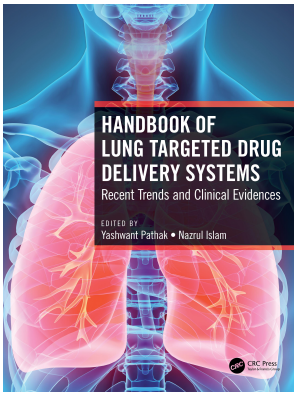

Handbook of Lung Targeted Drug Delivery Systems Recent Trends and Clinical Evidences

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Pulmonary Drug Delivery: The Role of Polymeric Nanoparticles

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13.1 Introduction

13.1.1 Pulmonary diseases

Generally pulmonary diseases or disorders could result from inhaled irritants, or viral infections, subsequently lowering the host's resistance and predisposing the patient to secondary infection or inflammation of the respiratory tract. The infections could be fatal if the airways become blocked by discharge and inflammatory swelling, or if the infection spreads through the lungs to other organs (1). For instance, the global pandemic, Covid-19, a pulmonary infection caused by the novel coronavirus, SARS-CoV-2 pathogen, has greatly affected the lives of people around the world. The disease is transmitted by the respiratory virus with droplets from infected persons which are inhaled into the lungs causing pneumonia and acute respiratory syndrome (2). Several complications from this lung infection, include coagulopathy, lung injury, and multiple organ failure (3–5) have resulted in morbidity and mortality worldwide.

Pulmonary disorders could be classified as infectious diseases, e.g. tuberculosis and pneumonia; obstructive conditions, e.g. asthma; restrictive conditions, e.g. fibrosis; and vascular diseases, e.g. pulmonary hypertension (1,6,7).

The nasal inhalation of nanoparticles for pulmonary therapy can be exploited for the treatment of disease. Recent reports indicate that the pulmonary route of drug delivery has generated immense research interest and investigations into the use of both local and systemic drug delivery systems. The focus of interest in pulmonary drug delivery is the high permeability and surface area of the lung, which is essential in the delivery of drugs for the treatment of pulmonary diseases (1).

Pulmonary drug delivery to the lungs is attractive and advantageous as there is relatively higher drug bioavailability due to the larger surface area of the lungs and a fast onset of action. There is improved patient compliance, as the formulation is self-administered, and the route of administration is non-invasive high drug permeability coupled with minimal drug degradation. The pulmonary route has been used for the delivery of vaccines, chemotherapeutics, antibiotics, proteins, peptides, protease inhibitors, and interferons (8).

Conventional dosage forms have associated limitations, such as frequency of administration due to a shorter half-life, patient non-compliance, and issues with peak and valley plasma concentration. These properties of conventional dosage forms are unable to achieve site specificity or targeted delivery of drugs. Formulation of modified release and targeted delivery systems, such as polymeric nanoparticles for pulmonary disease, is of immense benefit due to the ease of preparation, the control of the size distribution, good retention, and protection of the drug (9,10). The key areas to be considered in achieving efficient pulmonary drug delivery are the delicate balance between the patient, the design of the drug formulation, and the inhalation device employed (1).

Recent reports indicate that polymers have gained considerable attention as pulmonary drug delivery systems. They are well suited for drug delivery as they have high drug encapsulation efficiency and protect the drug from degradation, and exhibit modified and sustained drug delivery with a long shelf life. Polymers such as chitosan, gelatin, alginate, poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), and poly(ε-caprolactone) (PCL) are used for therapeutic purposes (8,11).

Functionalized polymer nano-particulate drug delivery systems have made a remarkable impact in inhalational drug delivery. Such polymer drug delivery systems are tailored to suit the prevention and treatment of lung diseases and disorders (9). Polymeric nano-based drug delivery systems are well suited to be developed into useful therapeutic strategies for emerging diseases such as Covid-19, and existing disorders of the lung which would require targeted drug delivery for optimal therapeutic outcomes (12).

An evaluation of the current strategies, approaches, advances, and future prospects of targeted polymeric nanoparticle drug delivery systems in the field of pulmonary drug delivery are essential for the prevention, treatment, and management of prevailing and emerging lung diseases and disorders.

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13.1.2 Anatomy and Physiology of the Respiratory System

The upper respiratory system consists of the nose, larynx, and pharynx, and the lower respiratory tract is composed of the trachea, bronchi, and lungs (1). The alveoli in the lungs play a key role in the respiratory system. The exchange of gases occurs at the alveoli, after which there is diffusion into the arterioles. The respiratory tract consists of the nose, oropharynx, larynx, trachea, bronchi and bronchioles. The lungs ensure the uptake and exchange of gases such as oxygen, which is absorbed through the alveoli, capillaries, and the arteries, and perfuses the tissue, after which carbon dioxide, the metabolic product, is exhaled (1,13,14).

13.1.3 Pulmonary Drug Delivery

13.1.3.1 Pulmonary Drug Delivery and the Treatment of Pulmonary Disorders

Pulmonary drug delivery has been employed for so many years for the local treatment of diseases like asthma, cystic fibrosis, chronic obstructive pulmonary disease (COPD), and infections. Developments and advances in pulmonary delivery have led to the systemic treatment of cancer, infections, autoimmune diseases, diabetes, and immune deficiencies. Generally the oral and nasal inhalation routes are used for pulmonary drug delivery. However a higher drug deposition has been associated with oral inhalation (15,16).

Drugs administered as aerosols are suitable for use in a variety of inhaler devices and delivery systems. Formulations that can be aerosolized are essential for inhalation drug delivery. Moreover, the delivery systems should deliver an aerosol with particles of appropriate size or droplets for deep lung deposition or at the peripheral airways for an optimal therapeutic outcome (16). Advantages associated with pulmonary drug delivery include the large surface area of absorption in the lung, the local or systemic effect that is produced, the fast onset of action, and the avoidance of the influence of pH, food and first-pass metabolism, the minimal effective dose associated with a reduction in side effects, and a non-invasive drug delivery approach. Usually the inhalation devices used are tamper resistant (14,16,17).

The efficiency of inhalation delivery depends on the site of drug deposition in the lung. This is crucial as the sophistication of deposition of drug in the lung relies heavily on the anatomy and physiology of the lung, physicochemical characteristics of the inhaled drug, drug formulation properties, and the kind of delivery system employed. The flow and deposition of the aerosolized drug depends on the nature and dimensions of the airways. The drug particles of a mean size (1–5 μm) and shape can be targeted at the alveoli, where there is maximal absorption.

Pulmonary infections can produce changes in the airways leading to a disrupted flow and deposition of inhaled drug. There are mathematical models available that predict the drug deposition and distribution of the inhaled drug (14).

Pulmonary drug delivery can be improved by attaching site specific ligands which improves targeting and site specificity, avoids the exposure of healthy cells to the drug, and allows dose reduction and less toxicity. In addition, delivery of proteins and genes could be achieved through the pulmonary route. This enhances drug stability as such drugs could be degraded by metabolic enzymes in the gastrointestinal tract and the liver if administered orally.

The application of nanotechnology in the design and formulation of drug delivery systems has enhanced targeted delivery of drugs specifically to diseased lung tissue, which is coupled with the reduction of side effects (18–20).

Pulmonary drug delivery is a convenient and effective approach for drug administration that is associated with a fast onset of drug action, is devoid of first-pass metabolism, has no potential lung toxicity, is non-invasive, and provides a simple approach for treatment.

The approach employed involves the use of the intranasal and oral inhalation approach. The intranasal route is convenient, safe, and enhances patient compliance. The nasal mucosa consists of the nasal epithelium, which is readily accessible for the absorption of drugs.

However, the oral inhalation route is usually preferred, as the intranasal route presents with narrow airway lumen as a limitation of that route (21).

Oral inhalation enhances the diffusion of drug into the peripheral areas and the alveoli of the lungs, thereby improving drug distribution with a better therapeutic outcome. Administration by the nasal route could be associated with a drug concentration loss of 85% as compared to that of 20% when administered by oral inhalation (22,23).

13.1.3.2 Challenges in Pulmonary Drug Delivery

The respiratory airway has ciliated epithelial cells which move mucus and alveolar fluids to the airways above. This mode of mucociliary clearance is useful for the removal of undesirable remains of degraded substances, unwanted secretions, and inhaled particles. In this way, the mucus undergoes a cycle of production and disposal. In addition, the alveolar macrophages serve as the host's defense mechanism by engulfing inhaled undesirable particles. The action of mucociliary clearance and macrophages could hinder the deposition and higher residence time of inhaled drug particles. Hence the appropriate drug delivery strategies should be able to overcome these limitations so the drug reaches the intended target in the lungs (20,24).

Usually the inhalation and deposition of drug in the lungs is influenced by processes such as inertial impaction, gravitational sedimentation, and diffusion. The drug particles size distribution in the aerosol is important. One challenge in the deposition of drug occurs in the highly branched airways, which have a narrow lumen between the trachea and the alveolar sacs. This causes the particles to only collide with the airway wall upon administration and become deposited deep or on the periphery of the lungs instead of flowing through the airways.

Pulmonary diseases such as acute respiratory distress syndrome in infants, pneumonia, cystic fibrosis, pulmonary hypertension, lung cancer, and lung infections can change the normal anatomy of the lung. This results in narrowing of the airway, thickening of the mucous, poor blood flow, which ultimately adversely affects the deposition of drug. In pulmonary

disorders, the constriction in the airway rather paves the way for the deposition of drug in the upper airways by the process of impaction. The air flow rate and the inhaled and exhaled volume affects the length of the residence time of the particles inhaled (20,24).

13.1.4 Pulmonary Drug Deposition

Pulmonary drug delivery could be achieved by the use of nebulizers, dry powder inhalers (DPIs), metered-dose inhalers (MDI), and aerosols, usually containing preparations such as nano-formulations, and biodegradable nanoparticles (15,25).

The use of aerosols is efficient in delivering drugs into the airways. Aerosols are pressurized systems that release a metered dose of fine mist spray after the activation of an associated valve system. A pharmaceutical aerosol contains the drug or therapeutic agent dispersed in a propellant in a suitable pressurized container and is administered for a local or topical effect. They can be administered to the lungs as inhalation aerosols or to the mouth as nasal aerosols. Aerosols usually target the delivery of a small quantity of the drug particles to a specific site for absorption. This produces a fast response (22).

Generally aerosols are introduced via nasal or oral inhalation. Usually the oral inhalation route is preferred as the nasal route is accompanied by constraints such a narrow airway lumen. Three main mechanisms associated with drug deposition after pulmonary administration follow.

13.1.4.1 Inertial Impaction

This is the movement of large particles that develop inertia, compelling them to move out of the direction of the main stream of particles. Subsequently these large particles move in a straight path and eventually impact the walls of the airways. Impaction in this way is useful for the treatment of asthma, tracheobronchitis, and COPD.

13.1.4.2 Sedimentation

Air velocity decreases when particles move deeper into the lung. The probability that deposition would be by impaction is decreased. Hence the gravitational force facilitates deposition by sedimentation.

13.1.4.3 Diffusion

Deposition of smaller particles sizes is influenced by diffusion due to their random movement or Brownian motion of the particles (1,16).

There are also other associated factors with lung deposition.

13.1.4.4 The Physicochemical Properties of the Drug and Formulation

Drug deposition in the lungs is affected by the diameter or particle size, density, particle shape, hygroscopicity of the particle, and electrical charge, and by the type of formulation, e.g. suspension, solution, or powder.

13.1.4.5 The Type of Delivery Device

Generally the devices for inhalation produce aerosols with varied particle sizes, even though particles of similar sizes would be preferred (1,22,25).

13.1.5 Pulmonary Drug Delivery Devices

Currently a lot of modern devices are used to target drugs to the lungs in the prevention and treatment of lung diseases, e.g. asthma and chronic obstructive pulmonary disease. The design of these pulmonary drug delivery systems is influenced by factors such as

1. Physicochemical properties of the drug
2. The patients to be treated, e.g. children, elderly
3. The clinical goals to be achieved
4. Regulatory requirements and legislation

Categories of pulmonary drug devices employed are

1. Dry powder Inhalers (DPIs): These are devices that deliver an aerosol of dry powder of the pure drug, or a combination of drugs with a drug carrier. The particles of drug are deposited in the upper airways or the deep lung. The velocity during deposition and the particle size are crucial for drug deposition.
2. Metered-dose inhalers (MDIs): The device is used to deliver drug in a fixed dose to the airways in patients with asthma, emphysema, bronchitis, and chronic lung disease. The device consists of the container, which is the canister, and the formulation, which includes the drug, excipients, surfactants and propellant, a metering valve, and an actuator or mouthpiece.
3. Nebulizers: These are designed to deliver suspensions or solutions of drug in an aerosol form into the respiratory tract. They can be useful for children with cough or respiratory and inhalation problems, and delivering local anaethesia in the trachea.

13.1.6 Methods of Formulation

Compatibility of excipients with active pharmaceutical ingredients are essential for formulation. Excipients found in polymeric pulmonary drug delivery systems play a role in drug absorption. The compatibility of these pulmonary drug delivery excipients with the drugs for treatment should be established before formulation. Long-term administration, especially of pulmonary formulations, requires that the potential for lung toxicity is eliminated.

13.1.6.1 Preparation of Particulate Matter

There are quite a number of techniques employed in the preparation of suitable drug particle sizes for pulmonary drug delivery. These techniques include spray drying, super-critical fluid technology, crystallization, double emulsion/solvent evaporation, and particle replication with non-wetting template methods.

13.1.6.1.1 Spray Drying Technique

Spray drying is a useful technique for the formulation of fine particles for pulmonary drug delivery, usually for the preparation of dry powder inhalers (DPIs) as it's a rapid process resulting in a product with unique properties. During the spray drying process, fine droplets, which are atomized from solutions or slurries, are passed into a stream of hot air, with subsequent evaporation of the moisture resulting in dry spherical particles. Spray drying produces free-flowing particles, with easily controllable sizes suitable for production on a large scale (25).

13.1.6.1.2 Supercritical Fluid Technology

Supercritical fluids exhibit the properties of both liquids and gases. These fluids behave as liquids, with properties such as solvency, flow, and polarity when above their critical temperature and pressure. The technique involves the controlled crystallization of drugs which is conducted from a dispersion in supercritical fluids, usually achieved with gases, e.g. carbon dioxide, nitrous oxide. The production of pulmonary drug delivery systems, e.g. nanoparticles, proteins, peptides, etc., can be carried out with this technique, which also has the potential of improving the formulation characteristics of the drug for pulmonary administration.

13.1.6.1.3 Crystallization

This method involves the production of a supersaturated solution, which subsequently encourages the formation of crystals. Even though the pace of the process is slow, there is minimal aggregation, defined crystal lattice, purity of the crystals formed, and a maximum yield.

13.1.6.1.4 Double Emulsion/Solvent Evaporation Technique

This method involves the preparation of a double oil-in-water or triple water-in-oil-in-water emulsion. The oil phase is eliminated by subjecting it to either non-solvent extraction or solvent dilution or evaporation. In the process the diffusion and evaporation of the organic solvent results in drug-loaded polymer particles.

13.1.6.1.5 Particle Replication

This process allows the formulation of similar sized nanoparticles, where the shape, size and constituents, and surface modification can be monitored and controlled (1).

13.2 Polymeric Nanoparticle Drug Delivery Systems

Nanoparticles are usually colloidal particles within the size range of 1–100 nm and could be classified as metal, lipid-based, ceramic, and polymeric nanoparticles based on the physicochemical properties. Advances and developments in the formulation and application of polymeric nanoparticles has generated immense research interest. Polymers employed for such drug delivery systems are of natural, synthetic, or semi-synthetic origin. The biodegradable forms are preferred due to chronic toxicity associated with the non-biodegradable forms. Polymeric nanoparticles could contain a drug, protein, and DNA material intended to target a cell or particular organ. The drug could be made soluble, attached, encapsulated, or entrapped in the matrix of the nanoparticle. Polymeric nanoparticles are regarded as smart polymers, due to their target specificity, reduction in side effects and rate controlling properties. Formulation of polymeric nanoparticles is less complicated than for regular nanoparticles and therefore more investigated. Polymeric nanoparticles have a larger surface area that allows them to exhibit a high number of surface functional groups such as ligands. The advantage of a smaller size is that it enables the polymeric particles to enter small capillaries, thereby targeting the cell of interest. This type of nanoparticle shows a good control of size and size distribution, and has a longer clearance time as compared to other nanoparticles, which is indicative of the fact that small quantities of drug are able to elicit better therapeutic effects with less side effects. Polymeric particles can be tailored to suit therapeutic needs, rate controlling with a high drug loading capacity. Limitations of this group of nanoparticles are linked to toxicity concerns and inability to halt therapy in an emergency. Scaling up for industrial purposes would require sophisticated equipment and high costs coupled with a strenuous process (9,26).

13.2.1 Types of Polymeric Nanoparticles

13.2.1.1 Lipid Polymer Hybrid Nanoparticles

Solid lipid nanoparticles are carriers, which contain lipids, and are useful for the delivery of therapeutic agents. This formulation is termed a lipid-polymer hybrid nanoparticles have the benefits of containing both solid and lipid phases and exhibit controlled release, protection of the drug load, and good tolerability with both lipophilic and hydrophilic properties. Due to the hydrophilic and lipophilic nature of the lipid-polymer hybrid nanoparticles, they are amenable to various formulations encapsulating different kinds of drugs (9,27,28).

13.2.1.2 Solid-Lipid Polymer Hybrid Nanoparticles

Development of solid lipid polymeric nanoparticles has yielded solid lipid polymeric nanoparticles with a unique formulation design and formulated with a core-shell, in contrast to solid lipid nanoparticles which are rather coated with a polymer shell. Solid lipid polymer nanoparticles have the advantage of the high encapsulation efficiency of hydrophilic drugs. Their drug delivery systems can be formulated with biopolymers like pectin and bovine serum albumin, and are biocompatible. The polymeric coating maintains the stability and colloidal integrity, and the solid lipid core enhances encapsulation efficiency (9,29).

13.2.1.3 Functionalized Polymeric Nanoparticles

Modification of the polymer in polymeric nanoparticles results in a functionalized polymeric nanoparticle. Functionalized polymeric nanoparticles have enhanced distribution and are

better protected from phagocytosis by the reticuloendothelial system. Consequently, since the nanoparticles are protected from degradation, there is an increased amount of drug in the blood circulation.

Functionalized polymeric nanoparticles can be categorized as long stealth nanoparticles, lectin-based polymerized nanoparticles, polysaccharide-based nanoparticles, and ligand-based nanoparticles (9).

13.2.1.4 Polysaccharide Conjugated Polymeric Nanoparticles

Polysaccharide conjugated polymeric nanoparticles are functionalized polymeric nanoparticles which usually consist of adsorbed polysaccharides on the surface of the nanoparticles. For instance hydrophobic polyesters such as PLGA and PLA are covalently incorporated with a polysaccharide made up dextran, chitosan, and hyaluronic acid. This drug delivery system has the advantage of being biocompatible (9,30).

13.2.1.5 Ligand-Based Polymeric Nanoparticles

Recent advances in polymeric nano-formulations have resulted in the formulation of ligand-based polymeric nanoparticles. They are designed to deliver therapeutic agents at targeted sites. For instance, for the sensing of cancerous cells, the green fluorescent protein is used. Slight modifications in the ligands enhances the cell affinity. Ligand-based nano-particulate systems are suitable for the diagnosis of disease and intracellular drug delivery (9,31).

13.2.1.6 Fluorescence Polymeric Nanoparticles

Luminescent polymeric nanoparticles have been developed with the use of fluorescent compounds such as luminescent polymers, fluorescent substances that exhibit coordination with metals. Aggregation induced emissions (AIE) are able to strongly radiate fluorescence due to the aggregation of fluorophores. Aggregation induced emission substances can are suitable for bio or chemo sensors. Fluorescent organic nanoparticles in water have good emission characteristics. The conjugation of aggregation-induced emission dyes in combination with polymers and block co-polymers are useful as agents for bioimaging and the treatment of disease (9,32,33).

13.3 Applications of Polymer Nanoparticles in Pulmonary Drug Delivery

Research in the area of polymeric nanoparticles has attracted heightened interest as there is increased therapeutic efficacy with less toxicity, a longer clearance period, and good size control. Different forms of polymeric nanoparticles exist as ligand-based nanoparticles, polymeric micelles, and dendrimers. Polymeric nanoparticles are carriers of therapeutic agents such as proteins, drugs, and DNA material for targeted delivery to an organ or cell (9).

13.3.1 Modifications of Polymer Nanoparticle Pulmonary Drug Delivery Systems and Safety Evaluations for Better Performance

Strategies recently adopted to improve hydrophilicity of nanoparticles which could subsequently enhance mucopenetration in pulmonary delivery, and avoid attack by opsonins, were considered and evaluated. This involved addition of polymers to the surface of nanoparticles. Polymers to be considered in this regard were methoxy polyethylene glycol (MPEG), polyethylene glycol (PEG), 1,2-dilauroyl-sn-glycero-3-phosphocholine (DLPC), and vitamin E, etc. The nanoparticles are either encapsulated in polymer carriers, dispersed in the polymer matrix, or loaded onto the surface of the polymer. A combination of polymers such as polyelectrolyte complexes, use oppositely charged polymers to entrap drugs into the polymer matrix of nanoparticles. Subsequently the drug is released via diffusion or polymer degradation.

Efficient lung deposition through the formulation of nanocomposites, was also investigated. Nanocomposites are produced by a combination of nanoparticle aggregates and an excipient such as a polymer, e.g. poly-DL-lactide-co-glycolide acid (PLGA). PLGA, which is safe to use in nanotechnology, has good controlled release characteristics and stability. Other applications of nanocomposites for efficient lung deposition and fast release of therapeutics such as salmon-calcitonon that have been studied involved the adsorption of salmon-calcitonin on PLGA, which when used as a coating on a lactose carrier is effective in the formulation of a nanocomposite.

Attempts have been made to exploit the electrostatic aggregation of nanoparticles as an approach to modify the carrier surface to include both cationic and anionic nanoparticle adsorption, in the field of the formulation of a nanocomposite for the development of a dry powder inhaler. The findings suggest that cationic and anionic poly lactic-co-glycolic acid/phosphatidylcholine (PLGA/PC) lipid and polymer hybrid nanoparticles could be adsorbed onto the surface of chitosan carrier nanoparticles. This hybrid polymer system has become of interest and consists of a polymer nanoparticle core and a liposomal layer (8).

13.3.2 Progress in Safety Evaluations

PLGA nanoparticles are extensively used in formulations delivered through the inhalation route. In view of its effectiveness, Haque et al., analysed the kinetics and clearance of polylactide-co-glycolide (PLGA) nanoparticles from the lungs to provide more information on the safety of these nanoparticles after extended use and provide a basis for clinical studies. The findings showed that lung kinetics and lung retention was significantly affected by particle size and lung clearance was affected by particle charge. There were temporary inflammatory changes observed after a single dose administration, influencing lung retention times. The study highlighted the significant insight into the role of the particle size and charge in the evaluation of the kinetics and the processes involved in the pulmonary delivery and clearance of PLGA particles (34).

13.4 Strategies, Approaches and Applications of Polymeric Nanoparticles in the Prevention and Treatment of Infectious Diseases

13.4.1 Pulmonary Infections

13.4.1.1 Advances in the Treatment of Pulmonary Viral Infections

Pulmonary disorders could be classified as infectious diseases, e.g. tuberculosis and pneumonia; obstructive conditions, e.g. asthma; restrictive conditions, e.g. fibrosis; and vascular diseases, e.g. pulmonary hypertension (1,6,7).

Several antivirals and immunomodulating drugs have ben hypothesized to be of immense benefit or investigated for their efficacy against the novel Covid-19 coronavirus that is in progress at the time of writing. The approach in this regard is to target the inhibition of the activity of proteases in the host cell and block the entry of the virus. Other approaches adopted are the development of nucleoside analogues which would target RNA polymerase, resulting in the inhibition of RNA synthesis, e.g. remdesivir, decreasing the production of pro-inflammatory cytokines or activation of CD8-T cells. Recent reports indicate the association of these drugs with adverse effects at the approved doses and also at higher doses. A formulation that could control the release of drug and maintain the minimum effective concentration, as well as reducing the side effects, could be recommended in this situation.

Polymeric nano-based systems have been studied in this regard. Mehta et al., hypothesized that advanced drug delivery systems that could enhance drug absorption and intracellular drug delivery, and maintain the concentration of drug in the lungs and systemic circulation with reduction of side effects would hold great promise as nanocarriers in the treatment of Covid-19.

Aerosol based drug delivery systems were usually employed in the treatment of pulmonary disorders. However, there is the likelihood of the undesirable transmission of viruses due to fugitive emissions from aerosol therapy, which could compromise the safety of healthcare workers treating Covid-19 patients. Novochizol, a chitosan biodegradable nanoparticle-based aerosol system holds great promise, as it adheres to the mucous membranes in the lung epithelium and provides sustained drug release. Novochizol is easily formulated. This polymer nanosystem is able to ensure the maintenance of optimal drug concentrations in the lungs and mitigate unwanted systemic distribution of drug (12).

There are remarkably promising approaches in nanotechnology that could be suitable for Covid-19 drug delivery and treatment. Noteworthy properties of nanoparticles useful for drug delivery include their small size improving targeted delivery, increased surface to volume ratio, thereby enhancing drug loading, and improved penetration of negatively charged mucosal membranes, due to the surface charge modification. Mechanisms of nanoparticle deposition in the respiratory tract include impaction and sedimentation for large particles and diffusion for smaller particles. Consequently, a combination approach of both nano- and microparticles has been investigated by Gartner et al. to possibly reduce mucociliary clearance and improve deposition in pulmonary delivery for the treatment of Covid-19 (35). Relevant strategies adopted to enhance Covid-19 therapeutic systems are the encapsulation of the therapeutic agent in the core of the nanoparticle to increase stability, improved targeting, and polymer performance to decrease the amount of required drug in the nano-based drug delivery system- (36).

Pulmonary viral infections, e.g. influenza viruses A and B, and SARS-Cov 2 and other microbial infections could be life threatening in patients with underlying pulmonary comorbidities and immuno-compromised patients. Oral or parenteral anti-infectives and anti-inflammatory agents administered in such situations could be associated with insufficient therapeutic levels of drug concentration at the site of interest in the lung. Localized inhalational drug delivery is well suited for drug administration in such situations. Chitosan is employed in such drug delivery systems for its mucoadhesive properties, binding action to microbial DNA with inhibition of mRNA, and protein synthesis as chitosan infiltrates the nuclei of microbes. Chitosan inhibits microbial growth by binding to the nutrients of the microorganisms. It is reported that low-molecular-weight chitosan has greater anti-microbial activity (20).

13.4.1.2 Advances in the Treatment of Pulmonary Bacterial Infections

Tuberculosis is caused by *Mycobacterium tuberculosis* resulting in an infection primarily of the lungs. The bacteria multiply within the granuloma, which are complex structures, which need to be accessible by the anti-tubercular drugs. Drugs to be systemically administered need to be administered in high doses for effective treatment of pulmonary tuberculosis (37). The pulmonary route is beneficial for tuberculosis treatment as it allows a higher bioavailability, with a larger lung surface area, and with higher perfusion, which targets the site of infection and avoids the first-pass effect. A study of chitosan nanoparticles showed a higher lung retention and longer residence time of administered anti-bacterials.

Research conducted by encapsulating isoniazid in chitosan nanoparticles enhanced the efficacy of isoniazid in *i*n vitro and in vivo models. Nanoparticles are able to better target the phagocytic cells where *M. tuberculosis* usually replicates.

Such results with promising outcomes could be evaluated in clinical studies as a suitable alternative for drug-resistant tuberculosis (38,39).

The current treatment of tuberculosis involves the administration of solid dosage forms such as tablets and capsules for four to six months. This dosage regimen could lead to side effects. Development of a chitosan nanoparticle-based dry powder formulation of rifampicin was successful in achieving dose reduction and frequency of administration as compared to the pure rifampicin powder.

Pulmonary delivery of the nanoparticles achieved sustained release as compared to the pure powder inhalation and showed an optimal pharmacokinetic profile. This study provided a useful therapeutic approach for the treatment of tuberculosis of the lung (40).

A formulation of ethionamide-loaded chitosan alginate nanoparticles was stabilized with different quantities of carageenan.

The findings indicate that in this study carageenan improved the stability in the processing as well as the entrapment efficiency of ethionamide. The nanoparticles exhibited controlled release over 96 hours, which reduced with increasing amounts of carageenan, with no drug excipient interactions. The formulated nanoparticles exhibited a significant activity against the *Mycobacterium* strain H37RA, and held great promise for inhalation therapy. The study also reiterates the immense potential of polymer nanoparticles in the pulmonary delivery of anti-tubercular drugs, with associated reduction in undesirable systemic effects. Polymeric nanoparticles have demonstrated their great potential in enhancing the efficacy of therapeutic agents and the ability to reduce their off target adverse effects (41).

Pneumonia is an infection that could adversely affect the alveoli in the lung causing respiratory failure. Development of antibiotic resistance to conventional treatment hampers the therapeutic outcomes. An anti-microbial peptide, BP 100, was studied as a suitable antibiotic alternative for treatment of pneumonia.

The antibacterial activity of BP 100 is optimized when carriers such as gold nanoparticles and polymers as coatings are used. With the use of a lung surfactant model, the effect of BP 100 transposition with polymeric carriers, e.g. polyethylene glycol (PEG) and polystyrene (PS), was evaluated. The results showed that the polymer PEG works by a mechanism of ligand competition for protection on the polymeric gold nanoparticle and BP 100 system. The findings highlighted the propensity of the use of PEG with gold nanoparticle carrier systems for antimicrobial peptides as a potential candidates for pulmonary disease (42).

13.4.2 Advances in the Treatment of Pulmonary Diseases and Disorders

13.4.2.1 Lung Cancer

Chitosan has attracted considerable interest in anti-cancer interventions, due to its mucoadhesive, penetration enhancement, and cell targeting properties for cancer treatment. The aerodynamic behavior of nanoparticles necessary for pulmonary inhalation could be augmented by microencapsulation of nanoparticles in pulmonary drug delivery.

Chitosan and its derivatives are useful materials in nano and micro carriers in pulmonary delivery of anti-cancer agents. It is biodegradable, biocompatible, anti-proliferative, and antimicrobial. The potential of chitosan as a backbone in lung cancer treatment and a carrier in pulmonary drug delivery has been examined.

Chitosan-based pulmonary delivery systems exhibit a reduction in systemic toxicity in anti-cancer therapy, a higher drug absorption in the lungs, and overall improved efficacy of anti-proliferative drug in lung cancer. Targeting with a ligand has shown better cell uptake and cancer cell apoptosis. Most studies have been conducted in vitro and ex vivo, and, as such, an in vivo evaluation for aerodynamic properties for inhalation in humans is necessary to establish their potential in lung cancer therapy (20).

The pulmonary delivery of therapeutics, e.g. peptides, is effective for the systemic absorption of therapeutic agents with problems of poor absorption. Moreover, pulmonary delivery is an attractive approach for the systemic absorption of anti-cancer agents, rather than the use of chemotherapy and radiotherapy in cancer treatment. Consideration for the use of phosphorylcholine, consisting of the copolymer MPC-DPA, is appealing as it is biocompatible and self-assembling to form diverse nanosystems (18).

The formulation of nanoparticles consisting of poly (2-methacryloyloxyethyl phosphorylcholine) and *b* poly (2-(diisopropylamino) ethyl methacrylate) (MPC-DPA) as carriers with a coating of n-trimethyl chitosan chloride which improves delivery for optimal concentrations in the cell, has exhibited remarkable applications in nanoformulation.

A number of nanosystems were analysed for their potential as suitably optimized MPC-DPA nanoparticles loaded with different quantities of an emerging therapeutical agent, curcumin, for their pulmonary delivery applications in the treatment of lung cancer. The necessary strategies to be adopted included the prediction, controlled and consistent production of particle sizes, drug loading capacity, effective airway travel, and permeation of lung tissue with suitable anti-proliferative indices. The nanosystems developed were effective and are recommended for further investigation in inhalation delivery and in vitro evaluation for pulmonary delivery for the treatment of lung cancer. This was a novel and promising study in the evaluation of anti-cancer curcumin-loaded nanoformulations of MPC-DPA for pulmonary delivery (43).

Ahmad et al., investigated novel chitosan-coated PLGA nanoparticles of catechin hydrate to assess the pharmacokinetics and probable improvement of the bioavailability after pulmonary delivery through the nose to the lungs, with the use of H1299 lung cancer cells. The particle size of the chitosan-coated nanoparticles were ~150 nm, with a polydispersity index of ~0.306. A high entrapment efficiency was achieved as the release was seen to be targeted at the cancer cells. A high apoptosis of cancer cells as well as a remarkable mucoadhesion was observed. The design of the chitosan-coated nanoparticles enhanced the safe delivery of catechin in rat lungs.

The findings showed a higher bioavailability after administration of the chitosan-coated PLGA nanoparticles of catechin hydrate in the lungs of the rat and provided a successful outcome for further investigations in the treatment of lung cancer (26).

In many ways, other polymeric nanoparticle applications have shown great promise in the treatment of cancer. The anti-cancer applications of gelatin-based nanoparticles were investigated. Anti-cancer drugs can be encapsulated in polymeric nano carrier systems. A formulation of cisplatin-loaded gelatin-based nanoparticles showed significant anti-proliferative activity against lung adenocarcinoma cells. The droplets of the nebulized aerosol were found to be suitable for deep lung drug delivery in vivo (44).

Doxorubicin-loaded poly-isobutylcyanoacrylate nanoparticles also exhibited cytotoxicity via alveolar macrophages. Alveolar macrophages show anti-cancer activity via the mechanism of the phagocytosis of the polymeric nanoparticles.

Doxorubicin can be conjugated with polymeric nano carrier systems for lung delivery, but the large particle sizes formed created a problem for pulmonary delivery. To overcome this, an aerosol of liquid droplets was formulated for the deep lung delivery of doxorubicin. Conjugation of hyaluronan-cisplatin

with nanoparticles was done and administered by lung instillation in vivo. There was an approximately five-fold enhanced anti-cancer activity than when the intravenous route was used. With regard to the delivery of cisplatin, both kidney and brain toxicities were reduced with the use of polymeric nanoparticles for drug delivery (45–48).

13.4.3 Advances in the Treatment of Asthma and Chronic Obstructive Pulmonary Disease

An optimal therapeutic outcome in the treatment of asthma and chronic obstructive pulmonary disease (COPD) is achieved when the drug is targeted at the site of action.

Therapeutic agents encapsulated in biodegradable polymeric nanoparticles are useful in pulmonary delivery. It is hypothesized that a combination of theophylline and budesonide improve the therapeutic outcome in the treatment of respiratory disease. A combination of budesonide and theophylline was encapsulated in polylactic acid (PLA) nanoparticles and investigated for their potential in pulmonary drug delivery. The nanoparticles were evaluated for their particle size, drug loading, zeta potential, and *in vitro* deposition characteristics during a nebulization procedure. The formulation produced a sustained drug release over 24 hours. The fine particle proportion of nebulization was in the ratio 75% of theophylline and 48% of budesonide. The study findings indicate that polymeric nanoparticles loaded with a combination of theophylline and budesonide are highly recommended in the treatment of asthma and COPD (49,50).

Budesonide has been extensively used in the treatment of asthma. However after inhalational delivery, it suffers the limitation of low absorption in the lungs. Ahmad et al., developed chitosan-coated budesonide nanoparticles, intended to improve the bioavailability, dispersion of the aerosol particles and the lung deposition, and evaluate the pharmacokinetic profile of budesonide. The particle size obtained after formulation was ~196 nm with a spherical shape and zeta potential of ~11.8. Pulmonary delivery of budesonide using the chitosan approach exhibited a higher bioavailability and lung deposition in the animal model, up to three times higher, than when administered orally, and twice as high when administered intravenously. There was no observed toxicity with this approach. The study is indicative of the potential of the chitosan-coated nanoparticles in enhancing the pulmonary delivery of budesonide (51).

Pulmonary targeting in respiratory diseases such as COPD and asthma improves drug efficacy and reduces the side effects (18). The particle size in inhalation therapy is crucial for drug delivery, drug deposition, and drug uptake. Usually the challenges to be overcome by the drug delivery system are the resistance posed by the secreted mucus, and the effects of the reticuloendothelial system on the nanoparticles. Other strategies useful for disruption of the mucosal barrier are the formulation of nanoparticles with magnetic properties, the use of mucolytic agents, and hydrolyzing enzymes. Moreover, biodegradable polymers are used to overcome the major barriers such as macrophage clearance and mucociliary barriers in drug delivery. Such polymers, e.g. dextran, gelatin, chitosan, poly (lactic-co-glycolic acid) (PGLA), poly(ε-caprolactone) (PCL), and alginate produce a longer half-life, higher diffusion ability, and a prolonged therapeutic effect (52). PEGylated dendrimers are suitable for inhalation delivery and for the treatment of disorders of the endothelium and to prevent inflammation. Muralidharan et al. studied the treatment of pulmonary inflammation with the use of inhalable dry powders in combination with dimethyl fumarate (53,54).

Poly-ethylene imines (PEIs), dendrimers, chitosan, and poly (lactic-co-glycolic acid) (PLGA) nanoparticles have useful applications in gene delivery (55). There are reports indicating the suitability of chitosan interferon (IFN)-γ-pDNA (CIN) in reducing hyper-responsiveness of airways in methacholine and ovalbumin-induced asthma in vivo. CIN has the ability to reduce to reduce inflammatory cytokine, and CD8+ T lymphocytes. A formulation of poly-l-lysine and polyethylene glycol nanoparticles linked by a cysteine residue was useful in the delivery of thymulin, exhibited anti-inflammatory, collagen deposition, and anti-fibrotic activity in an animal model. This nanoparticle drug delivery system was reported to be safe and immune compatible for the lungs of humans. In addition, biodegradable particles loaded with cytosine-phosphate-guanine adjuvant were found to be a promising therapy in the treatment of allergies caused by dust and were able to inhibit the Th2 asthmatic response. There have been concerns expressed over the safety and toxicity of inhalable nanoparticles. However, biodegradable nanoparticles with the use of polymers and lipids have been found to lower adverse inflammatory responses as compared to other non-biodegradable nano-drug delivery systems (56).

13.4.4 Advances in the Treatment of Lung Fibrosis

There has recently been a heightened interest in albumin for the formulation of nanoparticles as it is biocompatible, biodegradable, and less toxic. Albumin nanoparticles are able to exhibit targeted and controlled drug release which makes it suitable for inhalational delivery in infectious disease, lung cancer, and asthma. Targeted delivery with albumin nanoparticles can be achieved by ligand binding. Pulmonary delivery of albumin nanoparticles has met with some physical, physiological, and immunological limitations. These limitations could be addressed by monitoring the particle properties to obtain optimal lung deposition and targeted delivery of drug. Moreover, there is an associated improvement in patient compliance and therapeutic outcome with the inhalation route as compared to the parenteral route. Joshi et al., formulated albumin nanoparticles with tacrolimus, which is an immunosuppressant drug useful for the treatment of fibrosis. The particle size of the formulation was ~182 nm and had a zeta potential of -34.5 mV. Inhalational delivery of the tacrolimus albumin nanoparticles showed a 24-hour slow release, and exhibited a higher anti-fibrotic effect than when administered by the peritoneal route. This formulation approach for tacrolimus albumin nanoparticles that was adopted, coupled with the simple method of preparation, enables the ease of scale-up for industrial purposes (57).

Leal et al. sought to address unmet needs in the formulation of drug delivery systems for gene therapy relating to the intracellular delivery of the therapeutic agent. There was the need to overcome

both mucus and cellular penetration challenges in the pulmonary delivery of therapeutic agents in the treatment of cystic fibrosis. A peptide coated PEGylated nanoparticle drug delivery system enhanced the lung delivery of therapeutics over 600-fold in mice. This investigated intervention holds great promise in improving the absorption and efficacy of therapeutic agents in the treatment of cystic fibrosis (1)58.

13.4.5 Advances in the Treatment of Pulmonary Hypertension

Developments in targeted pulmonary delivery for the treatment of pulmonary hypertension have been insightful.

The activation of the mTOR pathway has been found to play a role in the progression of pulmonary hypertension in vascular modeling. Segurra-Ibarra et al. hypothesized that rapamycin-loaded polyethylene glycol- poly(ε-caprolactone) nanoparticles would be useful for targeted lung delivery in the treatment of pulmonary hypertension. The findings after the study showed that the use of rapamycin-loaded nanoparticles was useful in inhibiting the activated mTOR pathway, and effective in treating pulmonary arterial hypertension with fewer side effects. The findings indicate the potential of targeted lung delivery of the nanoparticles and further encourage the exploratory studies for inhalational delivery in the treatment of pulmonary hypertension (59).

Researchers such as Makled et al. investigated the pulmonary delivery of inhaled or nebulized sildenafil to the lungs. Before the study, it was observed that sildenafil was administered through the oral and parenteral route. The physicochemical properties, drug load, drug release, toxicity, and stability after sterilization and nebulization of formulated solid lipid nanoparticles loaded with sildenafil was conducted. The findings indicated a high encapsulation efficiency of above 80%, sustained drug release over 24 hours. Sterilization and nebulization did not affect the stability and drug load of the nanoparticles. The effects of the emulsifying agents in the coating on the mucin secretions was encouraging. It is envisaged that more interesting information would be derived from clinical studies (60).

It has been suggested that activation of the mTOR pathway plays a role in the progression of pulmonary hypertension. The efficacy of formulation of conjugated polyethylene glycol–distearoyl-phosphoethanolamine micelles loaded with fasudil was studied for the potential treatment of pulmonary arterial hypertension. The controlled release nanoparticle formulation exhibited an entrapment efficiency of 58%, enhanced the cell uptake, improved the half-life (five times higher than the control), and accumulated in the pulmonary vessels, suitable for reduction of the pulmonary arterial pressure (61).

13.5 Future Perspectives for Polymeric Nanoparticle Pulmonary Delivery of Therapeutic Agents in Emerging and Existing Lung Diseases

The inhalation of therapeutic agents in the form of aerosols is a convenient route for the pulmonary delivery which also enhances patient compliance. The use of polymeric nanoparticles among other nano-particulate drug delivery systems holds great promise for non-invasive targeted delivery for efficient cellular uptake of drugs to treat lung disease and assist lung repair. The prospects for polymeric nanoparticles, including its combination with cytokines, growth factors, small molecules, and stem cells for lung disease treatment are highly favourable (62).

Current trends indicate that chitosan and its modified forms have been extensively studied as the backbone of pulmonary targeted nanocarriers. They are useful for the delivery of therapeutic agents in cancer and infections. Chitosan has the advantage of being mucoadhesive, biodegradable, biocompatible, anti-proliferative, and anti-microbial. Developments in this area of research show a considerable interest in the use of chitosan over conventional carriers such as lactose. It is envisaged that further investigations in *in vitro* aerodynamic parameters, pharmacokinetics, and clinical studies would provide valuable information for therapeutics in this regard (20).

With regard to emerging antiviral medications, polysaccharides or polymers are of considerable research interest in the quest for anti-coronavirus interventions due to their peculiar antiviral properties and mechanisms of action. Such antiviral polymers are able to disrupt the life cycle of the infecting virus or improve upon immunity of the host. Carageenan, chitosan, and some traditional Chinese medicine polymers, of marine origin, have exhibited anti-coronavirus properties with a myriad of mechanisms of action potentially useful in the treatment of the Covid-19 infection. Hybridized polymeric nanoparticles have been investigated for their applications in the diagnosis and treatment of the influenza virus, human adenovirus, and HIV (63).

Recent studies with high prospects include the use of carageenan nasal spray with enormous antiviral efficacy against the influenza A virus, human coronavirus.

Further investigations with these findings in the intense search for novel ideas with the use of polymeric nanoparticles for pulmonary drug delivery are being birthed and should be pursued with much vigor in this era in the search for solutions for the treatment of Covid-19 (64,65).

13.5.1 Prospects for Emerging Disease Therapy with Polymeric Nanoparticles

The Covid-19 global pandemic has brought to light the importance of evolving drug development approaches and strategies in targeted pulmonary nanoparticle drug delivery systems with controlled drug release. Success in this area of research involves research collaborations and a concerted effort leading to the prevention of infection together with efficacious therapeutic drug delivery systems that would reduce mortality and improve control and recovery rates, and the response to epidemics (2,12).

Even though the changing nature of Covid-19 has created uncertainties in effective interventions, there are numerous promising therapies for the coronavirus infection with polymeric nanoparticles via the inhalational route, which addresses the critical issue of lung failure. Major developmental steps are being taken in research in this regard with potential successful outcomes (66).

Research into polymer drug conjugate-based nanoparticles is receiving much attention due to its immense potential in therapy, e.g. cancer chemotherapy. Polymer drug conjugate nanoparticles are designed to target tumor cells and tissues. Drug release can be triggered in response to certain stimuli. The strategy employed is to reduce systemic toxicity associated with the cancer drugs and optimize the therapeutic efficacy. Inhalational delivery of these polymer drug conjugate nanoparticles is attractive, as this approach is non-invasive (67). Polymer drug conjugates after inhalational delivery have the ability to improve the pharmacokinetics of the drug that is loaded, as well as optimize the controlled release of the drug as compared to the oral delivery or inhalation of the drug only. Polymer drug conjugates have a great potential if developed as pulmonary delivery systems. There is the need to further investigate and develop the physicochemical properties to enhance the effect of the drug conjugation on the polymer surface, the rate of drug release, therapeutic efficacy, required for preclinical studies necessary for rigorous clinical studies in cancer nanomedicine. It is envisaged that if exhaustive investigations are carried out in this regard, there would be remarkable advances necessitating clinical trials in the future (68).

Inhalable nanoparticle powder formulations play a key role in targeted pulmonary delivery. Safety of inhalable nanoparticle powders can be established through aggressive research. The use of polymers is essential for formulation development and the safety of inhalable drug delivery systems. Vibrant research investigations have been witnessed in the area of inhalable nanoparticulate powders with respect to vaccines, systemic drug delivery, surface modification in nanoparticle formulations, stability, and deep lung deposition. Formulation techniques in the processing of inhalational formulations have been improved with regard to freeze-drying, advanced spray drying, supercritical fluid extraction, condensation aerosol growth, and thermal condensation (8).

Strategies and developments in the area of polymer nanoparticles for pulmonary delivery with associated fields of interest have been evaluated. Challenges with this new era of research have been highlighted with potential solutions. There are interesting emerging opportunities for clinical studies and future development of promising therapies for lung disease (62).

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