A REVIVEW ON PULMONARY DRUG DELIVERY SYSTEM FOR NANOTHERAPEUTICS (NANOTECHNOLOGY)

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Abstract- **Drug delivery to the lungs is an innovative and challenging area of pharmaceutical research. Pulmonary drug delivery is relatively complex because the respiratory tract has evolved defense mechanisms to keep inhaled drug particles out of the lungs and to remove or inactivate them once deposited. Pulmonary drug delivery is a route of administration in which patients use an inhaler to inhale their medications and drugs are absorbed into the bloodstream via the lung mucous membrane. It is primarily used to treat conditions of the airways, delivering locally acting drugs directly to their site of action. Pulmonary drug delivery system refers to a device, technology or formulation of a drug meant for infusion into the body via the pulmonary route. Nano carriers offer advantages such as enhanced drug solubility, prolonged release, and targeted delivery to specific cells. this review explores the current state of nasopulmonary drug delivery, Nanomaterial's have the potential to sustained drug delivery, long time action ,less side effects, and improved patient compliance. Nano carrier systems is being designed for efficient delivery of drugs by researchers nowadays. Nanomaterial's undergoes easy adsorption in the larger surface area of alveoli. Some of them include dendrimers , liposomes, magnetic nanoparticles, solid lipid nanoparticles, etc in pulmonary system. Nanomaterial have the potential to sustained drug delivery, long time action, less side effects and improved patient compliance. Nanocatgerapeutics offer advantages such as enhanced drug solubility, and targeted delivery to the cells.**

*Keywords***: Pulmonary drug delivery, lung, nanocarriers, TB, COPD.**

INTRODUCTION:
Pulmonary drug delivery is an innovative and challenging area of pharmaceutical research Primarily used to treat respiratory diseases, they deliver locally acting drugs directly to the site of action .These drug delivery routes have advantages such as low drug doses, fewer side effects, and rapid onset of action .As an alternative to oral administration, pulmonary drug delivery can be used .These systems can be optimally used for both local and systemic measures .Pulmonary administration can be used for a variety of drugs .This is a technique that does not use needles .The origins of inhalation therapy lie 4,000 years ago in India, where people smoked Atropa he belladonna leaves to suppress coughs .In the 19th and early 20th centuries, people with asthma smoked asthma cigarettes, which were tobacco mixed with stramonium   powder, to treat symptoms of the disease. However, administering drugs via the lungs is technically difficult because oral deposition is high and different inhalation techniques can affect the amount of drug reaching the lungs .Pulmonary drug delivery remains the preferred route for administration of various drugs .This is an important area of research that has implications for the treatment of asthma, chronic obstructive pulmonary disease, and a variety of other diseases   .With advances in applications, pulmonary drug delivery is now used to treat COPD, angina, lung cancer, bone diseases, migraines, tuberculosis, acute lung injury, and more .Pulmonary drug delivery is not a new system. This system was already widely accepted in ancient times for lung and other respiratory diseases .In the 19th century, inhalation therapy was used to treat tuberculosis .Some drugs are easily absorbed into the alveoli and enter the systemic circulation directly. Thanks to these advanced pulmonary delivery devices, it is possible to deliver large doses to the lungs .For a decade, certain drugs have been marketed in compositions suitable for forming drug dispersions for pulmonary administration to treat a variety of human diseases .Pulmonary drug delivery systems have many advantages over administration routes in the treatment of certain pathological conditions, particularly lungassociated large protein molecules that are degraded in the gastrointestinal tract and cleared by first-pass metabolism in the liver .This advanced technology was originally used for systemic delivery of large molecules such as insulin, interferon-b, and alpha 1-proteinase inhibitors. When developing pulmonary drug delivery systems, particle size is one of the most important parameters to consider. Optimal particle size is critical for targeted delivery of drugs to the lungs .If the particle size is

too small, it will be exhaled, and if it is too large, it can affect the oropharynx and larynx. Drugs can be administered using carriers such as cyclodextrins, micro particles, liposomes, and nanoparticles.

Lung Anatomy and Physiology: The respiratory system works with the circulatory system to transport oxygen from the lungs to cells, remove carbon dioxide, and return it to the lungs for exhalation. The exchange of oxygen and carbon dioxide between air, blood, and body tissues is called respiration .Healthy lungs take in about 1 pint of air about 12 to 15 times per minute .All the blood in your body passes through your lungs every minute.
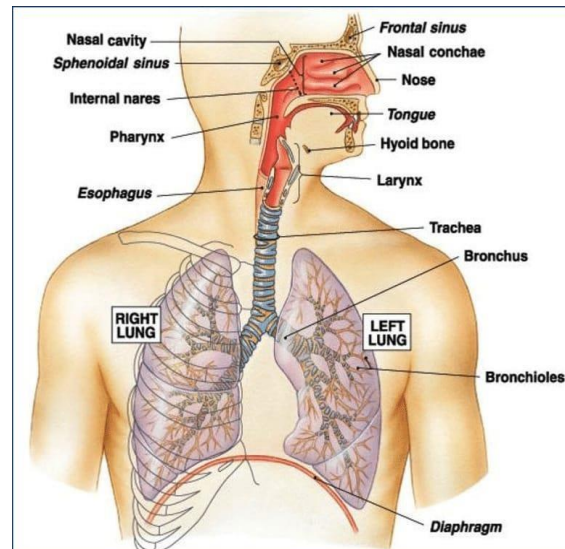

Fig. 1: Different regions of the human respiratory tract

The human respiratory system is a complex organ system with very close structural and functional relationships .This system consisted of two regions
➢   Conducting airway
➢   Breathing region

The airway is further divided into a number of folds, including the nasal cavity and associated sinuses, as well as the nasopharynx, oropharynx, larynx, trachea, bronchi and bronchioles .The respiratory area consists of respiratory bronchioles, alveolar ducts and alveolar sacs .The human airway is a branched system of airways .The main function of the lungs is gas exchange, adding oxygen and removing carbon dioxide from blood as it passes through the pulmonary capillary beds.

Lung Area: - The airways begin in the nose and end in the alveolar sacs deep in the lungs .There are many schemes for classifying different areas of the airway.

Nasopharyngeal Region: - This region is also called the "upper respiratory tract" and includes the airway from the nose to the larynx.

Tracheobronchial region: - This is also called the "central" or "conducting airway" and begins in the larynx, extends through the trachea, bronchi, and bronchioles, and ends in the terminal bronchioles.

Alveolar region: - This is also called the "airway," "distal airway," or "lung region" and includes the respiratory bronchioles, alveolar ducts, and alveoli.

Lung Epithelium: - The lungs contain more than 40 different cell types, six or more of which line the airways .The diversity of the lung epithelium can be explained by examining its structure at three major levels.

Bronchial tubes: - These are mainly lined with ciliated cells and goblet cells .Some serous cells, brush cells, and Clara cells are also present, along with some Kruchitsky cells.

Bronchioles: - These are lined mainly with ciliated cuboidal cells .The frequency of goblet cells and serous cells decreases as one progresses along the airways, whereas the number of Clara cells increases.

Alveolar region: - It lacks mucus and has a much flatter epithelium, resulting in a simple squamous type with a thickness of 0.1 to 0.5 μm.

There are two main types of epithelial cells: • Type I lung cells: Thin cells that provide a very short path length between the airways and the blood for the diffusion of gases and drug molecules.

•   Type I pneumocytes : occupy approximately 93% of the surface of the alveolar sac, but have only half the amount of type II cells.

•   Type II pneumocytes : cuboidal cells that store and secrete lung surfactant.
Alveolar macrophages constitute approximately 3% of the cells in the alveolar region .These phagocytes capture particles and transport them to lymph nodes and mucociliary escalators (2)

NANOTHERAPUTICS
The application of Nano science in nanomedicine and medicine offers a unique opportunity to develop unique Nano packaged therapeutics in aerosol format for direct delivery to the lungs. More recently, this has included newer emerging infectious diseases such as SARSCoV, as well as Middle East Respiratory Syndrome-related coronavirus (MERS-C), influenza A/H1N1, and SARS-CoV-2.
Therapeutic agent delivery in infectious and non-infectious disease
(NPs) have the ability to serve as effective delivery systems and transport compounds across biological membranes. As a result, nanopackaged therapeutics are now becoming part of the treatment arsenal for respiratory diseases such as CF, Mycobacterium tuberculosis (M.tb) infections, asthma, COPD, and lung cancer .We are in a difficult time, especially with the emergence of new infectious agents such as COVID-19, and targeting key components of both viral entry and cell replication within cells for vaccine development. There is growing interest in the possibility of nanopackaging certain humanized antibodies (3)

NANOCARRIERS
Unit .By modifying the composition, shape, size, and surface finish of nanocarriers, nanocarriers are colloidal drug delivery devices that contain submicron particles, typically 500 nm in size. Many studies have been conducted on nanocarriers over the past few decades as they have shown promise in drug delivery .Nanocarriers have the potential to alter the fundamental properties and biological activity of drugs due to their high surface area to volume ratio. Properties that nanocarriers can incorporate into drug delivery systems include improved pharmacokinetics and biodistribution, reduced toxicity, improved solubility and stability, controlled release, and site-specific delivery of therapeutic agents .Nanotechnology has recently emerged as a useful tool to overcome the limitations of traditional drug delivery technologies. Nanocarriers alter the fundamental properties and bioactivity of capsules for improved pharmacokinetic and biodistribution profiles, reduced toxicity, controlled release, improved solubility and stability, and site-specific delivery of payloads can do.

TYPES OF NANOCARRIERS USED IN DRUG DELIVERY SYSTEMS:
NOVEL GENERATION OF LIPID NANOCARRIERS SOLID LIPID NANOPARTICAL
Solid lipid nanoparticles (SLNTM) were developed in the mid-1990s as an alternative carrier system to existing conventional carriers such as emulsions, liposomes, and polymeric nanoparticles. 9.Solid lipid nanoparticles (SLNs) prepared using either physiological lipids or lipid molecules have a history of safe use in human medicine and are gaining attention as colloidal drug carriers. Under optimized conditions, they can be fabricated to accommodate lipophilic or hydrophilic active ingredients and appear to meet the requirements for an optimal particle carrier system. The advantages of SLNs are the use of physiological lipids, the absence of organic solvents, a potentially wide range of applications (dermal, oral, intravenous), and high-pressure homogenization as a wellestablished manufacturing method .Furthermore, by incorporating poorly water-soluble drugs into solid lipid matrices, improved bioavailability, protection of sensitive drug molecules from the external environment (water, light), and even controlled release properties have been achieved. Common disadvantages of SLNs are particle growth, unpredictable gelation propensity, unexpected dynamics of polymorphic transitions, and inherently low uptake rates due to the crystalline structure of solid lipids.
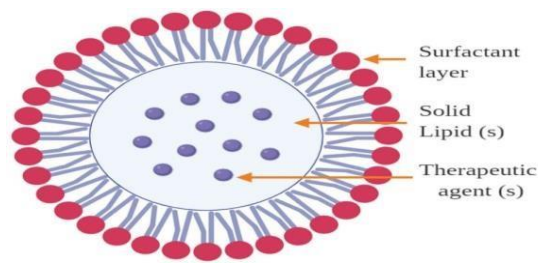
Fig 2 : solid lipid Nanopartical

Nanostructured lipid carriers (NLC)
A new generation of nanostructured lipid carriers (NLCs) consisting of a lipid matrix with special nanostructures has been developed .This nanostructure improves active ingredient loading and ensures firm binding of active ingredients during storage These NLCs can be prepared by high-pressure homogenization, and the process can be modified to produce lipid particle dispersions with solids content between 30 and 80% .Support system .However, NLC systems minimize or avoid several potential problems associated with SLNs.
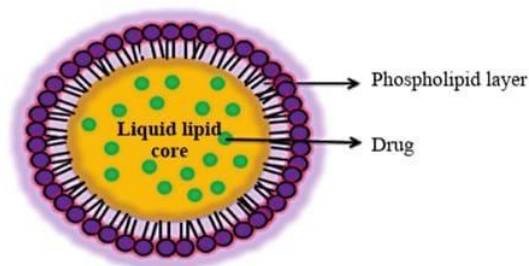

Fig 3 :-Nanostructured lipid carriers :

Nanocarriers for Nasal Vaccination:
The use of nanocarriers provides a convenient option for nasal delivery of antigen molecules .In addition to improving protection and facilitating antigen transport, nanoparticle delivery systems may also enable more effective antigen recognition by immune cells .These are critical elements for optimal processing and presentation of antigens and, therefore, for the subsequent development of an appropriate immune response. In this sense, the design of optimized vaccine nanocarriers provides a promising method to vaccinate the nasal mucosa66.(5)

Polymeric Nanocarriers
The use of polymers in the formulation of NPs as carriers for delivery of chemotherapeutic agents has significantly improved therapeutic efficacy through site-specific targeting of these drugs and minimization of side effects. Polymers are used alone or in combination with inorganic nanomaterial to create multifunctional drug delivery systems. The use of block copolymers or the introduction of surface modifications in the preparation of drugloaded NPs can improve the interaction between the NPs and the target tissue, improve biodistribution, increase circulation time, and reduce cellular uptake. It will be improved. The use of PNCs in the delivery of anticancer and diagnostic agents is increasing due to the ability to synthesize easily removable biodegradable polymers. Degradation pathways for polymers include thermal, mechanical, photochemical, and chemical degradation. Therefore, it is important to consider the main degradation pathways when selecting a polymer for a specific application. When used as drug delivery vehicles, PNCs utilize various strategies to improve payload delivery .These include improved extracellular penetration, intracellular drug release, and cellular uptake (6) .In recent years, inorganic materials as nanocarriers have shown great potential as drug delivery systems .The nanocarriers acts as a scaffold in the system and can load and release drugs, keeping the scaffold intact in the bloodstream and maintaining good biocompatibility and pharmacological
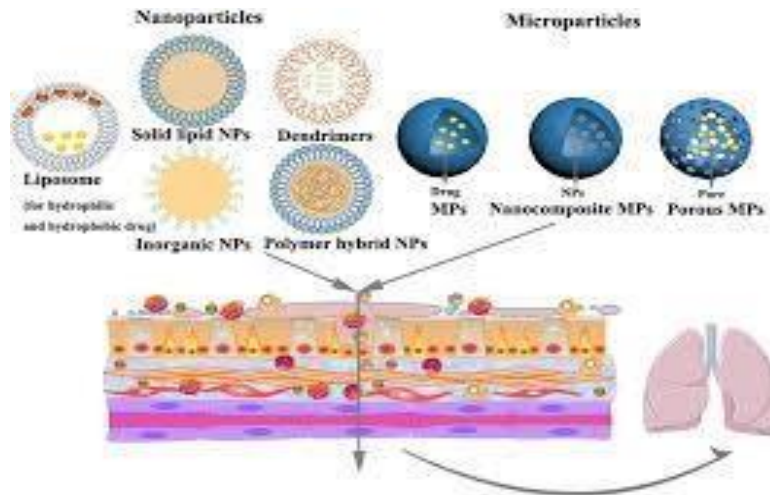
Fig no 4 :- Polymeric nanocarriers Inorganic nanocarriers

Inorganic nanocarriers :

In recent years, inorganic materials as nano-carriers have shown great potential in drug delivery systems . The nano-carriers serving as skeletons in the systems are capable of loading and releasing drugs, keeping intact framework in blood circulation, and holding good biocompatibility and pharmacological properties. The most commonly researched inorganic nano-carriers are mesoporous silica nanoparticles (MSNs), graphene oxide (GO), black phosphorus (BP) and gold nanoparticles (GNPs) . Even some of inorganic nanocarriers based nanomedicine are evaluated in clinic In this review, we mainly introduce the mechanisms of response and release, and the preparation and the application of MSNs, GO, BP and GNPs.

Fig No 5 :- Inorganic nanocarriers

Device types 1 Dry powder inhaler

Since the introduction of the first dry powder inhaler, Aventis' Spinhaler ® (1970) [7], DPI has occupied an important position in the global market .DPIs such as GlaxoSmithKline's Advair® and AstraZeneca's Symbicort® are blockbuster drugs (annual sales exceed his $1 billion).Compared with other delivery methods, inhalation administration has less mechanical damage, no gastrointestinal discomfort, convenient operation, and good patient compliance .Dry powder inhaler (DPI) is a specialized dry powder inhaler used to inject solid, micronized active pharmaceutical ingredients, alone or mixed with suitable excipients, in capsules, vesicles or multiple doses. It's a powder inhaler .It means to form a reservoir [1].Accurate dosing, non-irritating CFC-free propellant, excellent stability and convenient use by the patient offer many advantages over other sprays and aerosols.

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Fig no 6:- Dry powder inhaler

2 .Metered Dose Inhalers

Dose Inhalers Among various devices for pulmonary drug delivery, metered dose inhalers are the most promising technology .Recent advances in materials science, nanotechnology, biotechnology, particle engineering and related sciences provide opportunities to improve the use of metered dose inhalation therapy .Inhalation formulations with Nano sciencebased dosages can help improve treatment results and prevent unwanted side effects. Various drug delivery systems, such as polymeric nanocarriers such as polymeric nanoparticles and micelles, dendrimers, and lipid-based nanocarriers, have been integrated into MDI to study the pulmonary delivery process and therapeutic outcomes, and to study the pulmonary delivery process and therapeutic outcomes for the treatment of pulmonary diseases .Administering drugs .We demonstrated various nanocarriers used in metered dose inhalers. In this section, we have detailed the pulmonary delivery of various nanoparticles using metered dose inhalers
.(9)

3.Pressurized metered dose inhalers :

Pressurized metered dose inhalers: Pressurized metered dose inhalers (pMDIs) are sometimes considered obsolete and have been replaced by dry powder inhalers (DPIs).Here, we examine the technological advances that characterize modern (pMDIs)and discuss how they may impact the efficacy of drug delivery in patients with asthma and chronic obstructive pulmonary disease .Compared to older inhalers based on chlorofluorocarbons (CFCs), many pMDIs using hydrofluoroalkanes (HFAs) have more favourable plume characteristics, such as reduced velocity and increased particulate content. Taken together, these advances have led to the development of pMDIs that reduce orpharyngeal deposition and increase pulmonary deposition .Additionally, many HFApMDI clouds are warmer, which may make them easier to use by patients. In addition, the device is equipped with a dose counter, which increases reliability .In addition to an overview of technological advances in pMDIs, we also discuss the importance of tailoring inhalation therapy to each patient, taking into account personal preferences and natural breathing patterns. Because pMDIs and DPIs have very different handling characteristics, it is important to match the right inhaler to the right patient to ensure effective treatment and good compliance .Eventually, the majority of patients can be trained in the correct use of their pMDI .Training and regular monitoring of inhalation techniques are essential prerequisites for effective treatment .While there may not be an "ideal inhaler," pMDIs are a suitable and effective device option for many patients. pMDIs, like other types of devices, offer the opportunity to effectively personalize treatment.

4. Nebuliser

Nebulizer therapy is a method of treatment for respiratory diseases in which a therapeutic aerosol for the lungs is produced by a nebulizer device. With continuous improvements in manufacturing technology, vibrating mesh nebulizers (VMNs) are considered an effective method for delivering inhaled drugs, overcoming the main limitations of jet and ultrasonic nebulizers.

The vibrating mesh within the nebulizer contains a piezoelectric element attached to the bottom of the nebulizer chamber that vibrates when electrical current is applied .The up and down movement of the vibrating plate converts the respirable solution in the nebulizer chamber into fine droplets that are directed towards the patient. Compared to jet nebulizers, VMNs are lighter and more portable while providing higher inhalation volumes and lower residual volumes with aerosol delivery Pittance et al .They compared the quality of drug inhalation and drug concentration in urine using three different nebulizers .Results showed that mesh nebulizers delivered higher drug doses and lung deposition than compressed air nebulizers .We found that VMN was superior in treating asthma in children compared to traditional jet nebulizers, resulting in a significant reduction in asthma incidence in children.

Diseases Tuberculosis

Human Morbidity and Mortality .Until the COVID-19 pandemic, tuberculosis remained the leading cause of death from a single infectious agent, surpassing HIV/acquired immunodeficiency syndrome. The number of people newly diagnosed with tuberculosis decreased from 7.1 million in 2019 to 5.8 million .Tuberculosis (TB) is a major global public health problem and is on the rise in 2020, with limited access to TB diagnosis and treatment contributing to increased deaths from TB. Masu. Although progress has been made in reducing the global burden of tuberculosis, it has generally been insufficient to achieve the first milestones of the tuberculosis elimination strategy .In 2015, the World Health Organization (WHO) proposed a paradigm shift from the Stop TB Strategy to the End TB Strategy. To achieve this, WHO emphasized the important role of early, rapid and accurate identification of Mycobacterium tuberculosis (Mtb) and determination of drug susceptibility in the treatment and management of this disease. This article provides an overview of current diagnostic methods that focus not only on the identification of Mtb, but also on the detection of Mtb-specific host responses and new techniques for diagnosing tuberculosis.(12)

Chronic obstructive pulmonary disease (COPD :

Chronic obstructive pulmonary disease (COPD) is a common, treatable disease characterized by progressive airflow limitation and tissue destruction. It is associated with structural changes in the lungs due to chronic inflammation caused by prolonged exposure to harmful particles and gases, most commonly cigarette smoke .Chronic inflammation causes

narrowing of the airways and decreased lung function. The disease often manifests itself in the form of cough, shortness of breath, and phlegm. Symptoms range from asymptomatic to respiratory failure .(13)

Lung cancer

Lung Cancer In 2020, there were an estimated 19.3 million new cases of cancer and 10 million deaths worldwide.Lung cancer is the second most common cancer, accounting for approximately 11.4% of all cancer cases, and it is estimated that only 2.2 million people are affected by lung cancer. Lung cancer is the leading cause of death among other cancers.18% of all cancers are fatal .Smoking is the main cause of lung cancer .In some countries, smoking has reached its peak or continues to increase. This suggests that lung cancer incidence will continue to rise for at least several decades [1].The survival rate for lung cancer patients 5 years after diagnosis is 10-10 20%.Low-dose computed tomography (CT) screening can help detect lung cancer early and improve the effectiveness of lung cancer treatment. In general, it has been reported that patients have a better chance of living longer if cancer is detected, diagnosed, and effectively treated early .Medical experts are needed to analyze medical data and diagnose diseases, but experts often disagree when analyzing medical images due to their complexity .Artificial intelligence plays an important role in the medical field. Machine learning (ML) and deep learning (DL) algorithms have been used in recent years to analyse and process medical images and diagnose diseases, as they provide exciting solutions for medical applications .Providing predictive systems that make accurate diagnoses remains a challenge and the research field is still ongoing. The purpose of this study is to provide on overview of the achievements researchers have made over the past five years in developing the efficiency and accuracy of lung cancer diagnostic system performance . this study provide a detailed overview of each research work .
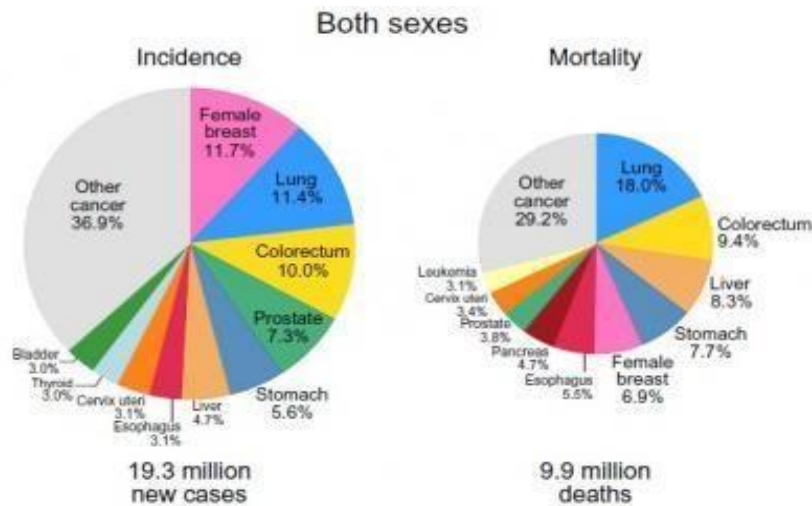

Fig no 7 :- incidence and mortality of ten common types of cancer in 2020.

In vitro and ex vivo:

Over the past two decades, reliable in vitro and Efforts to develop ex vivo model systems have been intensified .This development was driven by the need to streamline the drug development process and the desire for more ethical use of animals in testing (i.e., the 3R principles - Replace, Reduce, Refine).This article focused on human in vitro and ex vivo models used in biopharmaceutical inhalation studies .The lung is a complex organ with specialized structures and cell types to perform specific physiological functions and is often compared to a black box in the context of pharmacokinetics .The advantage of ex vivo and in vitro models is that this complexity can be at least partially eliminated .In this sense, several of these models have been developed and applied .Study of pathophysiological mechanisms of respiratory diseases, biopharmaceutical properties of drug candidates, and studies of inhaled formulations regarding their properties and safety profile in the lungs .The range of available models includes relatively simple continuous cell lines grown on plastic supports, multicellular co-culture models, 2.5D and 3D cultures, isolated lung tissue, and perfused lungs or lung lobes.

Summary

Nano pulmonary drug delivery, involving Nano carrier like nanoparticles, has gained attention for its potential in targeted drug delivery to the lungs. Nano carriers offer advantages such as enhanced drug solubility, prolonged release, and targeted delivery to specific cells. this review explores the current state of nasopulmonary drug delivery, highlighting advancements in nanocarriers technology and its applications. Nasopulmonary drug delivery system is a route of administration in which patient use an inhaler to inhale their medications and drugs are absorbed into blood stream via the lungs mucous membrane .pulmonary refers to a device , technology or formulation of a drug meant for infusion into body by pulmonary route. Nanomaterial's have the potential to sustained drug delivery

,long time action ,less side effects ,and improved patient compliance. Nanocatgerapeutics offer advantages such as enhanced drug solubility, and targeted delivery to the cells. Research in nasopulmonary drug delivery focuses on optimizing formulations, enhancing drug bioavailability, and developing specific delivery systems for various therapeutic agents. Overall, it represents a promising avenue for improving the treatment of respiratory diseases

conclusion pulmonary drug delivery system is important for direct action or fast therapeutics because lungs is most signified targeted area of body ,for fast absorption we are researching on nanotechnology so, nanothrapeutics having different drug delivery system we are studding in that nasopulmonary drug delivery represent a helpful or important path for targeted and efficient application. the unique properties of nanoparticles allow for enhanced drug stability. outlook for drug pulmonary delivery is to target specific cells or tissues within the respiratory system holds great potential for targeting various respiratory condition with increase efficiency, and bioavailability, and reduce side effects.

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