanoparticles include size, polydispersity index, morphology, surface charge, entrapment efficiency, drug loading capacity, drug release rate, and lipid or polymer decomposition. The tests should be stable-indicating and suitable for a particular formulation. Use of one parameter, such as mean size, is not sufficient to prove product quality.

10.4 Stability and Packaging

Stability studies investigate the stability of the product in terms of its physical, chemical, and microbiological properties under specific storage conditions. Aggregation, leakage, oxidation, hydrolysis, moisture absorption, potency loss, change in spray properties, and interaction with the packaging are some examples of failure mechanisms. The packaging should protect the drug and guarantee appropriate delivery over the desired shelf-life period.

10.5 Quality by Design

The concept of quality by design involves determining the critical quality attributes, materials attributes, and process parameters that impact performance. Risk analysis and experimentation can be used to determine a stable operation range. In case of combination products, an overall assessment of the formulation, packaging, device, and instructions for use is necessary.

11. CHALLENGES, REGULATORY AND CLINICAL CONSIDERATIONS

11.1 Biological variability

The variability can result from nasal congestion, mucus formation, airways inflammation, pulmonary function, and the technique of a participant. It is vital to choose an appropriate study population and, whenever possible, take into account realistic conditions of use. Laboratory aerosol testing is important; however, it does not fully determine the performance of aerosols.

11.2 Safety Assessment

Safety Assessment should cover issues of local irritation, impact on epithelial cells, cilia function, coughing, bronchospasm, immunology response, and system distribution, wherever it is relevant. With repeated uses, special attention should be paid to local long-term effects and excipient tolerance. The use of nanocarriers may require assessment of decomposition products, localization, and interaction with biological fluids.

11.3 Regulatory issues

Regulatory schemes differ between jurisdictions and between product classes. There will be a need for development to establish quality, safety, efficacy, and reproducible performance. With respect to inhaled products, device performance is heavily dependent on the characteristics of the formulation. In the case of nasal products, issues such as dose uniformity, spray performance, and tolerability become especially important. Claims need to be limited to what can be proven through clinical and analytical data.

11.4 Practical limitations

Issues related to cost, access to the delivery system and other supplies, ease of use, and manufacturability can serve as barriers to access. A delivery system that is technically sophisticated is not necessarily better if it is not easy to use or cannot be made reproducibly. Issues of simplicity and ease of use are important considerations in technology development.

12. FUTURE PROSPECTS AND RESEARCH DIRECTIONS

12.1 Development of the Aerosol and Device Design

Future devices will be expected to provide more consistent dosing, as well as decrease the degree of required coordination and feedback on inhalation techniques. Digital inhaler technologies may promote adherence to treatment, which, in turn, requires usability, proper data handling, and integration with the healthcare system.

12.2 Biologic Therapies and Precision Aerosol Delivery

Research is being performed on aerosolization of various therapeutic proteins and peptides, nucleic acid-based agents, and vaccines. In some cases, stabilization and control of immune response could be required. The concept of precision aerosol delivery is based on matching the aerosol and device characteristics with disease phenotype and patient characteristics, but this approach needs justification.

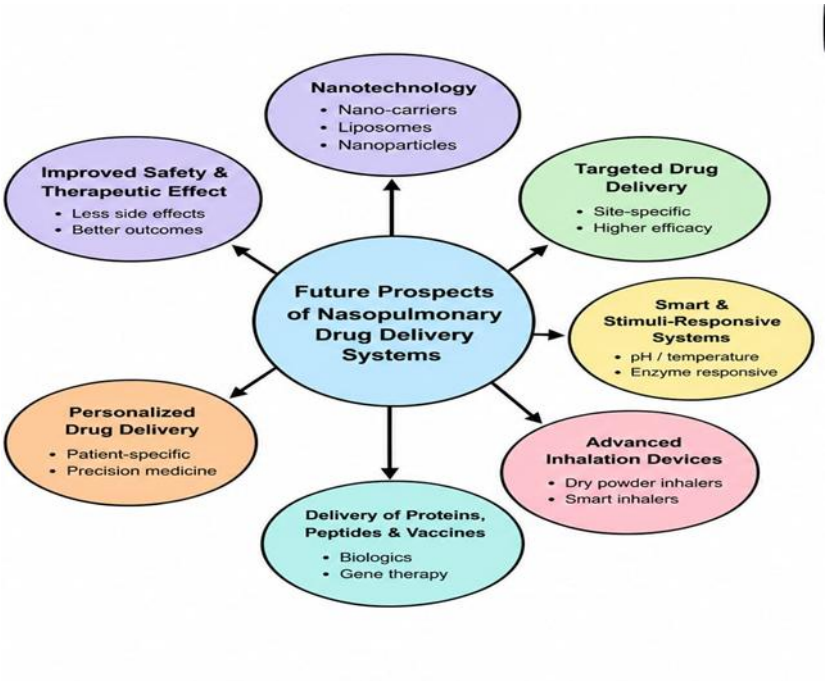
12.3 Smart Formulations for Responsive Drug Delivery

Responsive release devices, biodegradable matrices, and control release technologies allow tuning of the release characteristics to the local conditions. Nanocarriers such as liposomes and nanoparticles can be tailored to provide increased stability or muco-penetration, depending on the drug and target. However, increased complexity has to be justified.

12.4 Reproducible and Efficient Production: Reproducibility, energy efficiency, materials used, reduction in device waste, and packaging are areas that future research should focus on. Processes that produce particles with reproducible properties and reduce the waste of solvents and materials are likely to improve manufacturability. Stability and robustness during storage under realistic conditions are key to making technology accessible worldwide.

12.5 Directions of Future Research

Among the prominent directions of future research are in vitro-in vivo correlation, clinically realistic deposition models, safety of advanced delivery systems, and better techniques for regional deposition assessment. Head-to-head trials compared with currently used treatments are equally important. Proper methodology is essential to make a difference between lab data and clinically useful results.



Structure 7: future prospects of nasopulmonary drug delivery system

13. Discussion

Nasopulmonary administration has its own unique features in terms of local and systemic uses. The efficiency of the procedure is due to the complicated interplay between various factors, including anatomy, drug and formulation features, aerosol/spray parameters, apparatus, and patient skills. In case of nasal preparations, the volume and clearance characteristics are restricted, and in case of pulmonary formulations, there is a high variability of the deposition process that is dependent on the efficiency of the inhalation procedure. Advanced drug carriers, such as liposomes and nanoparticles, can overcome some of the shortcomings of the system by providing protection to the drugs and altering the release mechanism. However, the development of the advanced carrier systems should also consider the stability and safety issues.

14. Conclusion

Nasal and pulmonary drug delivery is an important part of modern pharmaceutical science. Old formulations such as sprays, inhalers, and nebulizers remain important, whereas new carriers can provide delivery options for molecules which cannot be delivered through other means. In terms of efficiency, an ideal drug should deliver (a) effective dose, (b) safely and stably, and (c) efficiently to the target population. Future developments will come from a combination of the formulation and device design along with proper testing and clinical trials.

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