REVIEW ARTICLE

Nanocarrier-Mediated Drug Delivery *via* Inhalational Route for Lung Cancer Therapy: A Systematic and Updated Review

Nargis Ara[1] · Abdul Hafeez[1]

Abstract

Lung cancer is one of the most severe lethal malignancies, with approximately 1.6 million deaths every year. Lung cancer can be broadly categorised into small and non-small-cell lung cancer. The traditional chemotherapy is nonspecific, destroys healthy cells and produces systemic toxicity; targeted inhalation drug delivery in conjunction with nanoformulations has piqued interest as an approach for improving chemotherapeutic drug activity in the treatment of lung cancer. Our aim is to discuss the impact of polymer and lipid-based nanocarriers (polymeric nanoparticles, liposomes, niosomes, nanostructured lipid carriers, etc.) to treat lung cancer via the inhalational route of drug administration. This review also highlights the clinical studies, patent reports and latest investigations related to lung cancer treatment through the pulmonary route. In accordance with the PRISMA guideline, a systematic literature search was carried out for published works between 2005 and 2023. The keywords used were lung cancer, pulmonary delivery, inhalational drug delivery, liposomes in lung cancer, nanotechnology in lung cancer, etc. Several articles were searched, screened, reviewed and included. The analysis demonstrated the potential of polymer and lipid-based nanocarriers to improve the entrapment of drugs, sustained release, enhanced permeability, targeted drug delivery and retention impact in lung tissues. Patents and clinical observations further strengthen the translational potential of these carrier systems for human use in lung cancer. This systematic review demonstrated the potential of pulmonary (inhalational) drug delivery approaches based on nanocarriers for lung cancer therapy.

Keywords lung cancer · nanostructured lipid carriers · polymeric nanoparticles · pulmonary drug delivery · targeted drug delivery

Introduction

Cancer remains the world's leading cause of death due to the uncontrolled growth and spread of malignant cells [1]. With approximately 1.6 million fatalities each year, lung cancer is one of the most fatal cancers in the world, among others, like colon, breast and prostate [2, 3]. Lung cancer patients continue to have a poor prognosis, even though its treatment has vastly progressed in the past 50 years. Lung cancer can be caused by a variety of environmental and genetic variables, as well as their

interactions. According to the histology of the tumour tissue, there are two forms of lung cancer: small (SCLC) and non-small-cell lung cancer (NSCLC), which are further split into adenocarcinoma, large cell carcinoma and squamous cell carcinoma [4, 5].

SCLC constitutes ~ 15% of all types of lung cancer, which have a very high proliferative rate, a significant propensity for early metastasis, and a poor prognosis [6]. SCLC patients have a poor prognosis, with few years of survival rate (< 5%) and an average total survival time of just 2–4 months for those who are not getting active therapy [7]. NSCLC is the most common type of lung cancer that is less susceptible to treatment than SCLC and accounts for about 85% of all lung malignancies. NSCLC originates from the epithelial cells of the lung placed in the interior bronchi to terminal alveoli [8].

In recent years, the understanding and therapeutic approaches to lung cancer have been improved significantly. The treatment plan is generally determined by the

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Theme: Inhaled Drug Delivery of Biologics for Therapeutic and Vaccination

✉ Abdul Hafeez
    abdulhafeez@iul.ac.in

    Nargis Ara
    nargisara@student.iul.ac.in

1   Faculty of Pharmacy, Integral University, Lucknow 226026, India

Table I Drugs Used for Lung Cancer Treatment, their Mechanisms of Action and Adverse Effects

Drug	FDA approval	Mechanism of action	Adverse effects	References
Afatinib	2018	Irreversibly inhibits epidermal growth factor receptor, leading to a decrease in tumour cell proliferation and vascularization	Stomatitis, paronychia, diarrhoea	[14]
Ceritinib	2017	Stops cell growth process by inhibiting anaplastic lymphoma kinase	Inflammation in lungs, peripheral neuropathy	[15]
Capmatinib	2020	Works by attacking the mesenchymal-epithelial transition protein	Inflammation, Diarrhoea, Hepatotoxicity	[16]
Entrectinib	2019	Blocks the proliferation of pro-B cell line	Vision disorders, Fatigue	[17]
Pralsetinib	2020	Works by attacking the rearrangement during transfection protein	Hyperglycaemia, hypertension, anaemia	[18]

kind and pathological stage of lung cancer. Despite substantial growth in lung cancer treatment to date, anticancer treatment efficiency in different individuals remains poor [9]. In most treatment approaches, non-localized drug administration has a low success rate and poor clinical efficacy; most of the chemotherapeutic medications are taken by the traditional route (i.e. oral or parenteral). As a result, targeted inhalation medication administration has piqued interest as an approach for improving chemotherapeutic drug activity in the management of lung cancer [10].

The pulmonary or inhalational route of treatment leads to rapid systemic absorption without the complications associated with parenteral forms of administration. In addition, clinical and preclinical research is continuing to look into using the pulmonary route of administration to treat cancer and infectious disorders [11]. There are three types of devices that are used to deliver medications to the lungs: metered dose inhalers (MDIs), nebulizers and dry powder inhalers (DPIs). Each of these systems uses a distinct principle to transport aerosols and the chemistry that corresponds to the product differs greatly [12].

Additionally, conventional chemotherapy is nonspecific in terms of targeting drugs to lung cancer cells, which also distributes and causes harm to healthy cells and results in systemic toxicity in patients [13]. Some of the conventional lung cancer treatments, as well as their mechanisms of action and common adverse effects, are summarised in Table I. Hence, the need for alternative treatment methods still exists. One of the most common ways is nanocarrier-based drug delivery. Drug nanocarriers are colloidal carrier systems with submicron particle sizes of less than 500 nm [19]. Nano-scaled drug carriers have received increased interest in comparison to free pharmaceuticals because of their capacity to alter pharmacokinetics (enhanced permeability), sustained release, improved stability, and decreased toxicities [20, 21].
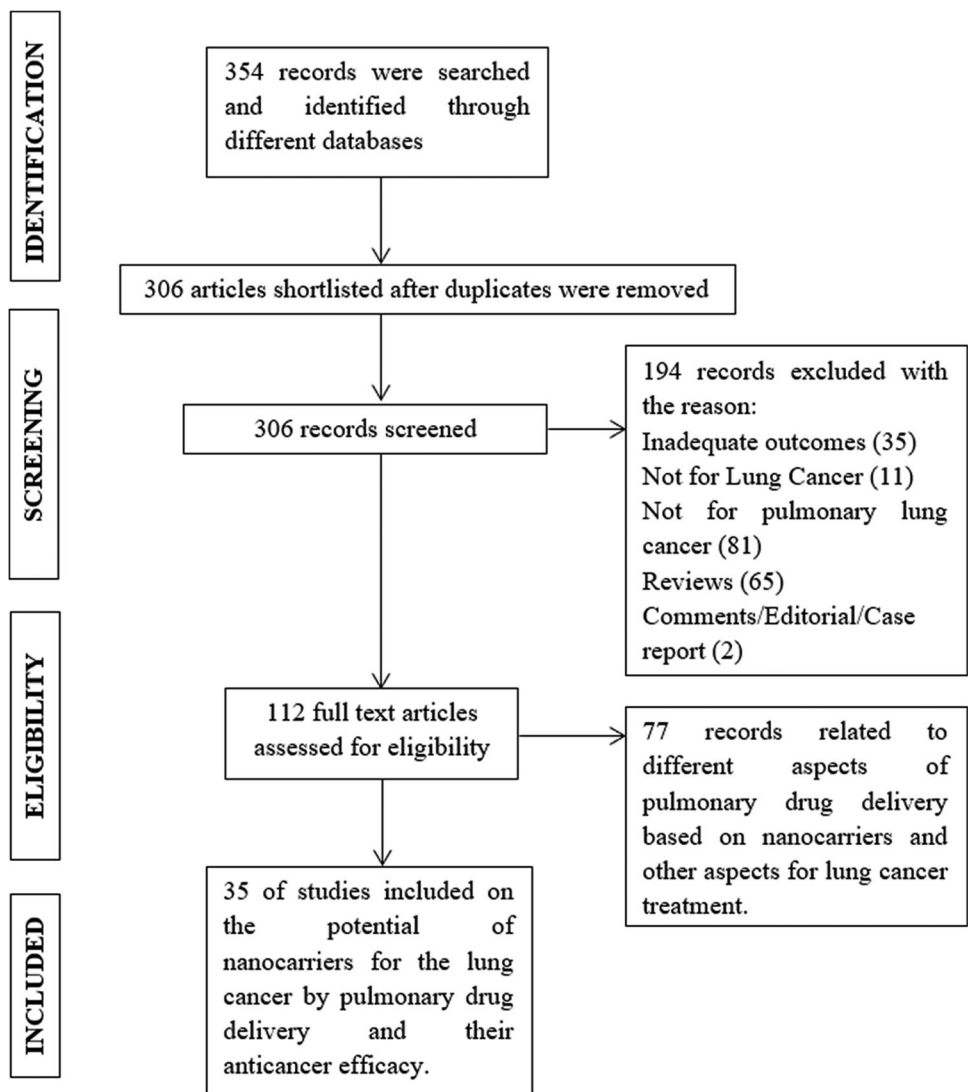
In recent years, many polymer and lipid-based nanocarriers have been developed and evaluated to enhance the drug loading and release features of anticancer medications used to treat lung cancer [22]. For example, bromonoscapine nanoemulsions [23], paclitaxel liposomes [24], docetaxel-nanoemulsion [25], docetaxel-baicalin solid lipid nanoparticle [26], gemcitabine-paclitaxel nanostructured lipid carrier, etc. [27] showed increased therapeutic activity in the management of lung cancer. For the management of lung cancer, this study summarises the many elements of pulmonary drug administration based on nanocarriers (such as microparticles, nanoparticles, dendrimers, liposomes, niosomes, nanoemulsions and solid lipid nanoparticles) through a description of preclinical and pharmaceutical characteristics. This paper describes the impact of different types of nanocarriers on lung cancer treatment in detail. This study also includes information on the latest investigations performed, clinical studies and patent reports related to pulmonary drug delivery based on nanocarriers for lung cancer management.

Methods

Literature Search Methodology and Selection Criteria

The Scopus, Springer, Elsevier, Science Direct, Bentham Science, Taylor and Francis, and PubMed electronic databases were searched for articles published between 2005 and 2023. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standard guidelines were followed when performing the literature search. The terms lung cancer, pulmonary drug delivery, nanocarriers were used to search the data based on inclusion criteria. Reviews and study reports with insufficient data, however, were not included. For further research, the references from the included papers and reviews were examined.

Fig. 1 PRISMA flow diagram for the identification, screening and inclusion of articles in the systematic review

IDENTIFICATION

354 records were searched and identified through different databases

306 articles shortlisted after duplicates were removed

SCREENING

306 records screened

194 records excluded with the reason:
Inadequate outcomes (35)
Not for Lung Cancer (11)
Not for pulmonary lung cancer (81)
Reviews (65)
Comments/Editorial/Case report (2)

ELIGIBILITY

112 full text articles assessed for eligibility

77 records related to different aspects of pulmonary drug delivery based on nanocarriers and other aspects for lung cancer treatment.

INCLUDED

35 of studies included on the potential of nanocarriers for the lung cancer by pulmonary drug delivery and their anticancer efficacy.

Data Screening and Analysis

Initially, 354 studies were identified, out of which 242 records were excluded on the basis of different reasons (Fig. 1). After this, 112 full-text publications were analysed for inclusion after the screening of the data, using a pre-specified format that takes into account the source, article title and reported characteristics, methodologies, anticancer potential and key outcomes. Figure 1 shows the method utilised for the selection and screening of articles.

Results and Discussion

According to the research's findings, of the 112 included articles, 35 dealt with the nanocarrier-mediated pulmonary drug delivery in the treatment of lung cancer, and 77 dealt with the important aspects of pulmonary drug delivery based on nanocarriers, patents, and clinical trials associated with the lung cancer therapy.

Important Aspects of Inhalational (Pulmonary) Drug Delivery

Pulmonary drug delivery involves inhaling medication into the lungs, where it passes through the alveolar epithelium and into the bloodstream. Pulmonary drug delivery is a non-invasive alternative to the injectable route of drug administration. The ability to employ a relatively low dose, a low incidence of systemic adverse effects, and for some medications, a quick commencement of action is all benefits of pulmonary administration [28, 29].

In addition to eliminating carbon dioxide and returning it to the lungs for emission, the respiratory system functions in tandem with the cardiovascular system to transport oxygen from the lungs to different cells in the body.

Fig. 2 Schematic diagram showing potential of nanocarrier-based inhalational drug delivery in the treatment of lung cancer
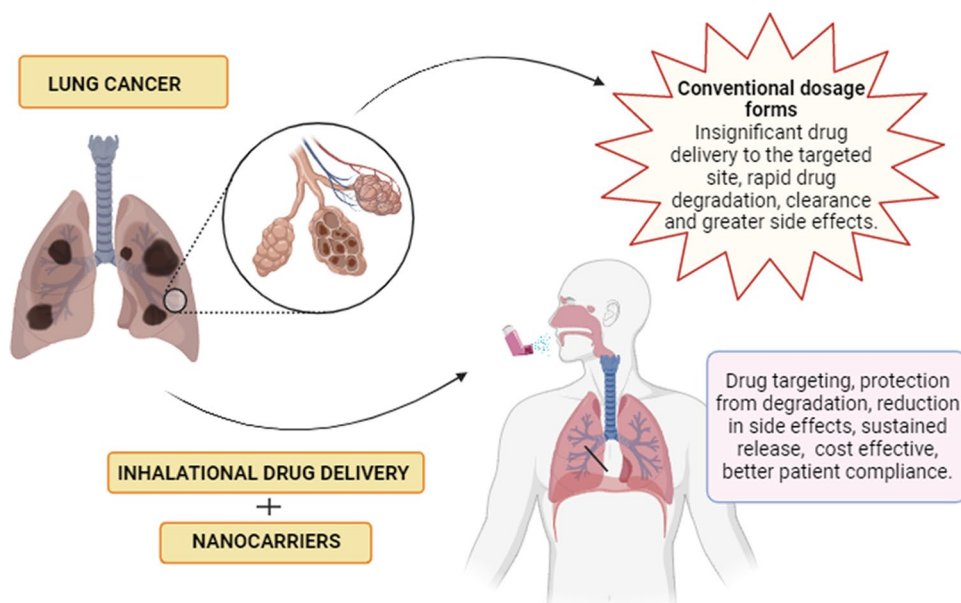
The process of breathing involves transferring oxygen and carbon dioxide from the air, blood and tissues of the body. Roughly 12–15 times each minute, a healthy lung takes in approximately 1 pint of air. Every minute, all the blood from different parts of the body passes through the lungs. The whole respiratory tract is divided into two divisions: the upper respiratory tract (includes throat, nose and nasal cavity) and the lower respiratory tract (includes lungs, larynx, trachea and bronchi) [30].

The lungs are very sensitive to disorders/diseases caused by hereditary factors, infections and pollution, and the whole respiratory system is vulnerable to a number of diseases. Asthma, bronchiolitis, COPD, cystic fibrosis, lung cancer, pneumonia and pulmonary hypertension are the major causes that create problems in the functioning of the lungs [31].

Particles enter the lungs by three routes: impaction, sedimentation, and diffusion. Because of curvature and decreasing air velocity, particles travelling through the respiratory system are subjected to continually changing forces [32]. The mechanism of inertial impaction deposits the biggest particles in the pharynx and early bifurcations. The minute particles remain travelling to the central lung (sedimentation), where the air velocity eventually drops to much lower levels. The optimal particle size for inhalation therapy ranges from 1 to 5 μm, depending on the targeted area [33]. Particles entering the respiratory system may vary not only in size and velocity but also in shape and density, depending on the kind of drug and the inhalation mechanism used for aerosol production [34].

The devices used to administer therapeutic agents to the lungs are classified into three types: MDIs, DPIs, and nebulizers. The mentioned systems operate on a distinct principle, and the performance associated with the result differs greatly between them [35]. MDIs are devices that release a set dose of medicine with each pulse and are used to deliver aerosolized pharmaceuticals. The drug is generally administered at a high velocity (> 30 m/s via the mouthpiece) in the form of particulate systems with a mass median aerodynamic diameter of ∼ 2–4 μm. The purpose of DPIs was to eliminate MDI's inherent coordination difficulties. DPIs do not require the administration of propellants, making them more ecologically friendly, and many of them have a dose left indicator. DPIs, unlike MDIs, do not need synchronization during actuation and breathing. DPIs require high rates of inspirations (generally ≥ 60 L/min) to guarantee effective de-agglomeration of powders. De-agglomeration is the change of clumped powder into free-flowing powder fractions called fine particle fractions. Nebulizers are capable of delivering high dosages of medication to patients who are unable to coordinate properly, as well as delivering many medications combined together in one solution. The minimum inspiratory flows required for a nebulizer's aerosol to reach the lungs are 6–8 L/min [36–38].

Studies Based on Nanocarrier-Mediated Inhalational Drug Delivery for Lung Cancer

If controlled or sustained release is needed, drug incorporation in particle carriers provides a way to manipulate drug release. In recent years, colloidal carrier systems have piqued attention as a means of delivering drugs to site-specific targets, particularly in cancer treatment [39]. Figure 2 shows the advantageous features of nanocarrier-based pulmonary drug delivery in lung cancer therapy in comparison to conventional treatment approaches. The vehicles employed as drug carriers may be split into two types based on the carrier material: polymeric nanocarrier systems and

lipid-based nanocarrier systems (Fig. 3). In the below sections, a detailed review of polymeric and lipid-based inhalable drug-loaded nanocarriers for lung cancer therapy is presented and summarised in Table II.

Polymer-based Nanocarrier Systems

Polymers are cross-linked polymer networks made up of numerous linear and branching copolymers. Polymer-based nanocarriers generally have matrix or reservoir-type structures made of branched polymers. In recent years, polymeric nanocarrier-based drug delivery systems have attained significant potential targeting drugs to cell surfaces and also intracellularly [40].

Microparticles The sphere-shaped polymeric microparticles have a size dimension of 1–1000 μm. These carriers are also considered nanocarriers because of their small sizes, and the other reason is that most of the nanocarriers are converted into microparticles to improve physicochemical and aerodynamic characteristics. Due to the fact that they deposit in the deep lung areas and do not aggregate when subjected to shear pressure, microparticles are commonly employed for pulmonary administration. Polymeric microparticles have been used to contain a variety of medications, including corticosteroids, insulin, and chemotherapeutics [41]. Because they are small and easily breathed, porous microparticles are considered to be an effective platform for delivering medications to the lungs. For this purpose, a delivery system consisting of PLGA (poly (d, l-lactic-co-glycolic acid) based microparticles loaded with doxorubicin (DOX) was developed. The mean particle size and mass median aerodynamic diameters were found to be ∼ 14.1 μm and ∼ 3.6 μm, respectively. Due to their significant potential as a long-term inhalational carrier system for the treatment of lung cancer, DOX was slowly released from DOX-PLGA microparticles over a period of two weeks. After pulmonary administration, it was found that DOX-PLGA microparticles were deposited in high concentrations in the lungs and stayed *in situ* for a duration of 14 days. The *in vitro* study showed reduced growth in B16F10 cells within 24 h. Tumours in B16F10-implanted mice treated with DOX-PLGA microparticles were significantly smaller in relation to mass and volume when compared with non-treated cancer-bearing groups [42].

Using an emulsification process, paclitaxel-loaded sodium alginate microparticles were created. Selection of appropriate parameters and methodology enabled the formulation of microparticles with a mean-volume diameter of ∼ 3 μm, mass median aerodynamic diameter of ∼ 5.9 μm, fine particle fraction of ∼ 13.9%, and encapsulation efficiency of ∼ 61%. The *in vitro* cytotoxicity study of paclitaxel-loaded microparticles was evaluated using A549 and Calu-6 (human non-small-cell lung cancer cell lines) and exhibited a significant reduction in the cell viability in comparison to free drug [43]. Sericin microparticles were developed and evaluated by Liu *et al*. To create DOX-loaded microparticles, tannic acid/ferric iron–based metal networks were coated on the microparticles. The encapsulated microparticles showed a mean particle diameter of 4.6 μm and better encapsulation efficiency of 74.35%. The DOX entrapped microparticles taken up by 4T1 cells and effectively killed cancerous cells. The *in vivo* study demonstrated high deposition of developed formulation in lungs after pulmonary administration and showed significant inhibition of lung metastatic tumour in comparison to conventional formulation of DOX [44]. In another investigation, PEGylated 6 μm polystyrene microparticles were made that included camptothecin (in the form of norvaline α-amino acid prodrug). In a xenograft lung cancer animal model, anticancer effectiveness was assessed and contrasted to a bolus injection of camptothecin. Compared to untreated rats, animals receiving either free camptothecin (2 mg/kg) or camptothecin-norvaline-microparticles (0.22 mg/kg camptothecin, 100 mg/kg microparticles) had statistically significantly less lung cancerous lesions (P0.05, P0.01, respectively). Additionally, 40% of the rats given camptothecin-norvaline-microparticles were discovered to be cancer-free, leading to a distinguished increase in the anticancer effectiveness of the developed formulation in a xenograft rat model of lung cancer [45].

Polymeric Nanoparticles Colloidal systems known as polymeric nanoparticles include pharmaceuticals that have either been integrated into the polymeric matrix or have been adsorbed on the surface of particles (nanospheres). In nanospheres, the drug is equally spread, and in nanocapsules, the drug is imprisoned in a cavity surrounded by a polymer layer [46]. Because of their superior pharmacokinetic features, polymer-based nanoparticles have been regarded as the most effective carriers employed in drug delivery applications. With recent advancements in cancer stem cells, methodologies for loading medication onto polymeric nanoparticles and their application for cancer stem cells targeting cancer therapy have been explored [47]. In order to gain higher anticancer activity in lung cancer therapy, methods for developing a nanosystem based on polylactide-tocopheryl polyethylene glycol succinate as a carrier of crizotinib are discussed. Drug trapped in the hydrophobic core of nanoparticles leads to a prolonged release pattern (∼ 40% in 24 h). The optimised formulation exhibited cytotoxic activity in lung cancer cells (NCIH3122) in a dose-dependent manner. A typical endocytosis-mediated cellular uptake of the polymeric nanoparticle was also demonstrated by predominate presence in the cytoplasm of the cell. The apoptosis assay (annexin V/PI staining-based) showed significant ∼ 40% apoptosis compared to only ∼ 25% by free crizotinib [48]. Jung *et al*. integrated taxanes into polymeric nanoparticles.

Fig. 3 Nanocarriers used through the inhalational route for lung cancer
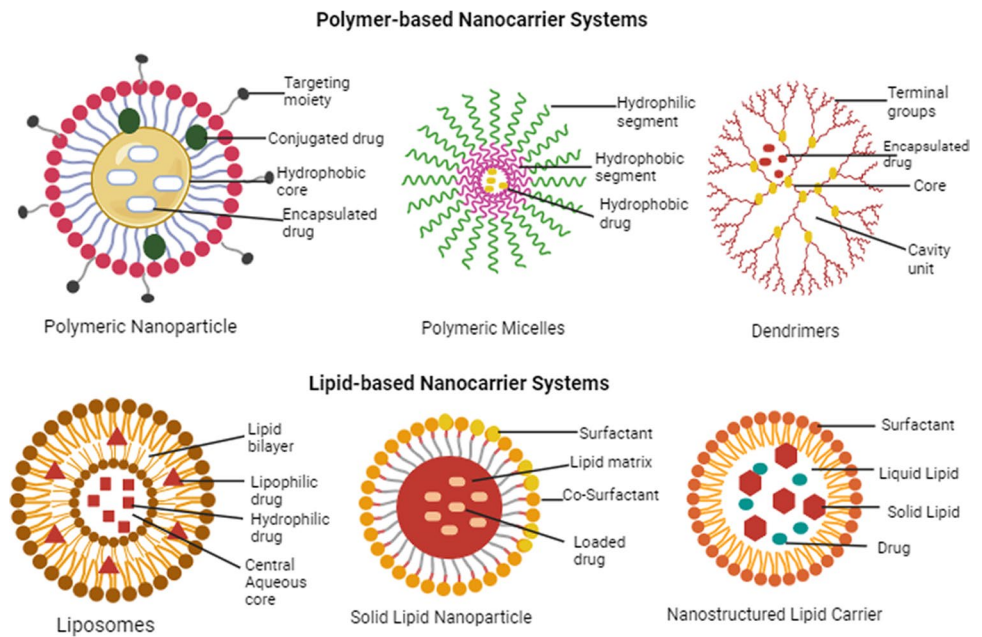
The average diameter of the polymeric nanoparticle-taxanes was discovered to be 45 nm (based on dynamic light scattering and transmission electron microscopy), and they were highly soluble in water. Moreover, they retained the anticancer effects of free taxanes and showed the features of active cell internalization. The tumour development delay in mice with tumours generated from A549 was investigated following the administration of polymeric nanoparticle-taxanes and/or ionizing radiation. In addition, the results also indicated that the polymeric nanoparticle-taxanes characteristics nominated it as a new and potent chemoradiation therapy agent and may have a useful and promising position in the treatment of human malignancies [49].

For targeted inhalation medication delivery, Elbatanony *et al*. developed afatinib-loaded biodegradable PLGA-based nanoparticles. Optimised drug-loaded nanoparticles were investigated for physicochemical characteristics (particle size ~ 180.2 nm; zeta potential ~ − 23.1 mV; entrapment efficiency ~ 34.4%). The good inhalable characteristics of Afatinib established by nanoparticle's median aerodynamic diameter of ~ 4.7 μm and fine particle fraction of ~ 77.8%, and this would result in effective particle deposition in deep lung areas. Optimised drug-incorporated nanoparticles showed sustained drug release characteristics with a cumulative release of ~ 56.8% after 48 h. In addition, cytotoxic studies exhibited that encapsulation of Afatinib into polymeric nanoparticles significantly enhanced cytotoxic potential in A549 and H460 cell lines (KRAS-mutated NSCLC cell lines). 3D tumour spheroid studies showed superior effectiveness of developed nanoparticles in tumour growth inhibition [50].

Zhong *et al.* investigated the chemotherapeutic efficiency of dual anticancer-loaded drugs (Sorafenib and Crizotinib) into nanoparticles by employing biodegradable triblock poly (ethylene glycol)-poly(-caprolactone)-poly(ethylene glycol) polymer. The Sorafenib- and Crizotinib-loaded nanoparticles showed less polydispersity, with a particle size of ~ 30.45 nm. *In vitro* drug release analysis revealed that the Sorafenib-Crizotinib nanoparticles released both drugs for a prolonged duration and in a sustained manner. The apoptosis rate of dual drug-loaded nanoparticles was higher when compared to free drugs in A549 and 4T1 cells. Compared to free drugs, co-drug-loaded nanoparticles showed a significant reduction of tumour volume and enhanced survival rate when administered to nude mice (xenograft model) with cancer induction by 4T1 cancer cells [51]. In another report, Tang *et al*. incorporated etoposide into Poly(ethylene glycol)-co-poly(sebacic acid) copolymers *via* melt polycondensation. The developed particles showed up to 40% of encapsulation efficiency of etoposide by weight. The release studies revealed an excellent release pattern for a pronged time of over 6 days. *In vitro* cytotoxic studies (human lung cancer cell line) showed significant anticancer activity. Intratumourally delivered drug-loaded nanoparticles showed suppression of lung tumour in an animal model (xenograft mouse) with a 100% survival rate after 31 days of treatment, and free etoposide showed 0% survival of animals after 24 days of observation [52].

Small interfering RNA (siRNA) blocks the expression of disease-causing gene, and it has become a potent therapeutic tool in recent years. By limiting first-pass metabolism, pulmonary distribution of siRNA-nanoparticles may reduce total medication dosage and off-target effects in comparison

Table II Summary of Nanoformulations Delivered Through Inhalational Route for Lung Cancer

Type of formulation	Polymers/Lipids	Name of drug	Method of preparation	Key findings	References
Microparticles	PLGA	Doxorubicin	w/o/w double emulsion-solvent evaporation technique	The developed formulation showed remarkably higher cytotoxicity in B16F10 cell-implanted mice than those in non-treated B16F10-implanted mice	[42]
	Sodium Alginate	Paclitaxel	Emulsification technique	Microparticles showed a reduction in the proliferation of A549 and Calu-6 cells in a concentration and time-dependent manner	[43]
	Sericin	Doxorubicin	water-in-oil (w/o) single emulsion method	Drug-loaded microparticles showed a significant reduction in number and size of the metastatic nodules (4T1 cells) in the lungs than free form of drug	[44]
	Polystyrene	Camptothecin	Emulsification followed by centrifugation and vacuum drying	Developed microparticles showed high lung and low systemic camptothecin concentrations at a dose ten times lower than that of a systemically administered dose of drug and resulted in a significant improvement in lung cancer in a rat model of lung cancer (orthotopic)	[45]
Polymeric Nanoparticles (NPs)	polylactide-tocopheryl polyethylene glycol 1000 succinate nanosystem	Crizotinib	Nanoprecipitation method	The developed nanoparticulate formulation significantly enhanced the anticancer activity of the drug and had a significant cytotoxic impact on NCIH3122 lung cancer cells in a dose-dependent manner	[48]
	Polylactic acid malvonate salt and amphiphilic block copolymer	Taxanes: Paclitaxel, Docetaxel	Ionic method	*In vivo* radiotherapeutic effectiveness was significantly enhanced by the injection (intravenous) of taxanes-loaded polymeric nanoparticles into the xenograft mice model	[49]
	PLGA	Afatinib	Emulsification method	The optimised afatinib-loaded nanoparticles exhibited enhanced internalization in A549 cell lines in comparison to free afatinib	[50]
	Triblock poly (ethylene glycol)-poly(-caprolactone)-poly(ethylene glycol)	Sorafenib and Crizotinib	Self-assembly in copolymerization	The co-drug-loaded polymeric nanoparticles significantly enhanced the anticancer efficacy, reduced side effects and promoted longer survival rate when delivered to nude mice xenograft model with 4T1 and A549 cancer cells	[51]
	Poly(ethylene glycol)-co-poly(sebacic acid)	Etoposide	Emulsification method	Developed nanoparticles exhibited efficient encapsulation and sustained drug release characteristics of etoposide and suppressed the growth of xenograft mice model of lung cancer	[52]
	poly-dimethylaminoethyl methacrylate and poly [oligo (ethylene glycol) methyl ether methacrylate]	siRNA	Living radical polymerization	The developed nanoparticles (star-siRNA) showed excellent aerosolisable characteristics and exhibited a significant reduction in lung tumour growth	[54]
Polymeric Micelles	Polyethyleneglycol-polylactic acid and Pluronic (P105)	Paclitaxel and ambroxol	Thin-film hydration method	The *in vivo* study proved that the aided therapeutic regimen of paclitaxel with ambroxol could promote the polymeric micelles to distribute more in the lungs and enhance the therapeutic effect in lung cancer	[57]
	tocopheryl succinate-polyethylene glycol 1000 and 5000 Da	Paclitaxel	Solvent evaporation	Drug-loaded micelles embedded in dry powder inhalational aerosolisable drug delivery system showed increased cytotoxicity and potential to be employed in lung cancer therapy than free form of paclitaxel	[58]
Dendrimers	carboxyl-terminated poly (amidoamine)	Doxorubicin	Conjugation method	After pulmonary delivery, the distribution of drug in the heart tissue was found to be reduced and showed improved lung accumulation/retention of DOX when compared to intravenous administration	[61]

Table II (continued)

Type of formulation	Polymers/Lipids	Name of drug	Method of preparation	Key findings	References
Liposomes	Polyethylene glycol-distearoyl phosphatidylethanolamine (DSPE-PEG2000) and PFV peptide	Daunorubicin and Dioscin	Film dispersion and the ammonium sulfate gradient method	The co-drug-loaded liposomes exhibited enhanced inhibitory effects on A549 cells, tumour metastasis, and vasculogenic mimicry channels	[68]
	Distearyl phosphatidylethanolamine-polyethylene glycol folate	Paclitaxel and Vinorelbine	Film hydration method	The folate-targeted and co-drug-loaded liposomal formulations exhibited high cellular uptake and enhanced cytotoxicity profile than free drug combination in LLC1 cell lines	[69]
	Bacterial (E. coli and L. casei)	Paclitaxel	Film method	After intratracheal administration, the developed formulation exhibited enhanced anticancer activity on the rat lung cancer model with the downregulation of VEGF and HIF-1α and the improvement of cancer cell apoptosis	[70]
	1,2-dipalmitoyl-sn-glycero-3-phosphocholine and cholesterol	Osimertinib	Thin-film hydration	Inhalable osimertinib-loaded liposomes were found to be significantly more effective against H1975 cell lines in comparison to free drug	[71]
	Stearyl amine, PLX 188 and HPCD	Curcumin	Spray drying technique	The optimised preparation showed rapid absorption and enhanced drug retention in the lung as compared to free curcumin powder, resulting in promising alternative in pulmonary lung cancer treatment	[72]
	Dioleoyltrimethylammoniumpropane and dipalmitoylphosphatidylcholine	CpG oligonucleotide	Thin-film hydration	The encapsulation of CpG in liposomes (cationic lipid-based) showed a significant reduction in tumour growth in the murine B16F10 model (metastatic lung cancer) after pulmonary administration	[74]
	L-α phosphatidylcholin, cholesterol, polyethylene glycol 2000 and dido decyl dimethyl ammonium bromide	Withaferin A	Thin-film hydration	Functionalization of withaferin A-loaded nanoliposomes utilising AS1411 aptamer improved stability and cellular uptake by tumour cells compared to non-aptamer-based liposomes	[75]
Niosomes	Span 60, Tween 60 and cholesterol	Ciprofloxacin	Remote loading method	Ciprofloxacin entrapped in niosomes showed significantly lower cytotoxicity (MTT assay) in human lung carcinoma cell lines (A549) in comparison to free drug	[78]
	Span60, Tween 65, Cholesterol and glycerol	Gemcitabine and cisplatin	Simple heating method	The optimised dual drug-loaded formulation reduced cytotoxicity effects against MRC5 and A549 cell lines when compared with the control (gemcitabine and cisplatin alone)	[74]
	Span 60 and cholesterol	Nintedanib	Thin-film hydration method	The optimised niosomal formulation displayed a significant cytotoxic effect on A549 cells and also showed good aerodynamic properties suitable for pulmonary drug delivery	[80]
Nanoemulsion	Palm oil ester (POE)	Quercetin	High-energy emulsification method	The results showed that POE-based nanoemulsion encapsulating quercetin has shown the potential for inhalational drug delivery for lung cancer therapy	[85]
	dl-α-tocopheryl acetate, soybean oil, polysorbate 80, ferric chloride and hyaluronic acid	Paclitaxel	High-pressure homogenization method	The investigated formulation showed high solubilization capacity of poorly soluble drug paclitaxel and inhibited tumour growth because of the specific tumour-targeting ligand hyaluronic acid (for CD44-overexpressed cancer cells)	[86]

Table II (continued)

Type of formulation	Polymers/Lipids	Name of drug	Method of preparation	Key findings	References
Solid Lipid Nanoparticles	Compritol/poloxamer 407	Erlotinib	Hot Homogenization method	The developed drug-loaded SLNs enhanced the cytotoxicity of erlotinib in the human alveolar adenocarcinoma epithelial cells (A549)	[89]
	Folate-grafted copolymer of polyethylene glycol and chitosan	Paclitaxel	Homogenization method	The coated paclitaxel-loaded SLNs displayed a positive pharmacokinetic profile following pulmonary administration and longer retention in the lungs after in vivo investigation	[90]
	siRNA encapsulation	small interfering RNA	Solvent evaporation method	Thin-film freeze-drying method showed a promising approach to preparing aerosolisable dry powder of drug-loaded lipid nanoparticles without a negative effect on siRNA	[91]
Nanostructured lipid carrier (NLCs)	Compritol, oleic acid, soybean phosphatidylcholine, DOTMA	Paclitaxel and Doxorubicin	Melted ultrasonic dispersion method	Co-delivery of paclitaxel and doxorubicin exhibited a high potential for tumour-targeting and showed potent antitumour activity in the NSCLC animal model	[20]
	Compritol, Miglyol, Sodium taurocholate	Celecoxib	High-pressure homogenization	The celecoxib-loaded NLC released the drug in a controlled manner and exhibited time-dependent cytotoxicity against A549 cancer cells	[96]

to oral or parenteral delivery methods. On the other hand, effective siRNA delivery straight to the lung is somewhat complicated [53]. Ma *et al.* developed a miktoarm star polymer-siRNA nanoparticle and studied the effects of the complexed star polymer on lung cancer cells' gene silencing activity, intracellular trafficking, and cell uptake. The developed nanoparticles showed a hydrodynamic diameter of 14.4 nm with a PDI of 0.18 and a surface charge of $+8.5$ mV. According to the findings of the *in vitro* research, star-siRNA nanoparticles integrated into lung cancer cells and bypassed the endo-lysosomal route to prevent the expression of the target gene in these cells. In mouse lung tumours, nebulized star-siRNA nanoparticles collected in the lungs suppressed PLK1 and βIII-tubulin expression, therefore postponing the aggressive development of the tumours. These findings showed that aerosol administration of star-siRNA nanoparticles is a viable therapeutic approach for the management of lung tumours [54].

Polymeric Micelles Micelles feature a hydrophobic interior core that can be utilised to encapsulate medications with limited solubility in order to enhance the dissolution of aqueous mediums. These nanocarriers can encapsulate and stabilize poorly active pharmaceutical ingredients, increase targeting to the lungs, decrease adverse effects, and improve treatment effectiveness in lung diseases when administered by inhalation route [55]. For clinical investigations, drug-loaded polymeric micelle-based formulations are in different stages, and some of these micelles have demonstrated potential anticancer activity [56]. In an intelligent approach, He *et al.* developed paclitaxel-loaded micelles utilising polyethylene glycol-polylactic acid and Pluronic P105. The functional activity of developed micelles was designed by incorporating biologically active ambroxol. Ambroxol was added to change the microenvironment of the lungs by regulating the pulmonary surfactant's secretion. The developed nanomicelles displayed particle size of ~ 16.7 nm, round-shaped particles, low CMC value and sustained drug release characteristics. *In vitro* findings suggested that ambroxol might boost the secretion of pulmonary surfactant and LC3 protein and enhance the cytotoxic activity against lung cancer cell lines (A549 cells). *In vivo* results further indicated that the dual drug-loaded micelles improved the drug distribution in the lungs and enhanced the therapeutic efficacy in lung cancer [57].

As an alternative to conventional systemic chemotherapy, Rezazadeh M. *et al.* formulated a novel micelle formulation of paclitaxel by using tocopheryl succinate-polyethylene glycol (1000 and 5000 Da). Lactose was incorporated into an optimised micellar formulation employing a spray drying procedure to obtain the spherical shape of the particles for easy inhalation. Particle size ranged between

102 and 196 nm, while zeta potential was between -9.4 and -13.8 mV. *In vitro* drug release studies revealed a very slow release of the drug, and $\sim 30\%$ was released after 72 h. Cytotoxicity results on A549 (lung cancer cells) demonstrated enhanced cytotoxic activity of paclitaxel-loaded micelles when compared with the free drug [58].

Dendrimers: Dendrimers are new polymer-based nanostructures with highly branched 3D structures and several functional group surfaces, making them suitable for drug delivery applications. They are being investigated to reduce medication toxicity by targeting with improvement in therapeutic efficacy [59]. Dendrimer's structure helps in the entrapment of chemotherapeutic drugs, which can be engineered for active and passive drug targeting through manipulable surfaces, and this may aid in the development of effective therapeutic as well as diagnostic approaches for cancer therapy [60]. Holt *et al*. developed polyamidoamine-based nanoparticles and attached a peptide with binding capability for lung cancer cells-based dendrimers. The dendrimers (positively charged) electrostatically bonded with nucleic acids (negatively charged). It was found that the developed platform complexed with DNA plasmids *in vitro* and transfected lung cancer cell lines. *In vivo* results established the transfection efficiency of the developed dendrimer-based system in RAG1KO mice [61]. A possible way to increase the therapeutic efficacy of DOX by lowering systemic toxicity is to combine it with carboxyl-terminated poly (amidoamine) dendrimers. The results showed an increase in the efficacy of DOX therapy in the mouse model of melanoma lung metastases (B16-F10) when administered through the pulmonary route, indicated by the decrease in tumour weight, and also showed a higher and longer accumulation/retention of the drug in lungs when compared with intravenous administration [62]. To entrap and transport anticancer drugs, alone or in combination with another substance or therapeutic nucleotide (siRNA/DNA), a variety of polypropylene imine dendrimer types have been developed. Cancer biomarkers may be utilised to make polypropylene imine dendrimers, which may then be employed as biosensors to identify different cancer types early and at different stages [63].

Lipid-Based Nanocarrier Systems

Drug development and cancer therapy have both shown a great deal of interest in lipid-based nanocarrier systems such as liposomes, solid lipid nanoparticles (SLN), niosomes and nanostructured lipid carriers (NLC) [64]. These nanocarriers have less toxicity, can encapsulate and transport both hydrophobic and hydrophilic drug molecules, and can prolong the length of medication's efficacy by having a longer half-life and controlled drug release characteristics [65].

Liposomes Lipid bilayer-based vesicles known as liposomes are frequently used as preferred delivery systems for both hydrophobic and hydrophilic bioactive substances [66]. Targeted drug delivery and controlled drug release have both been made possible by advancements in liposomal vesicle formation. This property is essentially helpful for cancer treatment, and liposomes have been found to enhance the therapeutic efficacy of anticancer drugs through the pulmonary route in lung cancer [67]. To treat NSCLC, targeted daunorubicin and dioscin co-delivery-based liposomes were developed using film dispersion and ammonium sulfate gradient technique. Dioscin was encapsulated within the lipid bilayer, and daunorubicin was encapsulated in the hydrophilic area of liposomes. This was modified with PFV peptide for targeted drug delivery. The developed liposomal formulation exhibited excellent physicochemical characteristics with enhanced cellular uptake and strong cytotoxicity against A549 cells. The targeted dual drug-loaded liposomes exhibited significant anticancer effects in tumour-bearing mice (BALB/c nude mice) [68]. Karpuz *et al.* developed a theranostic approach utilising folate-targeted liposomal platform and encapsulating Tc-99 m radiolabelled, vinorelbine and paclitaxel for NSCLC. *In vitro* cell line studies demonstrated significant cytotoxicity and enhanced cellular uptake of dual drug-loaded liposomes in LLC1 cells when compared with free drugs. The biodistribution studies conducted in C57BL/6 mice (NSCLC tumour bearing), the uptake of radiolabelled and actively folate-targeted, dual drug-loaded nanoliposomal formulation showed a higher presence in tumour tissues when compared to the formulation without active targeting [69].

For inhalation therapy of primary lung cancer, Zhang M *et al.* developed a novel paclitaxel-in-liposome-in-bacteria, a live drug-loaded carrier. Using electroporation, liposomal paclitaxel was internalized into bacteria (*L. casei* or *E. coli*), and this internalization had no effect on the growth of the mentioned bacteria. Drug-loaded liposomal formulation with E. coli showed the strongest inhibitory effect on A549 lung cancer cell lines. Paclitaxel-loaded bacteria in liposomes delivered the contents into the cells faster than the single components. E. coli-based formulation also exhibited the strongest anticancer activity on primary lung cancer evaluated on rat model of lung cancer [70]. Osimertinib's systemic delivery frequently leads to inadequate medication levels at the specific location in case of lung cancer and is linked to systemic adverse effects. The development of the drug's active and passive liposomes through the inhalational route showed a reduction in systemic exposure with accumulation at the tumour site. Active liposomes exhibited better encapsulation (78%) than passive liposomes (25%), and both showed outstanding aerosolization efficiency with an aerodynamic diameter of 4 μm and fine particles of

82%. Osimertinib's active and passive targeted liposomes decreased IC_{50} in H1975 cells by 2.2 and 1.2-fold in comparison to free drug, respectively. The 3D spheroid studies demonstrated that the developed liposomes were found effective in inhibiting tumour growth [71]. Adel *et al.* developed curcumin-loaded proliposomes using a nano-spray dryer technique; lecithin and cholesterol as vesicle matrix components; stearyl amine as positive charge inducer, poloxamer 188 as a surfactant, and hydroxypropyl-beta-cyclodextrin as a carrier to produce freely flowing powders. The optimised formulation had a percentage yield of 52.72 to 81.87%, particle size of 160 to 365 nm, zeta potential between -25.50 and -38.90 mV, encapsulation efficiency of 90.15 to 102.20%, and more than 95% *in vitro* drug release. The mass median aerodynamic diameter and fine particle fraction of spray-dried proliposomes were found to be 2.10 μm and 54.35%, respectively. A lung pharmacokinetic study revealed a higher AUC value of the developed formulation in comparison to free curcumin powder. The cytotoxicity of the optimised curcumin-loaded proliposomal formulation against the A-549 cell line revealed a comparably low IC50 value in comparison to free curcumin [72].

Unlike usual therapies by small organic molecules, which usually target proteins and provide transient effects, nucleic acid therapeutics can attain specific, long-lasting and remedial effects [73]. Loira-Pastoriza *et al.* used a cationic lipid, dioleoyltrimethylammoniumpropane and dipalmitoylphosphatidylcholine to encapsulate unmethylated oligodeoxynucleotides with CpG motifs and polyinosinic-polycytidylic acid double-stranded RNA in liposomes for local delivery in lung cancer. The cationic lipid in the optimised liposomes produced a positively charged particle ($+59$ mV) with a size of less than 200 nm, a low polydispersity index of 0.107, and an encapsulation efficiency of 98.2%. Additionally, *in vivo* studies on the pulmonary administration of CpG revealed that, in comparison to its intraperitoneal injection, the lungs produced more granzyme B, a pro-apoptotic protein, T helper type 1 cytokines, and chemokines. CpG encapsulation in cationic lipid-based liposomes significantly reduced tumour growth in metastatic lung cancer (murine B16F10 model) after pulmonary administration [74].

In recent work, Abeesh P *et al.* functionalized the PEGylated nanoliposomes loaded with withaferin A (PWN) for targeted drug administration using an innovative targeting approach AS1411 (anti-nucleolin aptamer) and was prepared by thin-film hydration technique. With an encapsulation efficiency of 82.5%, the produced formulation PWN contained spherically shaped nanosized particles with a size of ~118 nm. The results of the TEM investigation showed that PWN possesses homogeneous, spherical nanoparticles with good dispersibility. The *in vivo* study conducted on lung metastasis in C57BL/6 mice showed considerably increased anti-metastatic effectiveness of PWN and survival

rate when compared to groups given free medication. In mice with metastatic lung tumours treated with PWN, the expression levels of IL-6, TNF-α, and IL-1 β were down-regulated. The results exhibited the significant potential of nanoliposomal formulation of withaferin A for targeting metastatic tumours utilising the AS1411 functionalization with PEGylation [75].

Niosomes The vesicular structures known as niosomes are based on nonionic surfactants and are currently used as cutting-edge drug delivery systems. The size of niosomes can be varied, and nanometric scale is mostly used for drug delivery applications [76]. Niosomes are biodegradable and biocompatible in nature. They provide sustained and controlled release of drug molecules, can be modified to target a specific location in the body, and are more stable with an extended shelf life in comparison to other vesicular structures. The capability of niosomes to encapsulate and transport drugs has generated a lot of interest in formulation scientists in the recent decade [77]. Using various combination of nonionic surfactants and cholesterol, ciprofloxacin hydrochloride was encapsulated in niosomes and evaluated for its suitability in pulmonary drug delivery. Formulations consisting of Tween 60 and Span 60 with 40 mol% cholesterol demonstrated not only high encapsulation efficacy and stability but also a fine particle fraction and nebulization efficiency of around ~77.9% and ~61.9%, respectively. Against a number of lung pathogens, niosomal ciprofloxacin exhibited a lower minimum inhibitory concentration than free ciprofloxacin. Drug-loaded niosomal formulation showed significantly higher cytotoxicity against A549 cell lines (human lung carcinoma) when compared with the free drug [78].

Saimi *et al.* developed a low-dosage niosomal formulation for the treatment of lung cancer, encapsulating gemcitabine and cisplatin. This formulation was prepared by utilising a simple heating technique and optimised by D-optimal mixture design. The optimal Gemcitabine-cisplatin formulation showed -15.28 mV of zeta potential, 0.16 of PDI and 166.45 nm of size, and it was found to be stable at 27 °C for 90 days without any phase separation. The formulation's capacity to aerosolize was demonstrated by the aerosol output, which was 96.22%. Using the dialysis bag diffusion technique, an *in vitro* drug release study revealed controlled release for both drugs for up to 24 h. The results of cytotoxicity studies revealed that the optimised formulation showed reduced cytotoxicity activity against both MRC5 (normal lung cell line) and A549 (lung cancer cell line) when compared with the combination of free drugs [79]. In another study, Shukla *et al.* developed nintedanib-loaded niosomes using thin-film hydration technique for inhalational administration for the management of lung cancer. The optimised

niosomal formulation showed a size of ~ 195.5 nm with efficient aerodynamic qualities, sustained and prolonged drug release characteristics. Niosomes loaded with nintedanib demonstrated considerably greater cytotoxicity against A549 cell lines, which was supported by 3D spheroids (demonstrated higher inhibition in tumour growth for niosomal formulation in comparison to control) [80].

Nanoemulsions Nanoemulsions are colloidal dispersion systems that consist of immiscible liquids with emulsifiers (surfactants and co-surfactants) to create a single phase that is thermodynamically stable. Numerous studies on nanoemulsions as drug delivery systems have been in the literature for different routes of administration [81]. Nanoemulsion droplet size ranges between 10–200 nm. Nanoemulsion-based drug delivery systems are designed to enhance the solubility and bioavailability of active pharmaceutical ingredients [82]. Because they have a high drug loading efficiency, enhanced pulmonary deposition and retention, and lengthen the time that active compounds spend in the lung tissues, nanoemulsions have the potential to deliver active compounds to the lungs [83, 84]. Arbain *et al.* developed quercetin-loaded nanoemulsions based on palm oil ester employing high-energy emulsification method and optimised by D-optimal mixture design for pulmonary drug delivery. The optimised nanoemulsion showed an aerodynamic diameter of 4.25 μm, aerosols rate of 0.19 g/min and aerosols output of 99.31%. The developed nanoemulsion also showed good stability when stored at 4℃ for a duration of 90 days. The characterization results revealed the potential of palm oil ester–based nanoemulsion encapsulating quercetin for pulmonary drug delivery in lung cancer therapy [85]. Hyaluronic acid-complexed paclitaxel nanoemulsions were fabricated by Kim *et al.* using ionic complexing technique to solve the solubility issue and for lung cancer targeting. Paclitaxel nanoemulsions were prepared by high-pressure homogenization technique and contained DL-tocopheryl acetate, polysorbate 80, soybean oil, hyaluronic acid and ferric chloride. The developed nanoemulsion showed a droplet size of ~ 85.2 nm and a zeta potential of ~ 35.7 mV. The content of paclitaxel was 3.0 mg/mL, and the encapsulation efficiency was ~ 00%. *In vivo* anticancer activity of the hyaluronic acid-complexed paclitaxel based nanoemulsions in nude mice showed a significant reduction in tumour volume and showed the potential application of this platform for the treatment of NSCLC [86].

Solid Lipid Nanoparticles Solid lipid nanoparticles (SLNs) are lipid-based nanoparticles with diameters ranging between 50 and 1000 nm and can encapsulate active pharmaceutical ingredients with appropriate solvent and lipids, which are solid at room temperature. SLN-based delivery systems have emerged to overcome many drawbacks, such as complicated production methods, low percentage entrapment efficiency and difficulty in large-scale manufacture of other lipid carrier systems such as liposomes and ethosomes [87]. When compared to conventional colloidal carriers, SLNs have a number of distinguishing characteristics, including reduced toxicity, high surface area, delayed/sustained drug release, enhanced cellular penetration, and capability to enhance the solubility, bioavailability and targeting potential of pharmaceuticals [88]. Tyrosine kinase inhibitors such as erlotinib were loaded into SLN-based formulation and transformed into dry powder inhalers by Bakhtiary *et al.*, employing optimised concentrations of poloxamer 407/Compritol. The SLNs showed a size of 100 nm with a spherical shape and an entrapment efficiency of 78.21%. The optimised formulation displayed significant anticancer activity against A549 cells. To develop the SLN-based dry powder inhaler, the erlotinib-loaded SLNs were spray-dried into microparticles (1–5 μm). The dried particles showed desirable flow characteristics and aerodynamic attributes. Hausner's ratio (1.119), Carr's Index (10.66) and Next Generation Impactor results (fine particle fraction ~ 24.25%) established deep inhalational patterns of developed SLN-based microparticles of erlotinib [89].

Rosiere *et al.* formulated paclitaxel-loaded SLN with a new folate conjugated copolymer of polyethylene glycol and chitosan and obtained encapsulation efficiency of ~ 100%, mean particle diameter of ~ 250 nm, and zeta potential of + 32 mV. After pulmonary administration, the coated SLN penetrated M109 tumours *in vivo*, HeLa and M109-HiFR cells *in vitro*, and entered into folate receptor-expressing cells. The results demonstrated that after pulmonary drug delivery *in vivo*, the developed SLNs showed a favourable pharmacokinetic profile with prolonged pulmonary exposure of paclitaxel lasting up to 6 h and little systemic drug distribution [90]. Another investigation was conducted to develop dry, aerosolisable lipid nanoparticle powder of siRNA using a thin-film freeze-drying process. The siRNA-loaded SLNs were prepared using the solvent evaporation technique. The particle size, PDI, and zeta potential of SLNs were well-preserved after subjecting them to thin-film freeze-drying and reconstitution. The function of the siRNA-encapsulated in SLNs was not negatively affected by the thin-film freeze-drying process. It was concluded that the thin-film freeze-drying technique was a feasible approach for producing dry, aerosolisable lipid nanoparticles for pulmonary drug delivery [91].

Nanostructured Lipid Carriers To address some drawbacks of SLNs, a new generation of lipid nanoparticles called Nanostructured Lipid Carriers (NLCs) were developed. NLC also exists as a solid lipid matrix at body temperature

in addition to ambient temperature. Instead of using only a solid lipid, a part of the solid lipid is substituted with oil, resulting in a less ordered lipid matrix that improves drug loading and avoids drug leakage during storage [92, 93]. NLCs are being studied as drug delivery carriers for a variety of therapeutic applications due to their excellent biocompatibility and safety profiles. Due to their capability to enhance the physical and chemical stability of active pharmaceutical ingredients and to significantly increase the potential of therapeutically useful substances, NLCs are also being explored for different chemotherapeutic agents [94]. NLCs were developed in lung cancer to treat p-glycoprotein (P-gp) efflux and drug resistance, which is typically linked to overexpression of the MRP1 and BCL2 proteins, which are responsible for the drug efflux from cancer cells. To solve these problems, Garbuzenko et al. fabricated inhalation pulmonary delivery of anticancer drugs in conjunction with pump suppressors and non-pump cellular resistance. To evaluate this hypothesis, a nanoparticle-based delivery system consisting of DOX as cell death inducer and antisense oligonucleotides specifically targeted to MRP1 mRNA as pump resistance suppressor and to BCL2 mRNA non-pump resistance suppressor was developed and evaluated on a murine model (orthotopic) of human lung carcinoma. The results demonstrated the high antitumour activity and fewer adverse effects of the developed inhalable platform, which was not achievable by individual components administered separately [95]. Paclitaxel and DOX are often used together to treat solid tumours; however, the effectiveness of the free medication in combination is less due to non-targeting and improper pharmacokinetic profile. To combat the multidrug resistance brought on by a single treatment, an NLC-based delivery method for co-encapsulating paclitaxel and DOX was developed. Dual drug-loaded NLC-based formulation exhibited the highest cytotoxic activity in vitro against NCL-H460 human NSCLC cell lines in comparison to single drug-loaded NLCs. In vivo investigations on NSCLC animal models further established the potential of co-drug-loaded NLCs in the management of lung cancer [20]. Patlolla et al. encapsulated celecoxib into NLCs employing a high-pressure homogenization technique. Drug-loaded NLCs showed particle size of ~ 217 nm and entrapment efficiency of > 90%. The drug-loaded NLC released the celecoxib in a sustained and controlled manner; in vitro aerosolization of formulation showed a fine particle fraction of ~ 75.6% and aerodynamic diameter of ~ 1.6 μm. The developed NLCs showed time and dose-dependent anticancer activity against A549 cells. Nebulization of celecoxib-loaded NLCs exhibited fourfold higher AUC(t)/D in lungs in comparison to celecoxib solution. The systemic clearance of drug-loaded NLCs was slower (0.93 l/h) when compared to the drug solution (20.03 l/h) [96].

Latest Investigations Related to Nanocarrier-Mediated Inhalational Drug Delivery for Lung Cancer

Much recent research work has been conducted related to polymer and based nanocarriers for the management of lung cancer through the pulmonary route of drug delivery. The section below provides a detailed review of the latest investigations performed and is summarised in Table III.

In a very recent research work airway, mucus barrier was targeted for improvement in anticancer activity of quercetin. Tang et al. developed an inhalable silk fibroin (modified with Pluronic F127) nanoparticles of quercetin. The optimised nanoparticles showed particle size of ~ 200 nm with stable characteristics ascertained by negatively charged surfaces (zeta potential of ~ − 26.3 mV) and showed sustained release characteristics up to 24 h (~ 80%). Superior mucus penetrating capability was shown by Pluronic F127 coated nanoparticles in artificial mucus and monolayer cell model (Calu-3) established by photobleaching assay and transepithelial transport test. In vivo anticancer activity in mice melanoma lung metastasis model showed an enhanced therapeutic effect of coated nanoparticles was significantly improved in vivo in comparison to non-coated nanoparticles [97].

Gonsalves et al. developed an inhalable polymer-based nanoparticle (poly lactic-co-glycolic acid) formulation with Infasurf® (a biomimetic lung surfactant) (LS) for lung cancer therapy. The developed formulation showed a size of ~ 188 nm and was found to be stable in phosphate buffer saline, Gamble's solution (simulated lung fluid) and serum. Paclitaxel-loaded in Infasurf® lung surfactant exhibited burst release characteristics, and gemcitabine hydrochloride entrapped in polymeric core (PLGA) released the drug in a sustained manner. In vivo studies showed greater retention of lung surfactant-coated nanoparticles in the lungs of cancerous mice (C57BL/6 WT) compared to uncoated nanoparticles after intranasal administration. The results confirmed that Infasurf® coating is a potential platform for covering polymeric nanoparticles to prevent their fast lung clearance and enable prolonged pulmonary drug delivery [98].

siRNA-based therapeutics are showing significant therapeutic capability. However, hydrophilicity, high molecular weight, instability against nuclease and the presence of intrinsic negative charge hinder the translation of siRNA-based products into clinical developmental phases. Liu et al. designed a Tetra(piperazino) fullerene epoxide-based nanocomplex for lung delivery of siRNA through inhalational route. The development and optimisation of this was carried out by molecular dynamic simulation. The formulated siRNA-based nanocomplex protected the encapsulated siRNA against degradation by nucleases, improved

Table III Latest Investigations on Nanocarrier Mediated Inhalational Drug Delivery in Lung Cancer

Type of formulation	Polymers/lipids	Name of drug	Method of preparation	Key findings	References
Polymeric nanoparticles	Silk fibroin	Quercetin	Sonication followed by freeze-drying	Silk fibroin nanoparticles modified with Pluronic F127 loaded with quercetin showed improved penetration ability in artificial mucus and monolayer model (Calu-3 cell) with enhanced therapeutic effect *in vivo*	[93]
Polymeric nanoparticles	Poly(D,l-lactide-co-glycolide)	Paclitaxel, gemcitabine	Thin-film method	Paclitaxel loaded in Infasurf® lung surfactant showed burst release characteristics, and gemcitabine hydrochloride entrapped in polymeric core (PLGA) released the drug in a sustained manner and *in vivo* studies showed greater retention of lung surfactant coated nanoparticles in the lungs of cancerous mice (C57BL/6 WT) compared to uncoated nanoparticles	[94]
Polymeric nanocomplex	Tetra(piperazino) fullerene epoxide	siRNA	Solvent evaporation and complexation	The developed nanocomplex protected the encapsulated siRNA against degradation by nucleases, improved cellular uptake, enhanced gene knockdown efficiency, and prolonged the lung retention of siRNA after pulmonary delivery	[95]
Lipid nanoparticles	1,2-distearoyl-sn-glycero-3-phosphocholine	siRNA	Dialysis, evaporation and spray drying	This study showed the successful spray drying process of lipid nanoparticles encapsulating siRNA and maintained the integrity with strong gene silencing capability on mRNA as well as protein levels demonstrated by *in vitro* and *ex vivo* studies	[20]
Liposomes	Soya lecithin	7-ethyl-10-hydroxyl camptothecin and curcumin	Microfluidic method	The developed formulation showed enhanced antiproliferative outcome, enhanced induction of cell apoptosis and improved arrest of cell cycle (in A549 cells) in comparison to single drug treatments evaluated *in vitro*	[96]

Table IV Clinical Trial Studies for Lung Cancer Therapy

Drug	NCT number	Aim of the study	Inference	Study phase	Status
Afatinib	NCT01953913	Evaluation of afatinib in advanced NSCLC patients with mutation in epidermal growth factor receptor (EGFR)	Afatinib's safety was assessed in patients with locally advanced NSCLC who have an EGFR mutation but have never received any treatment with an EGFR-tyrosine kinase inhibitor	Phase 3	Completed
Crizotinib, Entrectinib	NCT04603807	Comparison of the efficacy and safety of entrectinib and crizotinib in patients with advanced ROS1 NSCLC	Patients with advanced or metastatic ROS1 NSCLC participated in the study to examine the efficacy and safety of entrectinib with crizotinib. The patients self-administered oral entrectinib or crizotinib. Treatments were continued until the worsening of the illness	Phase 3	Completed
Doxorubicin hydrochloride, Docetaxel, Cisplatin	NCT00082472	Evaluation of doxorubicin plus intravenous docetaxel and cisplatin in patients with NSCLC	This study evaluated the extra toxicities, determined whether inhaled chemotherapy may be added to a typical intravenous chemotherapy regimen, and provided preliminary signs of the combination medication's effectiveness	Phase 1 Phase 2	Completed
Doxorubicin hydrochloride	NCT00004930	Evaluation of inhaled doxorubicin hydrochloride in the treatment of patients with primary lung cancer	Maximum tolerated dose and dose for phase II were evaluated for inhaled doxorubicin hydrochloride administered after every 3 weeks in patients with primary lung cancer	Phase 1	Completed
Paclitaxel, Gemcitabine, Cisplatin	NCT02996214	Paclitaxel liposome for squamous NSCLC	This study compared the safety and efficacy of gemcitabine and cisplatin with paclitaxel liposome and cisplatin as first-line therapy for advanced squamous NSCLC in order to establish which drug was more effective and safer	Phase 4	Active
Enzastaurin, Pemetrexed, Docetaxel, Carboplatin	NCT00308750	Efficacy and safety Evaluation of combination chemotherapy for the management of advanced NSCLC	The efficacy and safety evaluation of enzastaurin with pemetrexed, plus carboplatin, pemetrexed with carboplatin, or docetaxel plus carboplatin, as well as evaluation of any potential adverse effects in the studied chemotherapy for NSCLC	Phase 2	Completed
Pemetrexed disodium, Bevacizumab	NCT00268489	Evaluation of pemetrexed disodium and bevacizumab in the treatment of patients with stage III/ stage IV NSCLC	The combined chemotherapeutic medication was administered in stage III/stage IV NSCLC patients and results showed the inhibition of the development of cancer cells by interfering the blood supply to the tumour	Phase 2	Completed
Simvastatin, Gefitinib	NCT00452244	Evaluation of gefitinib with or without simvastatin in NSCLC	Simvastatin and gefitinib combined therapy demonstrated improvement in anticancer activity when compared to gefitinib alone	Phase 2	Completed
Sotorasib	NCT05311709	Evaluation of sotorasib in advanced KRASG12C-mutated NSCLC patients with comorbidities	Evaluation of translational understanding about the mechanisms of relapse and differences in responses, including variations across patients with several co-occurring mutations, by sotorasib in KRASG12C-mutated NSCLC stage III/IV	Phase 2	Active

Table IV (continued)

Drug	NCT number	Aim of the study	Inference	Study phase	Status
Lorlatinib	NCT05297890	Evaluation of lorlatinib in participants with ROS1-positive NSCLC	Evaluation of the efficacy and safety of lorlatinib monotherapy in crizotinib and platinum-based chemotherapy for the management of locally advanced ROS1-Positive NSCLC patients	Phase 2	Active

cellular uptake, enhanced gene knockdown capability and prolonged the lung retention of siRNA after pulmonary delivery. Through the introduction of siRNA programmed death-ligand 1, this nanostructure significantly inhibited the advancement of metastatic lung cancer without any noticeable adverse event and toxicity observations in a mouse model of lung cancer [99]. In another study, Zimmermann *et al*. developed spray-dried lipid nanoparticles of siRNA for pulmonary delivery. Spray drying was conducted using lactose solution (5%, m/V), and mass median aerodynamic diameters of all powders obtained were between 2.85 and 2.9 µm. The nanoparticle size after redispersion of spray-dried powders obtained was ~ 200 nm and a PDI value of ~ 0.3. The spray-dried lipid nanoparticles penetrated the mucus layer of the lungs with the maintenance of bioactivity for more than 90% protein downregulation in a lung adenocarcinoma cell line. Additionally, the developed nanoparticles effectively achieved gene silencing (up to 50%) of the house keeping gene (GAPDH) performed in *ex vivo* lung slices (human precision cut) without any increase in cytokine levels [100].

Gao *et al*. developed a liposome-based co-delivery formulation of 7-ethyl-10-hydroxyl camptothecin (SN38) prodrug and curcumin for lung cancer therapy *via* the pulmonary route of drug delivery. SN38 was attached to TAT (cell-penetrating peptide) *via* polyethylene glycol linker to produce SN38 prodrug. Co-drug-loaded liposomes were prepared by the microfluidic method and exhibited a vesicle size of ~ 171.21 nm. *In vitro* anticancer cell line studies on A549 cells showed enhanced antiproliferative activity, enhanced induction of cell apoptosis and improved arrest of the cell cycle for developed liposomal formulation in comparison to single drug treatments. In the lung cancer model of BALB/c mouse, the combination drug-loaded liposomes showed significant inhibition of tumour [101].

Clinical Studies

Even though nanocarriers have a lot of potential for the management of lung cancer through the pulmonary route, there are not enough clinical investigations on them yet. As a result, there is a need to broaden their scope of applicability to include clinical trials under suitable ethical guidelines. Some of these approaches have been evaluated in various clinical trials awaiting results or with recently published results, while most of them are still in clinical trials in the recruiting phase (https://clinicaltrials.gov/). Some of the clinical trials related to pulmonary administration and lung cancer are summarised in Table IV.

Table V Patented Drug Formulations for Lung Cancer Therapy

Patent number	Year	Area of the invention	Inference	Reference
US20210046090	2021	Preparation method and evaluation of liposomal freeze-dried powder of ergosterol in combination with gefitinib	The developed formulation induced apoptosis in NSCLC cells. RGG cyclic /R8 peptide modified active targeted formulation exhibited stability, *in vitro* anticancer activity and *in vivo* pharmacodynamic efficacy in xenograft mouse model	[101]
CN111617048	2023	Preparation and evaluation of erlotinib sustained release formulation for NSCLC	The developed formulation of erlotinib enhanced the drug's bioavailability, improved its curative impact and enhanced the safety of erlotinib administration in NSCLC	[103]
IN201741005560	2018	Magnetic nanoparticle-based formulation of irinotecan for targeted delivery of drug in the management of lung cancer and other pulmonary diseases	External magnetic system–guided magnetic nanoparticles of irinotecan enhanced drug retention duration, boosted effectiveness, reduced adverse effects and showed potential for lung cancer therapy	[104]
CN108721251	2020	Preparation and evaluation of erlotinib encapsulated beta-cyclodextrin chitosan/hyaluronic acid complexed with nanoparticle drug carrying system	The observations showed the potential of beta-cyclodextrin chitosan/hyaluronic acid complexed with nanoparticles consisting of erlotinib in the treatment of NSCLC	[105]
EP3265063	2018	Liposomal formulation of docetaxel and doxorubicin for the management of NSCLC	The dual drug-loaded liposomal formulation (composed of unsaturated phospholipid, cholesterol, cationic lipid, and pegylated phospholipid) showed the potential in the management of NSCLC	[106]
CN109512821	2021	Preparation and application of nanomicelle injection formulation of crizotinib and 17-AAG composite polymer nanomicelle	The developed formulations showed particle size between 20 and 200 nm, enhanced stability, prolonged blood circulation time and exhibited potential in the management of drug-resistant ALK NSCLC	[107]
KR10158534500000	2016	Preparation and application of self-assembling albumin-based nanoparticles for combined therapy in lung cancer	The developed nanoparticles with encapsulated TnF-related apoptosis-inducing ligand with surface modification by fatty acids and anticancer drugs showed the potential in lung cancer management through pulmonary aspiration	[108]
CN103462897	2013	Preparation and evaluation of bufalin liposomes for lung cancer therapy	Bufalin liposomes were prepared by ethanol injection method and *in vivo* anticancer results demonstrated the higher potential of drug-loaded liposomes in reduction of tumour growth in comparison to free drug	[109]
EP2257312	2010	Active agents loaded nanoparticle-based formulation for targeted delivery in lung cancer management	The direct delivery of drugs to the lungs prolonged residence time in lung tissues, continuous/sustained release of significant drug doses at tumour sites and improved internalization of nanoparticulate formulation in cancer cells	[110]
WO2009156706	2009	Preparation and evaluation of cytotoxic platinum-based drug-loaded niosomes for lung cancer treatment	The niosomal formulation exhibited good characteristics for the delivery of drugs to the lungs and showed potential in lung cancer therapy	[111]

Patent Reports

An extensive search was performed for patents associated with the formulations for lung cancer through pulmonary route (patentscope.wipo.int, www.uspto.gov, patents.google. com, lens.org). Patent reports were screened, studied and documented. Table V lists the drug formulations that are patented related to lung cancer therapy through the pulmonary route of administration [102–111].

Conclusion and Future Perspective

Conventional methods of lung cancer therapy have significant difficulties, such as nonspecific targeting, narrow therapeutic efficiency, unfavourable adverse effects, drug resistance and patient noncompliance. Nanocarrier-based drug delivery systems have shown significant potential for diagnosis, monitoring, and therapy of different cancers. Several nanocarrier-based investigational therapies for lung cancer use targeting and tracking elements with anticancer drugs in their structure. Scientists have developed a number of drug-loaded nanocarrier systems via inhalation for lung cancer therapy to improve drug delivery (targeting, sustained release characteristics) and reduce systemic side effects. In light of these considerations, inhalational drug delivery with nanocarriers for use in lung cancer is promising [112]. Although the advancement of nanocarriers has been recognized as a potential option for lung cancer therapy, they cannot be regarded as flawless due to several unmet demands for their proper delivery. The size and shape of the nanocarrier are of primary importance for effective drug delivery to the lungs via the inhalational route. Changes in procedure or composition might have a deleterious impact on drug delivery. In addition, clinical and preclinical research is continuing to look into using the inhalational route of drug administration to treat lung cancer and other lung disorders. More molecular-level studies are required to understand the targeting of nanocarriers in lung cancer.

Declarations

Conflict of Interest The authors declare no competing interests.

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