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Nanoparticles for Pulmonary Drug Delivery System: A Review of Recent Development

Jaimin P. Panchal[1], Sanjesh Rathi*[2], Shubham Singh*[3]

[1]M.Pharm Research Scholar, School of Pharmacy, Rai University, Ahmedabad, Gujarat.
Email ID : jaiminpanchal072@gmail.com
[2]Professor and Principal, School of Pharmacy, Rai University, Ahmedabad, Gujarat.
Email ID : rathi.sanjesh@gmail.com
[3]Assistant Professor, School of Pharmacy, Rai University, Ahmedabad, Gujarat.
Email ID : singhrbgj@gmail.com
***Corresponding Author:**
Dr. Sanjesh Rathi and Dr. Shubham Singh,
School of Pharmacy, Rai University, Ahmedabad, Gujarat.
Email ID : jaiminpanchal072@gmail.com

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ABSTRACT

In recent years, the development of nanoparticles for pulmonary drug delivery has gained significant attention due to their potential in enhancing the efficacy and safety of therapeutic interventions. The unique properties of nanoparticles allow for targeted delivery, controlled release, and improved drug bioavailability within the lungs. This review article provides an overview of recent advancements in the field of nanoparticles-based pulmonary drug delivery systems. We discuss various types of nanoparticles, their preparation methods, physicochemical characteristics, and the impact of these parameters on drug delivery efficiency. Furthermore, we explore the challenges and opportunities associated with the translation of nanoparticle-based pulmonary drug delivery systems from bench to bedside. Overall, this review highlights the promising potential of nanoparticles for improving pulmonary drug delivery and underscores the need for further research and development in this field

Keywords: Nanoparticles; SLN; toxicity; Lung Cell Models; Aerosol; Nebulization; Lung Disease

INTRODUCTION

Lungs are an alluring objective for the aspiratory organization of dynamic drug fixings (APIs) as different medication conveyance frameworks. Additionally, this method has numerous advantages over conventional oral administration, including a high surface area, rapid absorption, and circumvention of the first pass effect due to high vascularization. Because of this selectivity, targeted drug delivery is possible, reducing side effects [1, 2]. As drug carrier systems for the application of various drugs via various routes of administration, colloidal drug delivery systems have been the subject of extensive research. Solid lipid nanoparticles (SLN) are one of the most interesting colloidal systems that has studied for more than a decade. SLN are aqueous nanoscale suspensions prepared mainly from phospholipids and the triglycerides of physiological tolerability. Along with SLN, biodegradable polymeric nanoparticles are also attaining importance due to the sustained release of APIs [3, 4]. These systems are an ideal platform for lipophilic drugs, which have poor solubility in aqueous systems. Thus, increased solubility in a lipophilic matrix adds a positive effect on the pharmacokinetics and therapeutic efficacy. Nanoparticle-mediated drug delivery systems open new perspectives by modifying the physical properties of the particles, such as increasing the drug solubility, encapsulation efficacy and surface alterations to enhance the drug release profiles and to obtain a maximum effect. Although most of these nanosystems have therapeutic effects, toxicological effects have to be considered, as well [5]. The toxicological testing in different cell culture models, i.e., in vitro, ex vivo and in vivo models, is necessary to determine a safe dose. Even though the results from the cell culture models cannot be directly extrapolated to an in vivo situation of an individual patient, the testing of nanosystems in such models is essential to reduce the risk of adverse reactions or toxic effects. The choice of the inhalation device in a specific patient population also plays a vital role in nanoparticle-mediated drug delivery systems for pulmonary application [6]. The complex relationship between nanoparticle systems and various parameters to be considered during formulation development is illustrated in Figure 1.

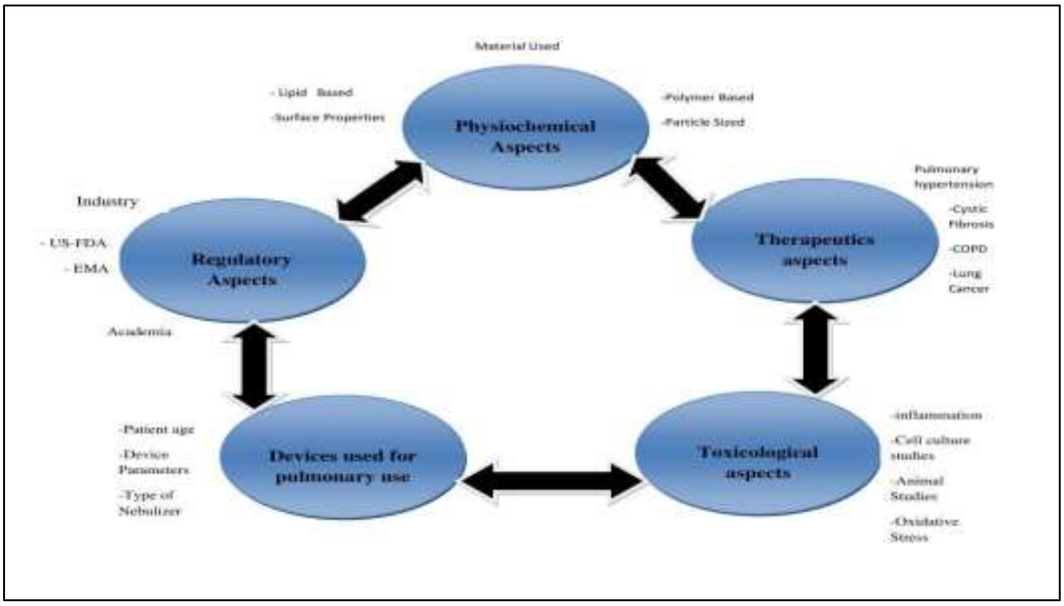

Figure 1. Complex Interplay of parameters in the research and development of pulmonary Drug Delivery System

Anatomy and Physiology of the Lungs

Anatomy of the Lungs- The exchange of gases and the delivery of oxygen to all cells are handled by the lungs. The lungs have five lobes in total, with three lobes in the right lung and two in the left. Alveoli, blood arteries, lymphatic tissue, bronchi and other smaller airways make up the lungs' interior. The primary and secondary bronchi, bronchioles, and alveoli are further divisions of the bronchi [7]. Over 300 million alveoli are found in the lungs. Additionally, pulmonary capillaries line each alveolus, creating a vast network with over 280 billion capillaries and providing a blood-gas barrier surface area of nearly 70 m2. The alveolar gas trade significantly happens at the connection point comprising of alveolar epithelium, endothelium and interstitial cell layers [8]. The alveolar epithelial cells (pneumonocytes) of Type I and Type II make up the alveolar wall. A single endothelial layer exists between the capillaries and the alveolar epithelium. Due to the extremely thin blood-gas interface and the small distance between the alveoli and capillaries (about 0.5 m), diffusion at the interface facilitates gas exchange. Phospholipids and surface proteins make up the majority of the alveolar fluids and mucus that coat the alveoli. This phospholipids surfactant layer at the alveoli helps to lower the surface tension and is necessary for the gas exchange to work properly. A thin layer of connective tissue provides support for these distant respiratory passages. Various cells, including macrophages, fibroblasts, nerves, and lymph vessels, surround this layer. With access to the pulmonary and lymphatic systems, this is an ideal location for drug administration [9].

Deposition of the particles- The formulation's particle size determines how much material is deposited in each area of the lungs. Three distinct drug deposition mechanisms—impaction, sedimentation, and diffusion—are identified based on particle size. The aerosol particles move quickly through the oropharynx and upper respiratory passageways during impaction. The particles are deposited in the oropharynx areas after colliding with the respiratory wall as a result of centrifugal force. With particles larger than 5 m, this process is typically seen in dry powder inhalation (DPI) and metered dosage inhalators (MDI). The patient's breathing is crucial to the deposition in the case of DPI. Due to the mass of the particles and the inertial forces, dry powder will deposit in the upper airways if the force of inhalation is insufficient. fast particle sizes also likely to cause the deposition of the particles, especially in the upper respiratory tract region, for the MDI, despite the fast speed of the created aerosol. The majority of the time, gravitational forces causes particles to settle. When given enough time and adequate mass, particles with sizes between one and five micrometers are deposited in the bronchioles and smaller airways, where they are slowly deposited. As a result, breathing style also affects sedimentation. A sufficient period of slow breathing allows for sedimentation. In the deeper alveolar regions of the lungs, Brownian motion is important in addition to impaction and sedimentation. The particles travel at random due to the Brownian motion of the molecules surrounding the aqueous lung surfactant. The dissolution of API in alveolar fluid upon contact with the lung surfactant is crucial for diffusion. Additionally, the diffusion process is impacted by the concentration gradient. Most of the particles, because of their lower sizes, are exhaled, with the exception of those smaller than one to 0.5 m, which are deposited in the alveolar region. Sedimentation is the most desirable mode of particle deposition for nanoparticulate systems. When released from an aerosol, nanoparticulate systems form micrometer-sized aggregates. It is believed that these aggregates have sufficient mass to sediment and remain longer in the bronchiolar region, achieving the desired effect. Aside from the instruments, boundaries, for example, the molecule size of the spray, molecule morphology and math, alongside surface properties, assume a significant part in statement peculiarities [10]. The deposition is also affected by humidity, air velocity, and tidal volume, as well as breathing frequency and holding breaths. Table-1 shows the relationship between drug deposition area and particle size-

Location	**Size**	**mechanism**
Primary Bronchi	5-10 μm	Impaction
Secondary Bronchi	1-5 μm	Sedimentation
Bronchioles	1-3 μm	Sedimentation
Alveoli	0.5-1 μm	Brownian motion

Clearance of the Particles- A thick mucus film covers the upper airways from the trachea to the tertiary bronchi and serves as a barrier to keep particles from getting out. Before the foreign particles can move to lower parts of the lung by coughing or swallowing, the mucociliary movements clear them immediately. The quantity and quality of mucus, the number of cilia, and the frequency of ciliary beats all play a role in this region's clearance. The transport mechanism is thought to be more complicated in the alveolar region, which is deeper in the lungs. A variety of proteins and lipids make up the alveolar lining, which prevents molecules from moving through it. The epithelial cells tight junctions, in addition to the alveolar lining, are the primary barrier to transport. Depending on the API's nature and chemical structure, the transporter proteins are crucial for either active absorption or passive diffusion. One more significant perspective in this locale is the leeway of particles by the alveolar macrophages, which should be thought about in the medication transport components. Alveolar macrophages phagocytose molecules that are able to cross the barrier or the cells take them up and further absorb them into the systemic circulation. Therefore, understanding the physiology of the lungs is essential for comprehending the drug formulation's uptake and clearance mechanisms. There is still a lack of information regarding the precise uptake, transport, and clearance of particles in the alveolar epithelium and the method by which API molecules reach the systemic circulation despite advancements in formulation development. Albeit a few in vitro models have been laid out for concentrating on the take-up and penetration of the APIs in the pneumonic epithelium (air-fluid connection point models), there are as yet open inquiries concerning the way of behaving of the cells in a sick condition [11]. The exchange of various cell types required alongside the affidavit systems is represented in Figure 2.

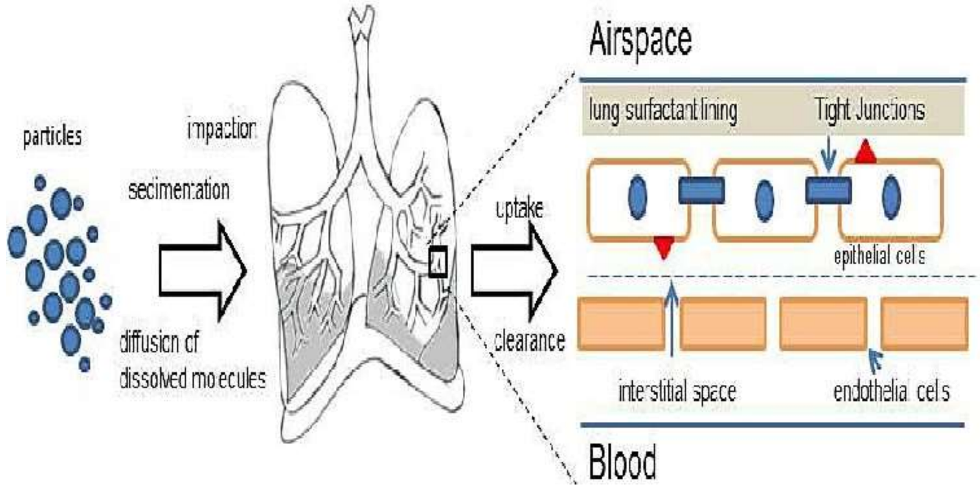

Figure 2. The deposition mechanism and uptake of particles in the lungs along with different cell types

Types of Nanoparticles for Pulmonary Drug Delivery

Lipid Based Nanoparticles (Liposome, Solid Lipid Nanoparticles, Nano-Emulsions)- For an extended period of time, lipid-based nanoparticles (SLN) have been thoroughly investigated for potential pulmonary medication delivery. SLN are triglycerides and phospholipids, which are physiological lipids, produced as nanoscale aqueous suspensions. The formulations are less toxic and therefore more suitable for pulmonary medication administration because they are based on utilizing physiological components. The deep regions of the lungs contain phospholipids in abundance, which are crucial for the proper operation of the respiratory system. To maintain ideal surface tension and minimize friction in the lung tissue, phospholipid-based surfactant proteins must be present at the alveolar surface. There have been studies on a number of different medications for the treatment of lung infections. The amino glycoside antibiotic SLN with amikacin was created utilizing cholesterol as the lipid and a high pressure homogenization process. The biodistribution of amikacin SLN following pulmonary dosing was also investigated by the authors. Radioisotope technetium (99mTc) labeled amikacin was employed to monitor the drug's deposition in various tissues for the biodistribution assessment. Rats were administered radio labeled amikacin or placebo via the pulmonary and intravenous routes for in vivo experiments. According to gamma scintigraphy studies, pulmonary administration of 99mTc-amikacin SLN was found to have a longer half-life in the lungs than intravenous administration. Furthermore, it was shown that the deposition of 99mTc-amikacin SLN in the lungs was greater than that in the kidneys. These findings demonstrate that extensive information about the deposition of an API in various tissues may be obtained via radio labeling assessments utilizing gamma scintigraphy. Using sick circumstances in animal subjects would undoubtedly be helpful because it can produce more accurate data in an in vivo model. In addition to SLN, several fatty acids can enhance the drug's solubility and boost biodistribution [12].

Polymeric nanoparticles (poly (lactic-co-glycolic acid, chitosan, gelatin)- Polymers have become increasingly important for the delivery of pneumonic drugs. A few polymers have been investigated for use in pneumonic. Polymers have a number of advantages, including altered surface properties, a high medication absorption and security of the medication from corruption, delayed drug delivery and a lengthy use life. The most often used polymers for practical uses include poly (lactic corrosive), poly (lactic-co-glycolic corrosive), poly (-caprolactone), alginate, chitosan, and gelatin base. These have had their surface and compound qualities changed to make them biodegradable.. In a recent work, polyethylene glycol (PEG5000) and polymer poly (ethylene oxide)-block-distearoyl phosphatidyl ethanolamine (DSPE) were combined to create paclitaxel-loaded polymeric micelles. Intratracheal instillation and intravenous injection methods were used to examine these micelles in in vivo models. Additionally, the commercially available taxol molecule and polymeric paclitaxel micelles were examined. When compared to intravenous administration, it was discovered that intratracheal instillation had superior drug absorption. Additionally, target drug administration was accomplished by localising the most drug in the lung tissue in comparison to other tissues. When compared to taxol, polymeric paclitaxel was found to have improved drug release patterns. In a different investigation, poly-glycolide--caprolactone with PEG and tocopheryl succinate were used to manufacture paclitaxel with an amphiphilic block copolymer. Paclitaxel was coupled with this block copolymer to improve encapsulation efficiency and increase cellular absorption. The copolymer-paclitaxel was marked with coumarin-6 to track the uptake of nanoparticles in an in vitro A549 cell model. The paclitaxel-block copolymer was compared to a commercial taxol product for cytotoxicity tests in addition to absorption tests, and the results revealed that the commercial taxol product had higher cytotoxicity than taxol and the free paclitaxel compound. It is possible to improve the drug's encapsulation efficiency and uptake in polymeric nanoparticles by changing the surface of the particles [13].

Inorganic nanoparticles (metal nanoparticles , Quantum dots)- Nanomaterials, such as quantum dots, nanoparticles, nanowires (NWs), nanotubes, and graphene, have received a lot of attention over the past two decades due to their suitability for the development of novel nanoscale biosensors1. Nanomaterials are very small structures that have at least one of their dimensions in the nanoscale (10 nm range). These nanostructures are ideal for studying most biological entities, including nucleic acids, proteins, viruses, and cells, because their size is comparable to that of bimolecular and chemical species. Additionally, because nonmaterial’s have a high surface-to-volume ratio, a significant number of the material's constituent atoms can be found at or close to the surface. Because of this, surface atoms play a crucial role in determining the electrical, chemical, and physical properties of nonmaterial’s, making them extremely sensitive devices that can detect single molecules and even low concentrations.NWs, which are extremely small wires with a cross section of the nanoscale size, have emerged as significant candidates among nonmaterial’s for applications in nanoscale sensing2. NWs have distinct electrical, physical, and mechanical properties that the corresponding bulk material does not share because of their size. NWs can be produced using metallic (Ni, Pt, Au), dielectric (ZiO, TiO2), composite, or semiconductor (Si, GaN, InP) materials. Due to the electronic property of semiconductors that can be easily tuned through doping and applied gate voltages, providing also a means of affecting the sensitivity capabilities, semiconductor materials are typically used for the purpose of bio- or chemical sensing. Biosensors frequently make use of silicon nanowires (Si NWs), a subclass of semiconducting nanowires. To be sure, SiNWs can profit from existing and mature silicon industry handling and be effortlessly incorporated with advanced field impact semiconductor (FET) innovation. Furthermore, Si NW-FETs are particularly appealing for the label-free detection of biological species because of their adaptability to silicon and silicon oxide fictionalization techniques [14].

Pulmonary Delivery Strategies For Nanoparticles- Although neat nanoparticles are capable of achieving lung deposition to varying degrees based on breathing rate and airway turbulence, their drug delivery to the pulmonary mucosa relies on Brownian diffusion, which is inefficient. In contrast, drug delivery to the lungs necessitates highly effective and repeatable particle deposition in order to provide dependable treatment and demonstrate compliance with regulatory requirements. As a result, nanoparticles destined for pulmonary deposition must either be aggregated or incorporated into a carrier so that their bulk size falls within the 1–5 mm aerodynamic diameter required for deep lung deposition. This has been accomplished through a variety of methods, including the creation of particle aggregates, solid dispersions, or liquid dispersions. Based on the active ingredient, aerosolization mechanism, and therapeutic requirements of the specific indication, each method must be evaluated for its distinct advantages and disadvantages [15].

Nebulized Dispersions- Nebulizing of an aqueous colloidal dispersion or suspension is an easy delivery method that enables nanoparticle deposition in the deep lung. Nebulization of dispersed nanoparticulates offers numerous benefits for medications that are not suitable for pulmonary delivery as an aqueous solution. First, compared to micronized drug dispersions, nanoparticles can be distributed more evenly throughout 1–5 mm droplets, enabling more uniform dosage delivery and more efficient deep lung deposition due to the higher drug presence in droplets smaller than 3 mm. Studies have demonstrated that larger average administered doses and enhanced dosage homogeneity can be attained when compared to a micro particle suspension. Second, compared to micro particles, nebulized nanoparticle dispersions have been found to have less detrimental effects on nebulizer function and aerosol droplet size due to their near-solution rheology. The nebulization of nanoparticles made via milling, antisolvent precipitation, rapid freezing, and supercritical fluid production methods has been studied by researchers. Many of these methods call for the addition of a stabilizing polymer or surfactant to prevent particle growth and/or aggregation. The choice of stabilising substance is an important factor to take into account when administering an aqueous dispersion of therapeutic nanoparticles to the lungs. Many synthetic surfactants and stabilisers, especially those in high concentrations, are not well suited for the lungs and are typically employed in oral and intravenous treatments. Surfactants often employed in pharmaceutical formulations (such as sodium lauryl sulphate) should be used sparingly or not at all in nebulized dispersions due to their toxicity and immunogenicity in the lungs as well as their propensity to froth during nebulization. In order to stabilize nanodispersion before being nebulized, nanodispersions for the lungs frequently include modest amounts of natural surface active agents or, alternatively, are designed with redispersion in mind. Dry formulations may have the advantage of requiring little to no surfactant because aqueous stability is only required for the brief period of time between redispersion and nebulization. Contrarily, reconstitution formulations frequently need a health professional's help, cause problems for the medical staff, and risk contamination [16]

Stabilized Nanodispersions- For the purposes of nebulization, surfactant stabilized colloidal dispersions have been created to aid in the administration of nanoparticulate drugs to the lungs. Dipalmitoyl phosphatidylcholine (DPPC), lecithins, and leucines are examples of natural surfactants that can be included in these formulations to ensure colloidal stability and avoid the agglomeration of dispersed particles. This formulation strategy has been used by inhalation researchers, who have discovered several aerosolization and physiological benefits [17].

Nanoscale Powders for Redispersion- Other researchers reduced potential instability by developing a formulation meant for dispersion before to delivery as an alternative to using a stabilized colloidal dispersion for nebulization. This method also has the added advantage of reducing or eliminating the requirement for stabilizing surfactants. Given that many therapeutics and polymeric carriers are subject to hydrolytic degradation and are not stable as dispersions for extended periods, growing interest in using nanoparticles as carriers for targeted and biopharmaceutical therapy has also led to the use of formulations for redispersion. Researchers found that stability is maintained without significantly affecting particle size when nebulizing powders reconstituted from lyoprotective substances such as lactose, mannitol, glucose, and sucrose matrices.

Drug Encapsulated Nanodispersions- Drugs are frequently enclosed in a carrier material in situations where the therapeutic molecule may be poorly soluble, prone to hydrolytic or enzymatic breakdown, or intended for regulated release. The ability to surface-modify these particles to provide targeting and/or stealth particle features is an added benefit. With the intention of achieving high concentrations of chemotherapeutic drugs in the lungs while minimizing systemic exposure, tumor-targeting nanoparticles have been researched for nebulization. After being exposed to nebulized aerosols containing surface-modified gelatin nanoparticles, tumor-induced nude mice's lungs showed preferential deposition of targeted nanoparticles. In this study, Gelatin nanoparticles were created in this study using an antisolvent precipitation method, glutaraldehyde was used to cross-link them to decrease their solubility, and biotinylated epidermal growth factor (EGF) was added to increase drug targeting. The results showed that these particles did, in fact, accumulate in lung tissue while exhibiting no adverse effects [18].

Lipid Nanoparticles- While thinking about a medication formulation intended for inhalation, pulmonary and systemic toxicity brought on by insoluble nanoparticles is a serious problem, as will be covered later in this chapter. Many researchers have used natural occurring excipients when developing medications for lung administration even though it has been demonstrated that some biodegradable polymeric polymers, such as PLGA, do not cause considerable toxicity. Because the delivery components contain many of the same saturated and unsaturated hydrocarbons prevalent in human tissues and fluids, liposomal medicine delivery to the lungs gets a lot of attention from academics and doctors. Numerous large-scale clinical investigations have been conducted and are being conducted to learn more about liposomal transport to the lungs. Despite the fact that liposomal delivery techniques are technically nanoparticulate (200 nm) in size [19].

Dry Powders For Inhalation- Numerous studies have shown that inclusion in a carrier enables the delivery of nanoparticles to the lungs. In a variety of preclinical and animal studies, the dispersion of nanoparticles into aqueous solutions for nebulization has shown to be an effective carrier; however, nanodispersions in liquid carriers are not without disadvantages. As a result of hydrolysis, particle settling, or aggregation, many dispersions stabilized as suspensions are likely to exhibit chemical and physical instability. Additionally, before being used on humans, these stabilisers must be shown to be safe and harmless in the lungs. While nanoparticles for redispersion provide more stability, they are normally administered by a doctor, making them inconvenient for routine medical care. Dry powder aerosol distribution of nanoparticles is a practical substitute for water nebulization. When opposed to nebulizer dispersions, the formulation of medications for inhalation as dry powders ensures superior chemical and physical stability. This advantage is mostly brought about by a dry system's lower molecular mobility, which reduces the molecular and interfacial interactions that cause degradation or agglomeration, respectively. Additionally, solid-form medication that is inhaled can frequently be administered as a single dose in a single breath, shortening treatment times and enhancing patient compliance-

Nanodisperse Microspheres- Microencapsulation is a common formulation strategy for oral administration that is used to control drug release, avoid enzymatic degradation, cover up taste, and enhance bioavailability. Microencapsulation may be employed for these goals for pulmonary administration; nonetheless, the main motivation for using this method is to create particles with the proper aerodynamic diameter for deep lung deposition. Spray drying is a common method for producing powders suitable for inhalation. Drug dispersions in a stabilizing matrix or respirable, neat drug particles are frequently produced using this production method. Specialists have likewise investigated this technique to produce nanoparticles scattered inside transporter micro particles. Gelatin and polycyanoacrylate nanoparticles were dispersed in a lactose matrix micro particle and characterized by dissolution, fluorescent labeling, and cascade impaction in a study to see if spray drying could be used to incorporate nanoparticles into carrier micro particles [20].

Aggregated Nanoparticles- According to the minor impact of the inertial and sedimentation forces required for impaction, it can be challenging to deposit discrete aerosolized nanoparticles in the lower airways. The formation of low density aggregates from a variety of nanoparticles is an intriguing and successful method for enhancing the effects of these forces on dry nanoparticulate aerosols. These nanoaggregates can be hollow spheres, spherical agglomerates, nonspherical flocculates, or aggregated plates. They usually have low densities (frequently less than 0.1 g/cm3). These nanoaggregates can now be produced more easily thanks to a number of production procedures, such as spray drying, salt flocculation, and quick freezing. Spray drying is frequently employed to create medications for inhalation, and it has been utilised to create aggregates of hollow and solid nanoparticles.

Nanoparticle Toxicology- Insoluble nanoparticles and their impacts on biological systems have been a growing source of concern for regulatory bodies and research organizations, despite the fact that nanomedicine is an exciting new subject with the promise for many therapeutic and diagnostic discoveries. In fact, the same high surface area and higher bioavailability properties that make nano sized medicines appealing for medicinal uses often translate into toxicity issues for nonbiodegradable materials, particularly when inhaled. The greater immunobiological reactivity of nanomaterials is caused by their greater surface area, which can be made worse by their protracted tissue retention due to their capacity to resist regular physiological clearance systems. Additionally, "ultrafine" particles—those with a diameter of less than 100 nm—can easily pass through tight junctions and intracellular space, enabling them to quickly enter the bloodstream after depositing in the lungs [21].

Physicochemical characteristics of Nanoparticles-

Particle Size and Zeta Potential Measurements- Measurements of the particle size and zeta potential are essential for the characterization of nanoparticles in order to guarantee the ideal distribution of the particle size and polydispersity index (PDI). The most normally utilized molecule size estimation procedures incorporate photon relationship spectroscopy (computers) furthermore, laser diffraction (LD). Particles measured by PCS typically range in size from a few nanometers to a maximum of three millimeters. The PCS method measures the light scattering caused by the dispersed particles' Brownian motion. The PDI, which measures the uniformity of the particles, can also be measured by PCS. A PDI value above 0.2 typically indicates multiple particle sizes in the formulation. As a result, the formulation's particle distribution becomes more uniform with a lower PDI. Based on the measurement of the diffraction angle as a function of the particle's radius, the LD method measures particles of larger sizes. LD estimates particles from the nanometer to a couple of millimeter size ranges. It's best to use both methods at the same time. Particle stability can only be predicted using zeta potential measurements. There is less aggregation when the zeta-potential is higher because there is more repulsion between the particles. Their shelf life is more stable the more evenly the particles are distributed [22].

Differential Scanning Calorimetry (DSC)- One of the most important methods for analyzing polymorphic changes in a lipid matrix is differential scanning calorimetry (DSC). The formulation's stability over time is revealed by structural changes in the lipid matrix. The appropriate parameters for determining polymorphic changes in lipid matrices are melting and recrystallization curves.

X-ray Diffraction- X-ray diffraction, along with DSC, is necessary for determining the lipid lattice's crystal structure and spacing. The lattice spacing and lipid/polymer structure are affected when an API is added. Crystallinity can be mapped in conjunction with DSC, and this method reveals patterns in the spacing as well as changes in the structure of lipids and polymers. Consequently, it is prescribed to utilize the two strategies at the same time while breaking down any lipid-based details Further developed techniques for physicochemical portrayal incorporate atomic attractive reverberation (NMR), Raman spectroscopy and infrared spectroscopy. These methods are more valuable apparatuses for the portrayal of blended frameworks, where various sorts of particles may coincide (SLN, micelles, liposomes, fluid gems).

Microscopical Techniques/Particle Morphology- The toxicity evaluation of nanoparticles systems in a variety of cell lines, tissue models, and animal models has been the subject of several studies. Poisonousness testing is fundamental to decide the deadly portion, as well as the restorative window of the medication stacked nanoparticles. Therapeutic efficacy, in addition to toxicity testing, is crucial, and various disease models have been developed to illustrate this. Several in vitro models for testing nanoparticles after inhalation have been developed using respiratory tract epithelial cells. The effects of various formulations intended for pulmonary application have been extensively studied with the help of models involving an air liquid interface (ALI) [23].

Recent Applications- Due to their unique properties—a high surface area-to-volume ratio, variable size, and capacity to encapsulate a variety of drugs—nanoparticles have received a lot of attention in the field of pulmonary drug delivery. Nanoparticles are an appealing option for the controlled and targeted delivery of drugs to the lungs because of these properties. Recent advancements and applications in the field of nanoparticle-based pulmonary drug delivery include the following:

Treatment of Respiratory Diseases- For the treatment of a variety of respiratory conditions, including asthma, COPD, lung cancer, and pulmonary infections, extensive research has been conducted on nanoparticles. Targeted and sustained drug delivery to the lungs can be achieved by encapsulating therapeutic agents such as bronchodilators, anti-inflammatory drugs, antibiotics, or anticancer drugs within nanoparticles, enhancing therapeutic efficacy and decreasing adverse effects.

Targeted Delivery to Specific Lung Regions- Nanoparticles can be made to target particular parts of the lungs, like the alveoli or the deep lung, which are where many respiratory illnesses start. Enhanced drug delivery to the targeted sites is made possible by surface modifications of nanoparticles with ligands or antibodies specific to receptors or antigens. While minimizing systemic exposure, this strategy increases drug concentration at the desired site.

Inhalable Vaccines- As vaccine carriers for inhalable vaccines, nanoparticles have demonstrated promise. The immune response can be enhanced by encapsulating antigens in nanoparticles, enhancing vaccine efficacy. Advantages of inhalable nanoparticle-based vaccines include the possibility of self-administration, ease of storage and transportation, and the lack of the need for a needle [24].

Controlled Release Systems- Nanoparticle-based controlled release systems enable prolonged drug release and reduced dosing frequency. This strategy has the potential to reduce drug concentration swings and increase patient compliance. To achieve controlled drug release in the lungs, a number of methods, such as nanoparticle encapsulation, surface modification, and polymer matrix systems, have been developed.

Imaging and Diagnostics- Lung imaging and diagnostics can benefit from the use of nanoparticles as contrast agents. The precise diagnosis and monitoring of lung diseases is made possible by the surface functionalization of nanoparticles with specific imaging agents or targeting ligands.

Combination Therapy- By encapsulating multiple drugs with distinct mechanisms of action, nanoparticles provide a platform for combination therapy. Improved therapeutic outcomes, decreased drug resistance, and synergistic effects are all made possible by this strategy. For the treatment of lung infections, for instance, nanoparticles can be used to deliver both an antimicrobial and an anti-inflammatory drug simultaneously.

Nanoparticle Safety and Toxicity Studies- In addition to the development of pulmonary drug delivery systems based on nanoparticles, extensive research is being done on the safety and toxicity of nanoparticles. For their successful clinical translation, it is essential to comprehend the potential adverse effects and optimize the physicochemical properties of nanoparticles to minimize toxicity [25].

Despite the fact that nanoparticle-based pulmonary drug delivery holds a lot of promise, more research is needed to address issues like large-scale production, regulatory approval, and long-term safety evaluation before widespread clinical use is possible.

Conclusion- In conclusion, a look at the most recent development in pulmonary drug delivery systems based on nanoparticles reveals significant advancements in this field. For targeted drug delivery to the lungs, nanoparticles have numerous advantages, including increased therapeutic efficacy, prolonged drug release, enhanced bioavailability, and decreased systemic toxicity. In order to overcome the difficulties associated with pulmonary drug delivery, a variety of nanoparticles formulations, such as liposomes, polymeric nanoparticles, solid lipid nanoparticles, and dendrimers, have demonstrated promising results. The optimal particle size, surface characteristics, and drug-loading capacity of these nanoparticles can be engineered to ensure effective drug release at the intended site of action and efficient lung deposition. The functionality and performance of nanoparticles-based pulmonary drug delivery systems have also been enhanced by the utilization of cutting-edge technologies like surface modification methods, formulations for inhalable aerosols, and nanocomposite systems. Asthma, chronic obstructive pulmonary disease (COPD), and lung cancer can now be treated with a wide range of therapeutic agents, including small molecules, peptides, proteins, and nucleic acids, thanks to these advancements. However, despite the promising developments, there are still a few obstacles to overcome. These include maximizing the stability of nanoparticles, regulating the distribution of particle sizes, ensuring long-term safety, and overcoming potential respiratory clearance mechanisms. In addition, the successful transition of nanoparticle-based pulmonary drug delivery systems from research to clinical applications necessitates the standardization of manufacturing procedures, considerations pertaining to regulations, and scalability of production. In general, recent advancements in pulmonary drug delivery systems based on nanoparticles have demonstrated significant potential for enhancing the outcomes of lung disease treatment. To overcome the remaining obstacles and realize the full potential of these innovative drug delivery systems in clinical practice, scientists, clinicians, and regulatory authorities must continue to collaborate and conduct research.

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