Critical Parameters for Particle-Based Pulmonary Delivery of Chemotherapeutics

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Abstract

Targeted delivery of chemotherapeutics through the respiratory system is a potential approach to improve drug accumulation in the lung tumor, while decreasing their negative side effects. However, elimination by the pulmonary clearance mechanisms, including the mucociliary transport system, and ingestion by the alveolar macrophages, rapid absorption into the blood, enzymatic degradation, and low control over the deposition rate and location remain the main complications for achieving an effective pulmonary drug delivery. Therefore, particle-based delivery systems have emerged to minimize pulmonary clearance mechanisms, enhance drug therapeutic efficacy, and control the release behavior. A successful implementation of a particle-based delivery system requires understanding the influential parameters in terms of drug carrier, inhalation technology, and health status of the patient's respiratory system. This review aims at investigating the parameters that significantly drive the clinical outcomes of various particle-based pulmonary delivery systems. This should aid clinicians in appropriate selection of a delivery system according to their clinical setting. It will also guide researchers in addressing the remaining challenges that need to be overcome to enhance the efficiency of current pulmonary delivery systems for aerosols.

Keywords: chemotherapeutics, clearance, particles, pulmonary drug delivery systems

Introduction

IN SPITE OF THE INHERENT ADVANTAGES of the pulmonary route for administration of chemotherapeutics, the presence of bio-barriers such as mucus, ciliated cells, and resident macrophages in the respiratory tract could considerably hamper the targeting, diffusion, and adsorption of the inhaled drugs.⁽¹⁾ The negative effect of chemotherapeutics on the lung parenchyma is another obstacle for their direct administration into the lungs.⁽²⁾ To overcome these challenges, particle-based pulmonary delivery systems (PPDS) have been recently employed to achieve localized supply of chemotherapeutics, enhance drug bioavailability, avoid various pulmonary clearance procedures, and minimize the metabolic degradation. For an effective drug targeting, several parameters, including the physicochemical characteristics of the chemotherapeutics, carrier properties, type of the inhalation device, as well as the tumor type and location, must be considered.

This work is an attempt to review different carrier-, device-, and patient-related factors that have been reported to significantly affect the PPDS success in the clinical setting. Therefore, it could aid researchers in appropriate selection, design, and customization of a PPDS according to their specific treatment procedure. Moreover, this review highlights a number of research gaps that could be addressed in future to increase the PPDS efficacy for treatment of various lung tumors.

Particle-Based Parameters

A desirable inhalation performance requires optimization of various particle properties. The particle composition, size, morphology, surface characteristics, aqueous solubility, dispersion/agglomeration state, fluid pH, targeting moieties, and the chemotherapeutic type are the most studied physicochemical parameters for optimization of the PPDS performance.

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A number of other influential factors such as particle density, molecular weight, osmolality, ionic strength, viscosity, penetrability through the airway mucus, ability to escape from the mucociliary clearance and phagocytosis, rate of entrapment and inactivation by the bacterial biofilms, and tendency to interact with host proteins are also considered significant in PPDS design. However, to the best of our knowledge, limited studies have specifically investigated the influence of these parameters on the PPDS efficacy and thus, these parameters were excluded in this review.

Material composition

Similar to other drug delivery systems, sufficient physicochemical stability in the biological medium, bioavailability at the target tumor, and biodegradability after drug release are the general material characteristics that must be considered in the PPDS design. Different carriers, including lipid-, polymer-, and gelatin-based particles, have shown potential to present these general properties and are, thus, widely employed in PPDS design. A number of metallic (e.g., iron oxide and gold) and ceramic (e.g., mesoporous silica) compounds have also been used in PPDS development. However, translation of these carriers into the clinical setting is challenging due to the remaining concerns on their low biodegradability and potential pulmonary toxicological effects.

Lipid-based carriers. The lipid-based carriers employed in PPDS design could be generally categorized to liposomes, solid lipid nanoparticles (SLNs), and nano-sized lipid carriers (NLCs). Liposomal formulations with compositions similar to lung surfactants could serve as potential carriers for pulmonary delivery of therapeutics, owing to their low local irritation to the lung parenchyma, high biodegradability, sustained release behavior,^(3–10) controllable surface charge,^(11–14) as well as capability of encapsulating hydrophilic,^(15–17) amphiphilic,⁽¹⁵⁾ or hydrophobic^(15,18–21) compounds. Liposomes could also be produced in both dry powder⁽²²⁾ and liquid suspension^(23–25) forms based on the pulmonary delivery setup.

In general, the liposomal aerosols could significantly extend the drug retention half-life, improve their intracellular diffusion and bioavailability, enhance the tissue tolerance against high drug dosages, and minimize the pulmonary clearance via protecting the chemotherapeutics from enzymatic degradation.^(25–27) For instance, the area under the curve (AUC), half-life, and mean residence time of gemcitabine encapsulated in inhalable liposomal dry powders were, respectively, found to be 8.3, 5.3, and 5.7 times higher than that of drug solution.⁽¹⁰⁾ Inhalation of doxorubicin-encapsulated liposomes induced considerably higher cell death at the target tissue in the mice lungs and substantially decreased negative side effects in the nontarget organs such as kidneys, liver, and spleen in contrast to free doxorubicin or doxorubicin-encapsulated liposomes administered intravenously.⁽²⁸⁾

SLNs and NLCs are other submicron-sized lipid-based biocarriers, composed of solid hydrophobic cores entangled by monolayer phospholipid shells.^(29–34) The SLNs and NLCs have been employed for pulmonary delivery of phenethyl isothiocyanate,⁽³⁵⁾ paclitaxel,⁽²⁹⁾ and celecoxib,⁽³⁶⁾ showing high potential for nebulization to lower lung regions when appropriate aerodynamic properties are achieved. After inhalation, SLNs could be uptaken into the lymphatic nodes,

and rapidly deposited in periaortic, axillar, and inguinal lymph nodes.⁽³⁷⁾

The therapeutic activity, transferred drug dosage, deposition/release rates, and cytotoxicity of the lipid-based carriers in the lung parenchyma depend on the lipid composition (e.g., phospholipid type and content, rigidity, cholesterol content, saturated–unsaturated lipid ratio, and other additives),^(38,39) size,^(40–43) surface properties,^(43–45) drug characteristics,^(38,41,43) drug-to-lipid ratio,^(39–41,43) process parameters,^(39,41) and delivery technique.^(27,46,47) Hence, alteration of the lipid composition and fabrication protocol could result in highly customized physicochemical properties that substantially affect the PPDS efficacy in the target site.

Polymer-based carriers. Polymeric carriers are mostly fabricated from synthetic or natural biodegradable compounds, including polylactic-co-glycolic acid (PLGA),^(48–51) polyethylene glycol (PEG),⁽⁵²⁾ and their conjugates with other biopolymers such as polyesters,⁽⁵³⁾ chitosan,^(54–57) and dextran,⁽⁵⁸⁾ which offer potential advantages over lipid-based carriers in terms of physical and chemical stability, drug encapsulation capability, sustained drug release, and prolonged pharmacological activity of their cargos. In particular, deep deposition in the lower lung regions, low aggregation tendency, and high mechanical stability under the shear forces make polymeric particles suitable for pulmonary delivery of chemotherapeutics. Different chemotherapeutics such as doxorubicin,^(49,51) paclitaxel,⁽⁵¹⁾ cisplatin,⁽⁵⁷⁾ and 5-fluorouracil⁽⁵⁹⁾ have been encapsulated within the polymeric particles.

A variety of carrier parameters, including concentration, morphology, hydrophilicity, molecular weight, and porosity of the polymeric carriers, as well as the environmental factors such as temperature, pH, solvent polarity, moisture content, and physicochemical stresses show crucial effects on the efficacy of pulmonary delivery by polymeric carriers.

Polymeric micellar structures have also been broadly utilized in PPDS development due to their structural similarity to biological compounds such as lipoproteins and viruses. The micellar structures generally exhibit high loading capacity and biocompatibility, which reflect their high potential for pulmonary administration.^(60,61) Due to their hydrophilic shell, micelles could evade clearance by the alveolar macrophages, diffuse through the mucus layer, and penetrate into the epithelial cells. In particular, the hydrophobic core allows encapsulation of the hydrophobic chemotherapeutics such as docetaxel,⁽⁶²⁾ which could further be easily uptaken by the tumor cells.⁽²⁸⁾

Polymeric compounds with dendrimer structure such as PEGylated polylysine have also been used in pulmonary delivery of chemotherapeutics.⁽⁶³⁾ Intratracheal instillation of the dendrimer-conjugated doxorubicin into the rat lungs resulted in around a 15% dose retention in the lungs after a week of administration. A comparison between the efficacy of administration route demonstrated that the pulmonary delivery of dendrimer-conjugated doxorubicin resulted in a higher than 95% reduction in the lung tumor volume after 2 weeks whereas only 30%–50% reduction was observed when the drug was received intravenously.⁽⁶³⁾

Gelatin-based carriers. Gelatin-based nanoparticles (GNP) have been employed in pulmonary delivery of doxorubicin⁽⁶⁴⁾ and cisplatin.^(65,66) Similar to other nanotechnology approaches, GNP demonstrated enhanced anti-cancer activity,

sustained drug release, and low toxicity. The IC₅₀ was as low as 1.2 $\mu\text{g/mL}$ for cisplatin-loaded GNP compared with free cisplatin (2.54 $\mu\text{g/mL}$).⁽⁶⁷⁾ In addition, cisplatin accumulation in the lung tumor after inhalation by mice was much higher for the particle-based formulation compared with the free cisplatin solution.⁽⁶⁰⁾

Comparative investigation of different material compositions. Comparative studies regarding the efficacy of various carrier compounds for pulmonary drug delivery are scarce. However, in an attempt to select a carrier that serves as the optimal choice for pulmonary delivery of anticancer drugs, different nanocarriers including liposomes, PEG, distearoyl phosphoethanol amine-amino PEG micelles (DSPE-PEG), mesoporous silicon nanoparticles (MSNs), and polypropyleneimine dendrimer conjugated with siRNA were analyzed and compared in terms of their degrees of lung accumulation as well as deposition profiles in different nontarget tissues (Fig. 1).⁽²⁸⁾

It was found that when the carriers were inhaled by mice, the accumulation and retention ratios in the lungs were more independent of the carrier material in contrast to intravenous administration. However, the accumulation degrees and retention periods of liposomes, micelles, and PEG in the lungs were relatively higher compared with those of MSNs and dendrimers.⁽²⁸⁾ Therefore, it can be concluded that PPDS development using liposome- or polymer-based particles could result in relatively higher efficacies in contrast to other carrier compounds.

Particle size

The effect of mass median aerodynamic diameter (MMAD) on the distribution pattern and deposition site of the inhaled

particles has been investigated in numerous studies.^(68–72) In general, the particles with different MMAD values are deposited by impaction, interception, sedimentation, or diffusion mechanisms.⁽⁷³⁾

In addition, the MMAD values could significantly affect the activity of various lung clearance mechanisms that intensify during lung diseases. These mechanisms are considered as the major obstacle that the inhaled particles encounter, leading to rapid clearance from the lungs before reaching the target site.⁽⁷⁴⁾ The inhaled particles are mostly cleared by mucociliary clearance or alveolar macrophages, depending on their deposition region. For instance, the particles with MMADs larger than 6000 nm that mostly accumulate at the upper airways are eliminated by mucociliary clearance in the epithelia tissue. When the foreign particles are trapped in mucus, cilia beat in a coordinated direction (pharynx) to remove the freight by either coughing or swallowing.⁽⁷⁴⁾ In general, the particles with MMADs of 1000 to 5000 nm are shown to evade the mucociliary clearance and accumulate in the narrower airways.⁽⁷⁵⁾

Clearance by the alveolar macrophages is the secondary challenge that the particles encounter during their travel in the pulmonary system.⁽⁷⁴⁾ Although the particles with MMADs of 1000–5000 nm are shown to escape the mucociliary clearance, the MMAD range of 2000–3000 nm is prone to a faster recognition and elimination by the resident alveolar macrophages.⁽⁷⁶⁾

In recent years, an increasing interest has been dedicated to the particles in nano-sized range due to their easier incorporation into the “respirable ratio,” leading to enhanced uniformity of drug distribution within the alveoli.⁽⁷⁷⁾ Moreover, the nano-sized carriers are able to deposit at the lining fluid and evade the lung clearance mechanisms.^(78,79) However, application of nano-sized carriers in pulmonary

FIG. 1. Comparative investigation of accumulation of different carrier materials in various tissues.⁽²⁸⁾ The particle size of liposome formulation was 600 nm, and the molecular weight of PEG particles was 2 kDa. PEG, polyethylene glycol.

drug delivery remains challenging due to their high aggregation tendency and low weight, which results in their rapid exhalation.

Due to this limitation, the drug-carrying nanoparticles require secondary carriers with appropriate MMADs to obtain the synergistic effect of both micron- and nano-sized carriers.⁽⁸⁰⁾ For instance, SLN nanoparticles encapsulated in mannitol microspheres⁽⁸¹⁾ as well as chitosan-encapsulating mannitol^(56,82) and sodium alginate⁽⁸³⁾ have shown desirable aerodynamic characteristics, high encapsulation capacity, and high biocompatibility/biodegradability, which indicate their potency for application as pulmonary drug delivery systems. These carriers could also be selected from the stimuli-responsive compounds that swell in the respiratory tract due to moisture absorption, resulting in preferred deposition in the deep lung and minimized elimination by the lung clearance mechanisms.⁽⁸⁴⁾

In order to avoid both clearance mechanisms, while simultaneously obtaining high fractions of respirable delivery and sufficient chemotherapeutic dosages in the lower respiratory tract, it is suggested to encapsulate nano-sized carriers with particle sizes of less than 200 nm into the secondary carriers with MMADs ranging from 3000 to 5000 nm.

Carrier shape

In addition to particle size, the particle shape also influences the PPDS efficacy via modulation of the alveolar macrophage clearance. Investigation of the geometrically opsonized and nonopsonized polystyrene particles with different morphological conformations, including oblate ellipsoids, elliptical disks, rectangular disks, spheres, and worm-like shape, indicated that the orientation and shape of these materials substantially affect their phagocytosis clearance hours.^(85,86) An orientation bias was observed in the macrophage function, where the elliptical disks where engulfed in less than 6 minutes due to the attachment of macrophages to their major axes. The spherical particles were also immediately cleared regardless of the macrophage attachment point. In contrast, macrophage attachment to the flat surfaces or minor axes of the rectangular disks, elliptical disks, and oblate ellipsoids could not clear these particles even in 2 hours.⁽⁸⁵⁾

Inhalation of the particles with a worm-like shape also resulted in significantly less phagocytosis clearance in contrast to spherical shape mainly because of their low curvature region. The worm-like carriers were engulfed only when the macrophages attached to the main axes possessing high curvatures, whereas the longitudinal attachment of macrophages resulted in minimized clearance because of their low curvature in this direction.⁽⁸⁶⁾

Surface properties

The particles' surface properties are known to significantly influence their bioavailability in the tumor cells. In particular, the surface properties determine the hydrophilicity degree, surface charge, biocompatibility or cytotoxicity, and stealth characteristics. In general, the particle distribution in the extracellular matrix as well as their penetration between and into the cells significantly rely on their degree of hydrophilicity. In contrast, lyophilic particles could more readily enter the cells due to their higher diffusivity in the lipid membranes.

The cell uptake is also controlled by the particles' surface charge, where the positively charged particles could penetrate

easily into tumor cells due to their higher binding activity with tumor cells. On top of that, the particles' stability in the suspension is greatly improved when the zeta potential values are above ± 30 mV.^(87,88) Investigation of the zeta potential values of various carrier compounds indicated approximately neutral charges for most of the common inhalation materials. Although the liposomes and micelles exhibit slight negative charges, however these materials are still classified as "neutral" carriers in the drug delivery application.⁽²⁸⁾

The surface properties also substantially influence the clearance mechanism in the pulmonary system, where adhesion interactions between the particles and mucus usually occur via electrostatic, hydrophobic, and hydrogen bonding.⁽⁸⁹⁾ For instance, in the patients who simultaneously suffer from cystic fibrosis, over-production of a highly viscous mucus drastically limits the drug bioavailability in the tumor site. More than a 10-fold increase in mucus production is also observed in chronic bronchitis patients compared with healthy subjects.

It is, therefore, necessary to manipulate the physicochemical properties of the carriers such as surface charge or hydrophobicity to provide "stealth characteristics" for minimization of absorption, degradation, entrapment in the mucus, and thus increasing the penetration depth and prolonging half-life of the inhaled drugs across the mucus layers. The stealth behavior is generally obtained by conjugation of a lipid⁽⁹⁰⁾ or formation of a hydration layer such as hyaluronic acid (a muco-adhesive polysaccharide available in the pulmonary system) on the particles' surface to suppress the immune recognition, phagocytosis, and biofouling.^(91,92) The hydrophilic polymers such as PEG, polyethylene oxide, and poloxamine have also been widely used as coating layers on various carriers such as liposomes and SLNs.^(44,92-94)

Secondary carriers

As previously discussed, nano-sized drug carriers require to be encapsulated in micron-sized "secondary carriers" to decrease their exhalation rate. Carbohydrate formulations such as glucose, mannitol (polyol), maltitol, sorbitol, xylitol, and lactose (α -lactose monohydrate) are the most widely used secondary carriers that have shown great potency to enhance stability, dispersability, and flowability of the encapsulated therapeutics. However, a number of studies have shown that mannitol is the optimal secondary carrier for enhancing dispersability of the encapsulated nanoparticles incorporated in dry powder inhaler (DPI) formulations.⁽⁹⁵⁾ On the contrary, the intracellular uptake of polylysine encapsulated into lactose has been found to be higher than other carbohydrates.⁽⁹⁶⁾

The drug dispersability and delivery efficacy could further be enhanced by addition of a ternary component such as L-leucine to the lactose formulation to occupy the sites with high bonding energies and, thus, reduce the carrier-drug interaction.⁽⁹⁷⁾ Moreover, addition of the coarser lactose particles to the initial fine lactose particles with MMADs of ~ 5000 nm could increase their fine particle fraction and disaggregation.⁽⁹⁸⁾

Chemotherapeutic agent

Combination chemotherapy using platinum-based drugs such as cisplatin is still the backbone regimen for treatment of various lung cancers. Cisplatin contains a central platinum atom surrounded by two chloride and two ammonia molecules in the *cis* position as the leaving and carrier

FIG. 2. Chemical structures of the platinum-based chemotherapeutics used in lung cancer treatment.

ligands, respectively (Fig. 2).⁽⁹⁹⁾ Cisplatin exerts its cytotoxic effect via formation of chemical bonds with genomic DNA and inhibition of the cell replication and transcription.^(99,100) When crossing the cell membrane, cisplatin undergoes a nonenzymatic conversion to reactive derivatives through displacement of its chloride atoms and further binds to the DNA bases through the N7 atom (preferably guanine).^(99,100)

The main limiting parameters in application of cisplatin are a relatively low aqueous solubility, high toxicity, and a short half-life.⁽¹⁰¹⁾ High reactivity of the chloride ligand leads to formation of irreversible conjugates with proteins before reaching the cell nuclei and rapid excretion from the body. Therefore, a number of cisplatin analogues such as carboplatin, oxaliplatin, nedaplatin, heptaplatin, and lobaplatin have been developed as the second- and third-generation platinum-based chemotherapeutics to achieve superior aqueous solubility, higher antitumor activity with lower adverse effects (AEs), and longer half-lives.⁽¹⁰²⁾

In particular, carboplatin and oxaliplatin have shown promising efficacies comparable to cisplatin in treatment of various lung tumors. Carboplatin is produced by replacement of chloride with bidentate dicarboxylate, resulting in higher aqueous solubility but lower reactivity and slower DNA-binding kinetics. In contrast, oxaliplatin contains cyclohexyldiamine carrier groups for enhanced antitumor activity as well as oxalato bidentate leaving ligands to obtain higher aqueous solubility and slightly lower reactivity (Fig. 2). Cisplatin is the most-highly protein bound (higher than 90%), followed by oxaliplatin (~85%), and carboplatin (24%–50%). The diminished reactivity limits protein-drug complexes, which further results in a higher half-life due to a slower excretion from the body (Table 1).^(99,100)

The possible AEs of platinum-based chemotherapeutics have been investigated in a number of clinical studies. Overall, cisplatin exerts more severe nephrotoxicity, neurotoxicity, ototoxicity, chronic vascular toxicity, as well as gastrointestinal toxicities such as nausea, vomiting, and diarrhea in contrast to carboplatin and oxaliplatin,^(103,104) probably due to its highly reactive leaving groups.⁽¹⁰⁰⁾ In contrast, dose-limiting myelotoxicity, particularly thrombocytopenia,⁽¹⁰⁴⁾ as well as relevant hematologic toxicity profile when used in equipotent dosages⁽¹⁰⁴⁾ represent the most prominent AE of carboplatin. On the other hand, sensory peripheral neuropathy has been reported as

the dose-limiting toxicity (DLT) of oxaliplatin therapy.⁽¹⁰³⁾ However, a meta-analysis study indicated similar grades 3 and 4 sensory neuropathies and thrombocytopenia in oxaliplatin and carboplatin/cisplatin therapies and less thrombocytopenia, neutropenia, and leukocytopenia in oxaliplatin treatments.⁽¹⁰⁴⁾

Currently, platinum-based regimens combined with other doublets are prescribed as the gold standard for chemotherapeutic treatment of lung cancer.⁽¹⁰⁴⁾ The combination regimens initially consisted of cisplatin plus vinblastine, vindesine, etoposide, mitomycin, ifosfamide, fluorouracil, or doxorubicin (second-generation regimens); whereas more recently, modern agents such as vinorelbine, paclitaxel, docetaxel, gemcitabine, camptothecin, azacitidine, or pemetrexed are widely employed (the third-generation regimens) as monotherapy or combined with platinum-based compounds (Table 1).⁽¹⁰⁵⁾

A number of randomized clinical trials have investigated the efficacy of platinum-based doublets in treatment of lung cancer.^(106–108) Recently, a meta-analysis on the efficacy of cisplatin, carboplatin, and oxaliplatin indicated that the oxaliplatin-based regimens combined with third-generation agents such as vinorelbine, paclitaxel, docetaxel, gemcitabine, and pemetrexed could provide comparable clinical efficacy to those of cisplatin and carboplatin with lower toxicity, as well as sufficient safety for outpatient setting without necessity of specific hydration treatments.⁽¹⁰⁴⁾ Therefore, oxaliplatin combined with third-generation chemotherapeutics could be used as an efficient intervention, especially for elderly patients or those who are unable to tolerate the toxicity levels of conventional platinum-based regimens.⁽¹⁰⁴⁾ The most common combination therapies used in PPDS will be highlighted in the following sections.

Targeting ligands

Active targeting using surface-bound ligands specific to the receptors overexpressed on the lung cancer cells is a potential approach to obtain improved drug accumulation in the tumor. More importantly, this strategy could allow drug internalization via the receptor-mediated endocytosis and overcome the drug resistance through bypassing the membrane efflux pumps.⁽¹⁰⁹⁾

All the receptors including epidermal growth factor receptor (EGFR or HER-1), echinoderm microtubule-associated protein-

TABLE 1. PHYSICOCHEMICAL PROPERTIES OF VARIOUS CHEMOTHERAPEUTICS USED IN INHALATIONAL DELIVERY (WWW.DRUGBANK.CA)

	Water solubility (mg/mL)	Half-life(min)	Log p	pKa	
				Strongest acidic	Strongest basic
Cisplatin	2.530	20–30 ^a	–2.19–0.04	—	5.06
Carboplatin	10.00	150–350	1.06	—	–6.60
Oxaliplatin	27.50	Triphasic ^b	–0.47	—	—
Vinblastine	0.0169	Triphasic ^c	4.18–4.22	10.87	8.86
Vindesine	0.07	~ 1440	2.79–3.53	11.34	8.68
Etoposide	0.978	240–660	0.73–1.16	9.33	–3.70
Mitomycin	10.1	8–48	–3.00–0.55	6.80	–0.30
Ifosfamide	15.0	420–900	0.10–0.57	13.24	0.12
Fluorouracil	5.860	10–20	–0.66–0.58	7.76	–8
Doxorubicin	1.180	1200–2880	0.92–1.41	9.53	8.94
Vinorelbine	0.0122	1660–2616	4.39–4.65	10.87	8.72
Paclitaxel	0.006	~ 53 ^d	3.20–3.54	10.36	–1
Docetaxel	0.013	Dose dependent ^e	2.59–2.92	10.96	–3
Gemcitabine	22.3	42–94 (short infusions) 245–638 (long infusions)	–1.50–0.14	11.52	–1.30
Camptothecin	0.511	~ 10	1.22–1.91	11.71	3.70
Azacitidine	12.1	240	–3.10–2.50	12.55	–0.38
Pemetrexed	0.0905	210	–0.25–0.19	3.34	7.13

^aAdministrations of 50 or 100 mg/m². The platinum-albumin complexes do not significantly dissociate, slowly eliminating with a minimum half-life of 5 days.

^bTwo short half-life distribution phases of t_{1/2α} (~ 25 minutes) and t_{1/2β} (~ 1000 minutes), followed by a long terminal elimination of t_{1/2γ} (~ 23,500 minutes).

^c35, 53, and ~ 1140 minutes.

^dFor a 24 hour infusion of 135 mg/m² given to ovarian cancer patients.

^eAt dosages lower than 70 mg/m², the terminal elimination phase was not detected due to the assay limitations. A triphasic elimination profile was seen at dosages of 70 mg/m² and higher, with half-lives of 4, 36, and 11.1 hours for the α, β, and γ phases, respectively.

like 4 anaplastic lymphoma kinase receptor (EML4-ALK), erb-b2 receptor tyrosine kinase 2 (HER-2), folate receptor α, transferrin receptor, epithelial cell adhesion molecule, intercellular adhesion molecule 1, interleukin-4, prostate-specific membrane antigen, as well as K-RAS, MET, RET, ROS-1, and B-RAF proto-oncogenes that are present in the lung tumor cells or those in the tumor cell vasculature such as vascular endothelial growth factor could be targeted by their corresponding ligands bound on the nanocarrier surfaces.

Numerous studies have been carried out to functionalize drug-carrying particles via attachment of monoclonal antibodies, small molecules, peptides, proteins, or aptamers as targeting moieties to different receptors overexpressed in the lung cancer cells (Tables 2 and 3). However, few attempts have been made to conjugate targeting ligands on PPDS to enhance their tumor selectivity and thus, a comparison of the efficacy of these ligands in pulmonary delivery is not currently possible.

In two early studies, luteinizing hormone–releasing hormone was conjugated on the doxorubicin/cisplatin-loaded MSNs⁽¹¹⁰⁾ and lipids⁽⁵⁾ for inhalation treatment of nonsmall cell lung cancer (NSCLC), resulting in preferential accumulation in the lungs and limited diffusion in the systemic circulation. More recently, the tumor necrosis factor-related apoptosis-inducing ligand (Apo2L/TRAIL) has also been conjugated on the PLGA⁽¹¹¹⁾ and lipid⁽¹¹²⁾ carriers to improve drug targeting and internalization via binding to the death receptors 4 and 5 (DR4 and DR5). Conjugation of nanocarriers with different ligands specific to the receptors overexpressed in lung cancer cells could be an interesting area of research to determine the best targeting moiety that

results in maximum targeting and internalization of chemotherapeutics.

Device-Based Parameters

In general, nebulizers are the preferred choice for delivery of chemotherapeutics as small droplets continuously over acceptable periods.⁽¹¹³⁾ These devices could provide a relatively high dosage to the lungs, which makes them suitable for application in emergency cases.⁽¹¹⁴⁾ Due to a remarkably little specialized inhaled coordination required in contrast to other similar devices, nebulizers are applicable for both children younger than 2 years and elderly patients who are generally unable to control their breathing or receiving mechanical ventilation.⁽¹¹⁵⁾

DPIs have also been used recently in inhalational delivery of drug carriers such as cisplatin-loaded chitosan.⁽⁵⁷⁾ The DPI advantages include high stability, noninvasiveness, sustained release profile, rapid onset of action, propellant freeness, environment friendly, and cost-effectiveness.⁽¹¹⁶⁾ In addition, the dried powder state seems ideal for the delivery of hydrophobic formulations with low shear tolerances. Compared with nebulizers, DPI is more convenient to use without necessity of storage in cold conditions or reconstitution into solution before inhalation.⁽⁷⁶⁾

Nebulizers and DPIs are the most widely used devices for generation of aerosols containing chemotherapeutics. However, a comparative study on the efficacy of different types of nebulizers and DPIs in inhalational delivery of chemotherapeutics has not been carried out so far. Although it may be assumed that the clinical performances of nebulizers and

TABLE 2. VARIOUS TARGETING MOIETIES CONJUGATED ON NANOCARRIERS FOR LUNG CANCER TREATMENT

Target cells	Marker	Ligand type	Ligand	Carrier	
Cancer	EGFR	Monoclonal antibody	Cetuximab	Mesoporous silica, ⁽¹²⁸⁾ gold/iron, ⁽¹²⁹⁾ Gold, ^(130,131) Liposome, ⁽¹³²⁾ PLGA, ^(133,134) Chitosan ^(135,136)	
			Panitumumab	Gold ⁽¹³⁷⁾	
			Matuzumab	Iron oxide ⁽¹³⁸⁾	
		Small molecule	Erlotinib	PCL/liposome ⁽¹³⁹⁾	
			Gefitinib	Gold, ⁽¹⁴⁰⁾ Mesoporous silica ⁽¹²⁸⁾	
			Afatinib	Gold ⁽¹⁴¹⁾	
		Peptide	EGF	Lipid, ⁽¹⁴²⁾ Gelatin ^(64,67)	
			EV	Liposome ⁽¹⁴³⁾	
			Crizotinib	Micelles ^(144,145)	
		EML4-ALK	Small molecule	Crizotinib	Layer-by-layer NPs ⁽¹⁴⁶⁾
	K-RAS			Selumetinib	Micelles ⁽¹⁴⁷⁾
	MET			Cabozantinib	Micelles ^(144,145)
	ROS-1	Small molecule	Crizotinib	Micelles ^(144,145)	
			FRα	Crizotinib	Micelles ^(144,145)
				Folic acid	Iron oxide, ⁽¹⁴⁸⁾ Mesoporous silica, ⁽¹⁴⁹⁾ PEG/PLGA, ⁽¹⁵⁰⁾ Chitosan, ⁽¹⁵¹⁾ Liposome ⁽¹⁵²⁾
	TFR	Glycoprotein	Transferrin	PEG, ⁽¹⁵³⁾ Lipid/PLGA ⁽¹⁵⁴⁾	
			IL-4	Peptide	Liposome ⁽¹⁵⁵⁾
			PSMA	Small molecule	PLA/PEG ⁽¹⁵⁶⁾
			ICAM-1	Peptide	PLGA ⁽¹⁵⁷⁾
			EpCAM	Monoclonal antibody	PEG/PLA ⁽¹⁵⁸⁾
	LHRHR	Peptide	RNA	PLGA/PEG ⁽¹⁵⁹⁾	
LHRH			Mesoporous silica, ⁽¹¹⁰⁾ lipid ⁽⁵⁾		
DR4, DR5			Protein	PLGA, ⁽¹¹¹⁾ Liposome ⁽¹¹²⁾	
Vasculature			VEGF	Small molecule	Gold ⁽¹⁶⁰⁾
				Aptamers	RNA

EGFR, epidermal growth factor receptor; EpCAM, epithelial cell adhesion molecule; FR α , folate receptor α ; ICAM-1, intercellular adhesion molecule 1; LHRHR, luteinizing hormone–releasing hormone receptor; PSMA, prostate-specific membrane antigen; TFR, transferrin receptor; VEGF, vascular endothelial growth factor; DR, death receptor.

DPIs with other therapeutics^(114,117) could be generalized for chemotherapeutics, comparative *in vitro*, *in vivo*, and clinical investigation of their performances when specifically used for inhalational delivery of chemotherapeutic-carrying particles could present a more clear conclusion in terms of overall performance, inhalation time, generated particle size, drug stability, delivered dosages to the lung, deposition rate, consistency of the delivered dosage, and drug loss.

Patient-Related Parameters

Development of new inhalational delivery systems necessitates an understanding of the lung cancer types and presence of other lung diseases that affect the lungs' structure.⁽¹¹⁴⁾

Cancer type

Lung cancers are typically classified into small cell lung cancer (SCLC) and NSCLC⁽¹¹⁸⁾ according to their histology and treatment approaches. The SCLC type, which represents 13%–18% of the total cases, has been traditionally categorized into two clinicopathological stages, including the limited stage (LS; affecting only the lungs) and extensive stage (ES; metastatic outside the thorax cavity). NSCLC, on the other hand, accounts for more than 80% of all lung cancers and is generally divided into nonmetastatic (Stages I and II), advanced with local confinement to the thoracic cavity (Stage III), and metastatic to other organs (Stage IV). Adenocarcinoma, squamous cell carcinoma, and large cell carcinoma are the most common types of NSCLC.^(118–120)

In general, most of the SCLC cases dramatically respond to the chemotherapeutics. A high objective initial response rate (RR) ranging from 60% to 90% and a complete response (CR) ranging from 45% to 75% are observed in chemotherapy of LS-SCLC. However, the response durations are often short with high recurrence rates and a median survival of only 1.5 to 2 years. Combination chemotherapy of the ES-SCLC type even results in high RR with considerable objective responses and CR of 15% to 30%.⁽¹¹⁹⁾

In contrast to SCLCs, NSCLCs are relatively insensitive to the chemotherapeutics. However, chemotherapy is widely carried out as a neoadjuvant or adjuvant therapy in patients with higher risk. Moreover, ~80% to 85% of the NSCLC cases are diagnosed at stages III and IV, which makes surgery inapplicable. Therefore, chemotherapy remains a treatment of choice for the locally advanced or metastatic NSCLCs, aiming at extending the survival rate and improving the quality of life.⁽¹¹⁹⁾

The majority of clinical trials investigating the inhalation delivery of therapeutics by nanocarriers have concentrated on treatment of NSCLC (Table 4) and other cancers metastatic to the lungs. The inhalational delivery seems appropriate mostly for targeting the primary lung tumors due to limited accessibility of this administration route to the secondary tumors metastasized from the lungs to other tissues. Therefore, the inhalational delivery may not be efficient in systemic treatment of most SCLC cases that are generally diagnosed at advanced stages due to their rapid metastasis at early stages.

TABLE 3. PHYSICAL PROPERTIES OF THE PARTICLES CONTAINING CONJUGATED LIGANDS TARGETING LUNG CANCER CELLS

Compound	Particle size (nm)	Zeta potential (mV)	Surface functionality	Chemo-therapeutic	LC (wt.%)	EE (%)	Ref.
Ceramics							
Mesoporous silica	100		MPTES	DOX			(128)
	160		MPTES	CIS, DOX		8 DOX 30 CIS	(110)
Metals							
Gold	44		PEG				(130)
	25	−20.4					(131)
	41	−35.0	PEG				(141)
	338	−13.7	PEG				(160)
Iron oxide	53–62	−8.0 to −4.2	Sulfo-SMCC NHS-PEG-MAL				(138)
	18.5		PEG				(148)
Gold-iron oxide	73	−29.0	PEG				(129)
Lipids							
Liposome	116		PEG				(132)
	130–150	~ 0	PEG				(143)
	100	−32.6	DSPE-PEG-MAL	DOX			(155)
	303	−2.7	DSPE-PEG				(152)
	160	−40.0	PLL-HA				(146)
Lipid	30		PEG-MAL				(142)
	110	~ 0	DSPE-PEG	DOX, PTX	5		(5)
Polymers							
PEG	147			DHA	10		(153)
PLGA	178			CPT		86	(133)
	80	−50.0	OCE	PTX		85–100	(134)
	286–303	−43.0 to −45.0	Pluronic F127	DOX		19–27	(157)
	11500		PEMA	DOX		86.5	(111)
	108	−21.3	Lipid	DOX		92.48	(154)
PEG-PLGA	149–186	−24.7 to −21.5		CIS, PTX	4.68		(150)
	136	36.1		DOX	7.3		(159)
PEG-PLA	80–100	−22.9	MAL	PTX		<86	(158)
TPGS-PLA	158						(144)
	162						(145)
CS	180	−5.1		DMC		98	(136)
	185	21.1	PEG	GEM		37.2	(151)
CS-γ-PGA	200	−17.0		DTX		42	(135)
Gelatin							
Type A	220	−9.3	NeutrAvidin				(67)
	120		NeutrAvidin	CIS	20	90	(64)
Composites							
DSPE-PEG	~ 12	−15.7					(147)
PCL-Liposome	150–180	−30 to −15	DSPE-PEG				(139)
Lipid-CP	20	10.0	DSPE-PEG	GEM		75	(162)

CIS, cisplatin; CP, calcium phosphate; CPT, capthothecin; CS, chitosan; DHA, dihydroartemisinin; DOX, doxorubicin; DMC, demethoxycurcumin; DSPE, distearoyl phosphoethanolamine; DTX, docetaxel; EE, encapsulation efficiency; GEM, gemcitabine; HA, hyaluronic acid; LC, loading capacity; MAL, maleimide; MPTS, mercaptopropyl trimethoxysilane; NHS-PEG-MAL, N-hydroxysuccinimide polyethylene glycol maleimide; OCE, oleyl cysteineamide; PCL, polycaprolactone; PEG, polyethylene glycol; PEMA, polyethylene-alt-maleic anhydride; PGA, polyglutamic acid; PLA, polylactic acid; PLGA, polylactic-co-glycolic acid; PLL, poly-L lysine; PTX, paclitaxel; SMCC, succinimidyl maleimidomethyl cyclohexane carboxylate; TPGS, tocopheryl polyethylene glycol succinate.

The efficacy of this approach could even be less for the metastatic NSCLC due to their relatively low cell sensitivity to chemotherapeutics. Therefore, the inhalational delivery of nanocarriers containing chemotherapeutics is probably more efficient for targeting of the nonmetastatic and locally advanced NSCLC as well as combination therapies together with systemic treatment of secondary tumors metastasized into the lungs.

The clinical efficacy and safety of inhalational carriers of chemotherapeutics have been assessed in two clinical trials (Table 4). The maximum tolerated dose, safety profile, and

pharmacokinetics of the inhaled lipid cisplatin (ILC) have been previously determined in a phase I dose-escalating study on patients with primary or metastatic lung carcinoma.^(12f) The cisplatin and lipid (dipalmitoyl Phosphatidylcholine with MMAD of 3.7 μ m) concentrations in this study were, respectively, 1.0 and 16 mg/mL in the aqueous solution. The administrated dosage of ILC was 1.5 to 60 mg/m², nebulized for 1 to 4 consecutive days/week and 1 to 3 weeks/cycle.

Investigation of the safety profile up to the maximum deliverable dosage of 60 mg/m² indicated no DLT such as hematologic, neurologic, auditory, or renal toxicities.

TABLE 4. CLINICAL TRIALS ON INHALATIONAL THERAPY OF DIFFERENT LUNG CANCERS

Identifier	Year	Phase	Status	Device	Drug	Cancer type
00004930	2000	I	Complete	Nebulizer	Doxorubicin	NSCLC (recurrent, stage III, stage IV) SCLC (recurrent, ES) Lung metastatic cancers
00005610	2000	II	Complete	Nebulizer ^a	Sargramostim	Lung metastatic melanoma
00017121	2001	I	Complete	Nebulizer	Sargramostim	Lung metastatic melanoma
00020124	2001	I	Complete	OncoMyst ^b	Doxorubicin	NSCLC (recurrent, stage III, stage IV) SCLC (recurrent, ES) Lung metastatic cancers
00066365	2003	II	Complete	Nebulizer	Sargramostim	Lung metastatic osteosarcoma
00082472	2004	I/II	Unknown	OncoMyst	Doxorubicin, IV docetaxel, cisplatin	NSCLC (stage III, stage IV)
00102531	2005	Ib/IIa	Complete	Nebulizer	Liposomal cisplatin	Lung metastatic osteosarcoma
00250120	2005	I	Withdrawn	Nebulizer	Liposomal camptothecin	NSCLC (any stage)
00277082	2006	I/II	Complete	Nebulizer	Liposomal camptothecin	NSCLC (stage IV)
00652860	2008	II	Complete		liposomal doxorubicin, Sargramostim, cisplatin, ifosfamide, mitomycin C	NSCLC (stage III)
01590069	2012	I/II	Ongoing	Nebulizer	Interleukin-2	Lung metastatic osteosarcoma
01650090	2012	II	Ongoing	Nebulizer	Liposomal cisplatin	Lung metastatic osteosarcoma
02009436	2013	I	Recruiting	Nebulizer	Azacitidine	NSCLC (stage IV)

^aConnected to a standard air compressor to generate the aerosol mist.

^bConsisted of a Pari LC Plus nebulizer placed inside a spray-capturing system.

NSCLC, nonsmall cell lung cancer; SCLC, small cell lung cancer.

Nausea, dyspnea, fatigue, vomiting, and hoarseness with grades 1 or 2 were the most widely observed AEs. However, a number of reversible local AEs such as decreases in the forced expiratory volume in one second and diffusing lung capacity for carbon monoxide, which are generally not seen during systemic administration of cisplatin, occurred with grades 1 to 2 after one course in few patients.

The pharmacokinetic studies showed a very low measurable systemic exposure to cisplatin only in three patients with the longest repeated inhalations (6.66–8 hours per week). The plasma concentration of cisplatin in two patients who received 48 mg/m² ILC was ~0.4–0.5 μ M after the last session, whereas this value was increased to around 1.4 μ M in the patient receiving 60 mg/m² ILC. Therefore, ILC was found safe and feasible, leading to a stable disease in 12 out of 17 patients.⁽¹²¹⁾

Due to the encouraging results, a phase Ib/IIa clinical trial was further carried out to characterize the clinical performance of ILC in recurrent osteosarcoma patients with only pulmonary metastases.⁽³¹⁾ ILC was nebulized every 2 weeks with dosages of 24 or 36 mg/m². The most common AEs were respiratory (e.g., cough, wheezing, nasal dryness, postnasal drip, and rhinorrhea), observed in 13 out of 19 patients, as well as gastrointestinal (e.g., nausea/vomiting) with grades 1 and 2. However, a patient was hospitalized due to a grade 3 vomiting after administration of 24 mg/m² ILC. The hallmarks of systemic cisplatin administration such as hematologic toxicity, nephrotoxicity, ototoxicity, hearing loss, or long-term abnormalities in the pulmonary function testing (PFT) parameters were not observed in the patients.⁽³¹⁾

The platinum level in the tumor tissues of the patients who subsequently underwent metastasectomy ranged from 200 to 18,900 μ g/kg,⁽³¹⁾ which was significantly higher than that measured after intravenous or intra-arterial administration of 150 mg/m² cisplatin (from undetectable to 950 μ g/kg).^(122,123) A low systemic exposure of the encapsulated cisplatin was again confirmed in this study,

where its serum concentration 18–24 hours postdose (47.0–153.5 ng/mL) was significantly lower than that (400–3500 ng/mL) reported for intravenous administration of 100–120 mg/m², which is the typical dosage in treatment of osteosarcoma.⁽¹²⁴⁾

Investigation of therapeutic efficacy of ILC in recurrent osteosarcoma highlighted the significance of lesion size and necessity for surgical resection,⁽³¹⁾ where the patients with lesions smaller than 2 cm or those who underwent complete surgical resection had sustained benefits. Overall, among eight patients with small lesions, one patient achieved a CR radiographically, two patients experienced a stable disease in two cycles and CR after metastasectomy, one patient showed a sustained partial response, and the remaining had stable diseases.⁽³¹⁾

A clinical trial was also performed by using liposomal 9-nitrocamptothecin (9NC) with a droplet size of 1–3 μ m for treatment of primary or metastatic lung cancer.⁽¹²⁵⁾ Various dosages, including 26.6, 20, 13.3, and 6.7 μ g/kg per day, were used to determine the optimal concentration with a sufficient clinical efficacy and minimal side effects. At 26.6 and 20 μ g/kg per day, the DLTs were grade 3 chemical pharyngeal mucositis and fatigue, respectively. At dosage of 13.3 μ g/kg per day, all patients tolerated the treatment well without a grade 3 AE. The most widely observed grade 2 AE was nausea, followed by cough, anemia, vomiting, wheezing, fatigue, peribuccal rash, and neutropenia.

The most remarkable finding of this study was the lack of hematological toxicity, which is widely observed when 9NC is used by oral administration.⁽¹²⁶⁾ Therefore, a dosage of 13.3 μ g/kg (equivalent to 0.5 mg/m²) per day was recommended for administration of liposomal 9NC via two consecutive 30-minute nebulizations per day from a nebulizer reservoir with 4 mg of 9NC in 10 mL of sterile water for 8 weeks. The pharmacokinetic studies indicated post-dose plasma concentrations of 9-NC ranging from 32.0 to

120.4 ng/mL, which was significantly narrower than that observed after its oral administration (26–517 ng/mL). However, the median values of postdose plasma concentration obtained using inhalational liposomal 9NC and oral cisplatin (76.7 ± 39.1 and 111 ng/mL,⁽¹²⁶⁾ respectively) were not statistically significant.

The obtained clinical results showed the feasibility and safety of aerosol administration of liposomal 9NC and its potential in stabilization of the primary lung cancer in three out of the six patients. Moreover, partial remissions of the uterine cancer and liver metastasis were also observed, demonstrating the systemic potential of aerosol delivery of this drug.

Overall, the inhalational liposomal formulations carrying cisplatin or 9NC were demonstrated to be well tolerated and causing minimal changes in PFT, without typical toxicities associated with systemic administrations of these drugs. Moreover, given the complete or partial responses observed in the patients who received these products, inhalational delivery of chemotherapeutics using liposomes shows potential as an effective approach for inhibition of the micrometastases, treatments of various lung tumors, and prolonging the patients' life.⁽³¹⁾

Other lung diseases

A majority of patients (in particular the patients older than 70 years) with lung cancer also suffer from other lung diseases such as asthma, chronic obstructive pulmonary disease, bronchiectasis, and cystic fibrosis, which complicate deposition and absorption of therapeutics due to their crucial impact on the lung architecture.

A significant deformation of the bifurcation angles as well as obstruction of lung airways due to an increased mucus accumulation generally leads to decreased cross-sectional area and, subsequently, increased air velocity and turbulence. Turbulent flow of the aerosol could significantly affect the distribution and deposition profiles of the inhaled particles. Moreover, obstruction of the airway often occurs in the regions that require to be targeted by the therapeutic compounds to obtain an effective clinical outcome,⁽¹²⁷⁾ whereas the airways obstruction navigates the inhaled aerosol to the unobstructed airways of the healthy regions, leading to a remarkably low drug deposition in the affected areas.

Conclusion

The pulmonary system is known as a promising route for local administration of chemotherapeutics, presenting a large surface area and low enzymatic activity. However, the lung clearance mechanisms, rapid metabolic degradation, as well as low control over the deposition rate and site of the inhaled therapeutics remain the major obstacles for successful pulmonary drug delivery.

Several approaches have been investigated to avoid the lung clearance mechanisms and to prolong half-life of the inhaled chemotherapeutics. In particular, the particle-based delivery systems have been shown as a promising solution for overcoming the physiological barriers present in the pulmonary system, thus enhancing the bioavailability of therapeutic compounds at lower lung regions.

The particle-based delivery systems must effectively evade the pulmonary clearance mechanisms, protect their cargo from rapid metabolic degradation, reduce the drug

absorption, improve localized delivery to the tumor area, enhance the sustained release, decrease the dosage frequency, and minimize the systemic toxicity. To achieve these requirements, identification of the influence of different physicochemical parameters such as carrier composition, size, shape, and surface chemistry is imperative to tailor their biological behavior in the physiological environment. Understanding the critical characteristics, including particle-particle interactions, aggregation, proteins' adsorption on the particle surfaces, and their potential to provoke the immunological responses, is also beneficial to develop an effective pulmonary delivery system.

In spite of the great advances in the design and development of particle-based pulmonary systems, clinical translation of this approach for inhalation of chemotherapeutics in lung cancer therapy is still challenging. It is well known that the biophysical characteristics of the inhaled particles often differ crucially from those formulated during fabrication. This is mostly due to the particles' interaction with the proteins and lipids during contact with the lung lining fluid, which results in formation of biomolecular hard and soft coronas on the particles' surfaces. Therefore, it is the biomolecular corona that defines the biological behavior of the inhaled nanoparticles and thus becomes the major biological entity of the particles.

The corona type and density is significantly affected by the particles' characteristics such as composition, size, surface charge, and surface functionality. As a result, the majority of developed PPDS suffer from the short half-life and low bioavailability of the therapeutic agents at the target region, which cause inefficient therapeutic influence and adverse side effects. Therefore, synthesis of carriers with minimal absorption of proteins and lipids that allows escaping the various lung clearance mechanisms and provides prolonged deposition at target tissue remains extremely complicated.

Further research for detailed exploration and understanding of the lungs' function and molecular bases of the lung clearance mechanisms could aid in better overcoming of the biological barriers that the inhaled therapeutics encounter while reaching the deep lung areas. Once these barriers are successfully avoided, the patients could even receive their chemotherapeutic treatment at home with a cost-effective approach compared with the current standard treatment, resulting in reduced hospitalization cases.

Sufficient understanding of the critical influential parameters in particle-based pulmonary delivery of anticancer drugs could help in formulation and development of pulmonary delivery systems with higher safety and efficacy levels. Therefore, considerable effort is still required for eliminating the laboratory and clinical gaps and to enable translating the PPDS into the commercial therapeutic products.

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