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An Update on the Use of Lipid-Based Nanocarriers for the Intrapulmonary Administration of Anticancer Drugs for the Treatment of Lung Cancer

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Abstract: Lung cancer is still the most frequent cancer worldwide and the leading cause of cancer-related fatalities. Even though lung cancer diagnosis and treatment methods have advanced significantly, many patients still show resistant reactions to tried-and-true treatments. This emphasizes the vital need for the innovation and development of novel therapeutic approaches. Nanotechnology has become increasingly important in the treatment of cancer recently because it facilitates improved medication delivery, specificity, lower dosages, and effective elimination. Low-particle-size nanoparticles, or lipid nanoparticles (LNPs), can be tailored for certain delivery purposes. The present review centres on the importance and usefulness of lipid-based theragnostic nanoparticles for cancer treatment, as well as the elements, fabrication process, and variables influencing lipid nanoparticles. preparation, as well as the LNPs' clinical trials and patents. Chemotherapy, photodynamic treatment, immunotherapy, gene therapy, photothermal therapy, and sonodynamic therapy are some of the therapeutic methods used in lung cancer therapy. applications for diagnostic imaging such as NIR, PET, CT, MRI, and optical fluorescence imaging. As LNPs are utilized increasingly often in lung cancer therapy, current research aids in providing answers to problems with traditional treatments. Because of their capacity to adjust to certain medical treatments and the application of with their many parts, they could be used to treat lung cancer. To sum up, by increasing bioavailability, encouraging drug delivery, and reducing barriers, LNPs provide a workable treatment plan for lung cancer. They can contain a variety of therapeutics, including immunomodulatory drugs, siRNA, and chemotherapeutic drugs, for individualized treatment. To effectively address scalability, long-term safety, and optimized manufacturing procedures for lung cancer therapy, more research and clinical validation are needed.

Keywords: lung cancer, lipid-based nanocarriers, liposome, drug delivery system

Introduction

A malignant growth inside the pulmonary organs is called lung cancer, sometimes known as lung carcinoma. The American Cancer Society estimates that there will be 238,340 cases of lung and bronchus cancer, with 117,550 males and 120,790 females afflicted. The estimated death toll from these cases is 127,070, with 67,160 males and 59,910 females. Lung cancer is caused by genetic alterations in the respiratory epithelium cells' DNA. These genetic differences give the affected cells the ability to proliferate uncontrollably, which leads to in the development of a carcinogenic mass. Lung cancer is caused by cells. These genetic differences give the affected cells the ability to proliferate uncontrollably, leading to the formation of an oncogenic mass. Without treatment, these tumors may progressively invade and affect lung parenchymal function. Furthermore, lung tumors frequently metastasis, or spread to other parts of the body. Lung cancer that is not small-cell The two main kinds are Non-Small Cell Lung Cancer (NSCLC) and Small-Cell Lung Carcinoma

(SCLC), with NSCLC being the more frequent variety. Other subtypes include sarcoma, carcinoid, and mesothelioma. Smoking habits, genetics, urbanization patterns, and environmental variables, such as exposure to pollution, arsenic, asbestos, and other environmental toxins, are the main etiological causes of lung cancer.

Lung cancer rates

Rank	Country	Number	ASR/100,000
	World	*2,206,771*	*22.4*
1	Hungary	10,274	50.1
2	Serbia	8,048	47.3
3	France, New Caledonia	166	42.9
4	French Polynesia	144	40.4
5	Turkey	41,264	40.0
6	Montenegro	443	39.7
7	Belgium	9,646	38.3
8	Bosnia and Herzegovina	2,513	37.8
9	North Korea	13,672	37.0
10	Denmark	5,047	36.8

Numerous diagnostic methods, such as a review of the patient's medical history, a thorough physical examination, and imaging methods like computed tomography (CT), bone scanning, magnetic resonance imaging (MRI), positron emission tomography (PET), and integrated PET-CT scanning, can be used to diagnose lung cancer. Moreover, tissue biopsy is utilized using medical imaging to conduct a thorough analysis. Conventional therapeutic approaches for lung cancer include immunological checkpoint inhibitors, chemotherapy, radiotherapy, and molecularly targeted medications. These treatment alternatives have a number of major adverse effects, including cytopenias of the blood, baldness, fatigue, nausea, and hepatic issues. New Developments in nanotechnology and drug delivery are being made to reduce the side effects of traditional lung cancer treatment. These technologies reduce the need for dosage and medication-related toxicity when used as drug delivery systems. Nanoparticles (NPs) are discrete particles smaller than 100 nm. Researchers have investigated the potential applications of LNPs, polymeric nanoparticles, dendrimer nanoparticles, liposomes, gold nanoparticles, carbon nanotubes, mesoporous silica nanoparticles, solid lipid nanoparticles (SLN), quantum dots, and nanostructured lipid carriers (NLCs). Lung cancer treatment.

Lung Cancer Death

Rank	Country	Number	ASR/100,000
	World	*1,796,144*	*18.0*
1	Hungary	8,920	42.4
2	Serbia	7,084	40.0
3	French Polynesia	129	36.0
4	Turkey	37,070	35.9
5	Guam	86	35.1
6	Poland	27,444	32.8
7	Bosnia and Herzegovina	2,240	32.1
8	Montenegro	370	31.6

9	France, New Caledonia	124	31.4
10	Croatia	2,984	30.9

Methodology

Using a variety of keywords, including "Inhaled/aerosolized/nebulized/dry powder inhalers/inhalable chemotherapy for LC," "inhaled liposomes for LC," "aerosolized solid lipid nanoparticles (SLNs) for LC," "DPIs of nanostructured lipid carriers (NLCs) for LC," "inhalable nanoemulsions (NEs) for LC," "lipid-based nanoparticles for LC," etc.), the PubMed, Google Scholar, ScienceDirect, and Wiley Library databases were manually searched for published literature on inhalable chemotherapy via lipid-based nanocarriers. This study contained examples of the most current (2010–2021) in vivo trials involving liposome formulations loaded with anticancer drugs for inhalation. This study analyzed all of the published studies on the other lipid-based nanocarrier types (NEs, SLNs, NLCs, niosomes, and others) intended as inhalable formulations loaded with anticancer drugs for the diagnosis and/or therapy of lung cancer.

Lipid-Based Nanocarriers

The most promising colloidal DDSs that are already on the market use nanoparticles (NPs) made from natural polymers such proteins, phospholipids, and polysaccharides. Such systems have been shown to be more successful than synthetic polymers in terms of drug loading volume, biocompatibility, and reticuloen dothelial system (RES) opsonization. Furthermore, studies have demonstrated that natural polymers are better than synthetic polymers in terms of their absorption by the body and the less toxic end products they produce when destroyed. Given their relative safety and ease of preparation, NPs derived from naturally separated polymers would be a better option for the colloidal drug delivery technology intended for human use. Hydrophobic chemotherapeutic medicines can be effectively administered via a nanotherapeutic method, hence circumventing drug delivery issues. Because lipid-based nanocarriers resemble the membrane components of cells, they offer the benefit of being readily absorbed into cells and having less adverse effects. The main benefit of employing lipid-based nanocarriers for cancer treatment is that the hydrophilic cancer targeting reagent can be linked to the surface and the hydrophobic chemotherapeutics can be put within. Which target material is affixed to the lipid-based nanocarriers determines the efficacious delivery of anticancer medications to cancer cells. In order to improve the effectiveness of their delivery to cancer cells, lipid-based nanocarriers use different functional groups on their surface to promote the attachment of different molecules, such as medicines, polysaccharides, and antibodies. Furthermore, lipid-based nanocarriers can be delivered by oral, parenteral, ocular, intranasal, and dermal/transdermal routes, among other methods.

Table 1
FDA-Approved Drugs Used in Different Stages and Types of Lung Cancer (LC) Treatments

Drug	Cancer Stage	Target	Date of Approval	Company
Atezolizumab	II to IIIA NSCLC	PD-L1 expression	10/15/2021	TECENTRIQ®, Genentech Inc.
Atezolizumab	Metastatic NSCLC	PD-L1 expression	05/18/2020	TECENTRIQ®, Genentech Inc.
Brigatinib	Adult patients with Anaplastic lymphoma kinase (ALK)-positive metastatic NSCLC	Anaplastic lymphoma kinase	05/22/2020	ALUNBRIG, ARIAD Pharmaceuticals Inc.
Cemiplimab	Advanced NSCLC	Tumors with PD-L1 expression	02/22/2021	Libtayo, Regeneron Pharmaceuticals Inc.
Durvalumab in combination with carboplatin/cisplatin	Extensive-stage SCLC (ES-SCLC).	-	03/30/2020	IMFINZI, AstraZeneca

Drug	Cancer Stage	Target	Date of Approval	Company
Lorlatinib	Metastatic NSCLC	ALK-positive	03/03/2021	Lorbrena, Pfizer Inc.
Nivolumab + Ipilimumab	Metastatic NSCLC	First-line treatment for EGFR or ALK genomic tumor abnormalities	05/26/2020	OPDIVO, Bristol-Myers Squibb Co. YERVOY, Bristol-Myers Squibb Co.
Osimertinib for adjuvant therapy	NSCLC	Tumors have mutated EGFR	12/18/2020	TAGRISSO, AstraZeneca Pharmaceuticals LP
Ramucirumab + Erlotinib	Metastatic NSCLC	Tumors with mutated EGFR	05/29/2020	CYRAMZA, Eli Lilly and Company
Amivantamab-vmjw	Metastatic NSCLC	With EGFR exon 20 insertion mutations	05/21/2021	Rybrevant, Janssen Biotech Inc.
Capmatinib	Metastatic NSCLC	Tumors had a mutation that caused exon 14 of the mesenchymal-epithelial transition (MET) to be skipped.	05/06/2020	TABRECTA, Novartis
Lurbinectedin	Metastatic NSCLC	On or after platinum-based chemotherapy	06/15/2020	ZEPZELCA, Pharma Mar S.A.
Mobocertinib	Advanced or metastatic NSCLC	EGFR exon 20 insertion mutations	09/15/2021	Exkivity, Takeda Pharmaceuticals Inc.
Sotorasib	Locally advanced or metastatic NSCLC	RAS GTPase family inhibitor, for adult patients with KRAS G12C mutated	05/28/2021	Lumakras™, Amgen Inc.
Tepotinib	Metastatic NSCLC	Harboring mesenchymal-epithelial transition (MET) exon 14 skipping alterations.	02/03/2021	Tepmetko, EMD Serono Inc.

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Note: The data used in this table were retrieved from the FDA.

The oral route is the most preferred method due to its minimal risk of side effects, including injection-site responses, non-invasiveness, and reduced expense. Although the nasal administration approach is believed to be the most successful in terms of drug delivery for LC treatment, its effectiveness has not yet produced any particularly noteworthy outcomes. Different architectures can be formed by lipid-based nanocarriers based on the way they are formulated. There could be variations in the drug loading and delivery effectiveness of certain formulation techniques. Table 2 lists the most widely utilized lipid-based nanocarriers as DDS in LC.

Table 2

Lipid-Based Nanocarriers Used in Drug Delivery Systems for LC Treatment

Lipid-Based Nanocarriers	Pros	Cons	Drug; Target Cancer; Phase; Status (Source-FDA)
Liposomes	Improved drug-target selectivity; improved pharmacokinetics and pharmacodynamics; lowered toxicity; improved therapeutic efficacy against pathogens[37],[38]	Expensive to produce; short shelf life and low stability[37]	Irinotecan Hydrochloride Liposome Injection (LY01610); SCLC; Phase 2; Recruiting
Lipid Micelles	Extends the circulation time of drug in blood; solubilizes hydrophobic drugs; has defined sizes and particle sizes[39]	Dilution might induce shift in the equilibrium towards the unimer state that leads to their dissociation[39]	Paclitaxel (Genexol®) Drug: Paclitaxel-loaded polymeric micelle (Genexol-PM®); NSCLC; Phase 2; Completed
Solid lipid nanoparticle (SLN)	Protects drug against harsh environmental conditions; high biocompatibility, and biodegradability[40],[41]	Crystalline structure; low drug loading efficiency; and drug expulsion due to storage conditions[40]	Not available
Lipid nanoparticle (LNP)	Easy synthesis using microfluidic techniques; improved charge-dependent drug loading such as nucleic acid	Few reports of side effects such as hepatotoxicity due to the use of polyethylene glycol[42],[43]	Not available

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Abbreviation: FDA, US Food and Drug Administration.

Inhalable Anticancer Therapy via Lipid-Based Nanocarriers: Main Advantages and Critical Challenges

Lipid-based nanocarriers are primarily used to deliver drugs via the intravenous and pulmonary modes of administration for the treatment of lung cancer. In some circumstances, localized medication delivery techniques at the tumor site are also taken into consideration. Research on lipid-based nanoparticles for LC therapy and pulmonary administration of anticancer medications is developing rapidly. This method of medicine delivery can be self-administered, is non-invasive (needle free), and improves patient compliance. It can be utilized to get around some of the disadvantages of oral or intravenous methods, such as high systemic toxicity, limited anticancer agent water solubility, low drug accumulation within the tumor, and high tumor relapse rates. When treating LC, inhalable lipid-based nanocarriers may offer several benefits over traditional methods, particularly for individuals whose LC is surgically incurable. In terms of pharmacokinetics, inhalation permits the transport of chemotherapeutic drugs to the intended cancer cells while avoiding hepatic metabolism; as a result, quick start-up times, reduced dosages, and fewer toxicities and systemic distribution are anticipated. Furthermore, in comparison to other organs like the liver and the gastrointestinal tract, the alveolar region of the lungs has a vast surface area of around 100 m2, substantial vasculature, and low drug-metabolizing enzymatic activity. Furthermore, compared to the upper bronchial tree's (50–60 m) epithelium, the alveolar epithelium is incredibly thin (0.1–0.2 m). As a result, medication bioavailability and absorption in the intended area may be further enhanced. Furthermore, about 90% of lung surfactants are composed of phospholipids, which are important components of many lipid-based nanoparticles, particularly liposomes, and are found in the lungs. This promotes the development of lipid-based formulations that are more biocompatible and improves the anticancer drug's lung tolerance. The development of drug resistance, treatment failures, and chemotherapy interruptions that lead to the repopulation of malignant cells may all be significantly reduced by these factors. Consequently, inhalational therapy may also be effective for cancers that are resistant to conventional systemic chemotherapy. Anticancer medications can target and reach

different types of lung tumors through different paths when delivered to the lungs through lipid-based carriers. The inhaled medicine can directly penetrate lung cancers by achieving raised local concentrations and noticeably high concentration gradients of therapeutic agents at the lung tumor site, following deposition in the respiratory tract. Certain lung tumor forms that are located adjacent to or inside the airways, such as squamous cell carcinomas or bronchioloalveolar cell carcinomas, may absorb the drug directly through penetration. Additionally, medications delivered to the lungs using lipid carriers that can be inhaled can be absorbed into the local blood circulations. Depending on the location of the tumor, a sufficient drug concentration may be able to reach lung cancers that are not directly connected to the main airways because of the connectivity between the bronchial and pulmonary circulations. Lung tumors located in the conducting area are fed by the bronchial vasculature, whilst those positioned in the respiratory region are fed by the pulmonary circulation. However, a number of variables, including the drug's and the particles' physicochemical properties, the composition and characteristics of the formulation used, the location of the drug's deposition, the respiratory system's histological features, and the underlying pathological condition, can affect the absorption, lung clearance mechanisms, biodistribution, and tumor penetration of inhaled drug-loaded particles. By comparing the pulmonary pharmacokinetic behavior of drug-loaded 3H labelled PEGylated liposomes after intratracheal administration to both healthy rats and rats with bleomycin-induced lung inflammation, Haque et al. assessed how inhaled liposomal formulation affects pre-existing lung disease. According to the findings, liposomes were initially removed from inflammatory lungs more quickly than from healthy ones, but after three days, the rates of lung clearance were identical. This was noteworthy because, in spite of indications of increased mucus retention in inflamed lungs and decreased liposome interaction with lung tissue, mucociliary clearance from healthy lungs was more effective. 3H-phosphatidylcholine's plasma pharmacokinetics showed longer absorption from inflamed lungs and increased liposomal bioavailability. After a single pulmonary dose of liposomes to rats with inflamed lungs, concentrations of the pro-inflammatory cytokine IL-1 were elevated in bronchoalveolar lavage fluid. However, no other notable alterations in inflammatory lung indicators were found in either healthy or bleomycin-challenged rats. Furthermore, medicines ingested are also eliminated by the lymphatic system; these substances are frequently found in the lymph nodes of the lungs. As a result, these nodes are thought to be possible targets for the medication that is inhaled to prevent cancer from spreading to and from the lungs. The biodistribution of solid lipid nanoparticles (SLNs) tagged with 99mTc was reported by Videira et al. after the particles were injected intraperitoneally into male Wistar rats. A gamma-camera was used to capture dynamic images for 60 minutes, after which static images were collected every 30 minutes for up to four hours after inhalation. Organ samples taken after the animals were slaughtered were counted for radiation. The findings showed a high distribution rate in the periaortic, axillar, and inguinal lymph nodes as well as a notable uptake of the radiolabeled SLNs into the lymphatics following inhalation. Owing to all these outstanding benefits, inhalation therapy has the potential to develop into a safe and efficient delivery system for the treatment of lung cancer.

Physicochemical Considerations, Passive, and Active Targeting for Efficient Pulmonary Delivery of Anticancer Drugs via Lipid-Based Nanocarriers

The nano- or microcarriers' physicochemical characteristics of anticancer medications should Notwithstanding the benefits indicated above, it is important to remember that there are certain obstacles and restrictions associated with the pulmonary drug administration of anticancer medications using lipid-based nanocarriers for LC treatment. Due to the cytotoxic nature of anticancer medications, one of the main worries is lung tolerance and the possibility of local pulmonary toxicity as well as other side effects. Furthermore, the health of LC patients' lungs is frequently compromised by either LC complications or the existence of other concomitant lung diseases like asthma or chronic obstructive pulmonary diseases, which can have a substantial impact on the patients' capacity to tolerate inhalable anticancer therapy. be carefully taken into account when creating inhalation formulations, since this will impact the duration of the drug's residency in the lungs and, in turn, the effectiveness of the treatment. Anticancer drugs need to reach malignant cells in a time frame that allows for the necessary pharmacodynamic effects. The condition may then not be effectively treated by medications that are easily absorbed by the lungs. Because lipophilic medicines have a better ability to diffuse in lipid membranes, they are generally absorbed from the lungs quickly (log $P > 0$). Drugs that are hydrophilic (log $P < 0$) on the other hand typically have longer lung residence periods. Therefore, formulation strategies that increase the lipophilic medicines' lung residency and lengthen their exposure duration to cancer must be used. Various mechanisms, including inertial impaction, sedimentation, and Brownian diffusion, can deposit drug-loaded lipid-based nanoparticle aerosols on the respiratory epithelium. These techniques can be applied as liquid dispersions or as dry powders. The aerodynamic diameter (Dae) of the produced aerosol particles essentially controls these mechanisms. The most accurate metric for determining the size of aerosol particles

is the Dae. Since it is computed using the particles' geometric size, density, and dynamic shape, it can correlate the dynamic behavior of the particles. The research is in agreement that in order to achieve effective pulmonary delivery, inhaled particles should have a diameter of 1-3 m for the respiratory zone and a dae of 1-2 m to reach the lower respiratory tract. Smaller particles, those with (Dae < 0.5) m, are anticipated to be expelled from the body by the expiratory airflow, whereas larger particles, those with (Dae > 5) m, will be deposited in the upper respiratory tract. Lipid-based nanocarriers can be dispersed via nebulization and aerosolized, thereby entering the lungs as dispersions. In order to be administered as dry powders, they must simultaneously be integrated into secondary carriers, or microparticles, because of their minuscule geometric size. They were created using a variety of particle engineering approaches, which are covered in Section 5. Because particle form can control the amount of alveolar macrophage clearance, it can also significantly influence the therapeutic efficacy of inhaled anticancer mulation. Previous research has examined the association between the forms of various particles (such as elliptical disks, spherical, oblate ellipsoids, rectangular disks, and worm-like geometries) and the amount of time it takes for phagocytosis to clear them. It was discovered that these particles' phagocytosis clearance time is highly influenced by their shape and orientation. For every form, phagocytosis was started in at least one orientation. Elliptical discs were consumed in less than six minutes as a result of the macrophages' adhesion to their primary axis. The spherical particles were likewise removed right away, regardless of the macrophage attachment point. Remarkably, even after two hours, macrophage attachment to the flat surfaces or minor axes of the oblate ellipsoids, rectangular disks, and elliptical disks was unable to remove these particles. Worm-like particles also produced substantially less phagocytosis clearance than spherical particles due to their low curvature region. Lipid-based nanocarriers with varying morphologies could be incorporated in microparticles to potentially improve their delivery through the application of particle-engineering methods. The inhaled particles' surface charges may impact not only their clearance and retention in the lungs but also their cellular absorption. Because of their stronger inclination to connect with tumor cells, positively charged particles were said to have more penetration into tumor cells. Furthermore, it was demonstrated that, in contrast to neutral and anionic nanoparticles with equivalent hydrodynamic dimensions, cationic nanoparticles were rapidly absorbed by lung epithelial cells and/or macrophages following administration. As a result, cationic nanoparticles are limited in their ability to translocate to lymph nodes and the circulation by being trapped in lung cells for a longer period of time.

Characteristics of Liposomes as DDSs

Because of their unique characteristics, liposomes have been employed for medication delivery for a very long time. A liposome is a region of aqueous solution surrounded by a hydrophobic membrane that stops hydrophilic solutes from dissolving and accumulating lipids. Due to the fact that hydrophobic compounds can dissolve into the membrane, liposomes can receive both hydrophilic and hydrophobic molecules. The process of using liposomes to transfect or convert DNA into the host cell is known as lipofection. Liposomes can be utilized as carriers in addition to delivering genes and drugs. When liposomes were first developed thirty years ago, they were a more simpler drug delivery system than they are now.38 In different stages of clinical trials, about 12 liposome-based drugs have been approved for use in medicine. The primary components of liposomes are phospho- and sphingolipids, which can be produced artificially or naturally. Randomly distributed throughout each liposomal vesicle are other components of the membrane bilayer, such as cholesterol and lipids linked to hydrophilic polymers. Amphiphilic lipids consist of two chains of saturated or unsaturated fatty acids and a glycerol molecule attached to a phosphate group. The phosphate group can be connected to another organic molecule. Depending on which chemical group they belong to, natural phospholipids are categorized as phosphatidic acid, phosphatidylcholine (PC; sometimes called lecithin), phosphatidyletha nolamine (PE), phosphatidylinositol (PI), phosphatidylglycerol (PG), and phosphatidylserine (PS). The two forms of glycerophospholipids that are involved in the creation of liposomes are synthetic and natural. The main naturally occurring phospholipids used to make liposomes are PC and PE, which are abundant phosphatides found in both plants and animals. Nonetheless, PC membranes with relatively low PE are typically seen on liposomes and other lipid-based DDSs. Under biological circumstances, PE can produce non-bilayer structures that lead to membrane fusion and destabilization. Other phospholipids, like PS, PG, and PI, can also be utilized to form liposomes, depending on the desired liposome features.

Liposomal Dry Powder as DDSs in LC Therapeutics

Dry nanoparticulate powders containing anticancer drugs are thought to be a promising treatment for lung cancer (LC). As LC treatments, Zhu et al. worked on a liposomal dry powder (LDP) containing docetaxel (DTX). The folic acid-conjugated liposomes containing DTX showed notable cytotoxicity and superior tumor targeting capabilities. The re-dispersed liposomes derived from the redispersion of inhaled dry powders are distinct from the original liposomes in terms of both pharmacology and pharmacokinetics. According to a study by Gandhi et al., gemcitabine HCl could be successfully incorporated into LDP by the lyophilization process. In vivo investigations and the human cancer cell line A549 demonstrated the potential utility of prepared LDP. According to the results of these studies, LDP formulations can be applied to the entire lung and are useful for the non-toxic treatment of lung cancer.

Liposome-Mediated Targeting of LC

Liposomes can be added to different functional groups, which makes them useful for cancer treatment. The distribution behavior of triptolide is altered when it is encapsulated in liposomes. Congcong Lina et al. report that dual-ligand modified triptolide-loaded liposomes produced the strongest anticancer response during the experiment and showed no obvious systemic side effects. This demonstrates how the therapeutic advantages of triptolide-loaded liposomes can be enhanced by concurrently treating them with anti-CA IX antibodies and lineage-homing cell-penetrating peptides. RGD (arginine, glycine, and aspartic acid) tripeptide-modified PTX for LC therapies was employed in a recent study, which discovered that RGD-modified co-loaded liposomes are viable options for anticancer drug delivery. The prognosis of the patient may be improved by transporting PTX in large cationic liposomes, which may mitigate some of the drug's detrimental effects, such as tissue toxicity. Encasing PTX in cationic liposomes is the method employed. High biocompatibility, improved internalization, and antitumor efficaciousness of PTX were noted in multicellular spheroids, cancer stem cells (CSCs), and human and mouse LC cells in culture. It is well established that quercetin (QR) has a strong therapeutic effect on tumor cells when it comes to treating LC via targeting transferrin receptors. This study effectively produced nontargeted quercetin-loaded liposomes with an encapsulation effectiveness of 95% and T7 (HAIYPRH) surface-functionalized liposomes with different T7 peptide densities. Anticancer activity in normal lung cells (MRC-5 cells) and LC cells (A549 cells) was investigated using synthesized liposomes. Liposomes with T7 surface functionalization (2% T7-QR-lip) enhanced A549 cell cytotoxicity, cellular uptake, S-phase cell-cycle arrest, and mortality. In contrast, nontargeted QR-lip resulting from receptor-mediated endocytosis is observed; nevertheless, in MRC-5 cells, there were no appreciable variations in cytotoxicity or cellular uptake between T7-QR-lip and QR-lip. Moreover, the 2% T7-Cou6-lip showed far deeper penetration in 3D lung tumor spheroids.

Characteristics of Lipid Micelles as DDSs

Lipid micelles are the result of self-aggregation using lipid as the primary component, which produces nanoparticles in an aqueous solution. Lipids with long hydrophobic chains and polar head groups that include lipids contribute to the amphiphilic characteristics of lipids that make up lipid micelles. A micelle is formed when the hydrophobic chain aggregates and the polar portion of the lipid confronts water. Micelles have the amphiphilic qualities that make them ideal for loading both hydrophilic and hydrophobic medications. Anticancer medications are released gradually and under control thanks to the lipid micelle structure, which also gives the medication chemical and physical stability.

Lipid Micelle-Mediated Treatment of LC

Since micelles are easier to make and have a smaller size than liposomes, they are utilized in treatment by loading different anticancer medications. For the treatment of lipocystic arthritis (LC), the epidermal growth factor receptor (EGFR) is a frequently employed medication delivery target. While using antibodies to target the EGFR is common, aptamers based on nucleic acids have gained popularity recently. When compared to monoclonal antibodies, aptamers are less expensive and can be produced more easily. EGFR aptamer-coated micelles efficiently transport medications to LC. Salinomycin, a medication that can destroy cancer stem cells in LC, was added to micelles for this investigation. It was established that the 24 nm-sized micelles, which included salinomycin and the EGFR aptamer, could efficiently target LC in mice and stop the progression of cancer.

Even though EGFR is the target of LC therapy medication delivery, many individuals have EGFR mutations. Because of this, EGFR-induced signaling system blockage is occasionally employed. EGFR-mutant NSCLC is being treated with afatinib, an agent that inhibits the tyrosine kinase of the intracellular EFGR signaling system. Since transferrin receptors are overexpressed in LC, a micelle with transferrin decoration on the surface was created for the efficient delivery of afatinib to LC. In addition to successfully inhibiting LC growth in the mice in vivo, afatinib's transport efficiency by micelles was found to be four times greater for LC than for afatinib alone.

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Moreover, various medications have been delivered via LC's overexpression of transferrin receptors. The most widely used anticancer medication, PTX, is known to produce serious side effects. Additionally, PTX was put into micelles and used to treat LC by focusing on transferrin receptors. It was demonstrated that PTX@FT-NB, a micelle containing transferrin on the surface and loaded with PTX, could be delivered to LC with great efficiency and could also stop the progression of cancer in mice in vivo.

Characteristics of Solid Lipid Nanoparticles (SLNs) as DDSs

A newer approach to drug delivery that replaces the conventional colloidal delivery mechanism is called solid-state nanomedicine (SLNs).30 The benefits of the SLN, which combines polymeric nanoparticles with liposomes, can be used in therapy.30 Because the SLN has a lipid surface, it has a very high biocompatibility and is very well tolerated by the body and lungs. As a result, it can be used as a medication delivery system to treat liver cancer. Physiological solid lipids, which are solid at body temperature and room temperature, are the primary ingredient used in the preparation of SLNs. It disperses in water, when the internal lipid unites to create a structure. For the manufacture of SLNs, polyvinyl, compritol, glycerides, and steroids are frequently utilized. LC Treated by SLN-Mediated Approach Like other lipid-based nanocarriers, SLN is also appropriate for enclosing hydrophobic medicines. A hydrophobic anticancer medication called DTX is used to treat NSCLC, head and neck cancer, and breast cancer. Cytopenia, vomiting, and hair loss are typical DTX side effects. Research is being done to eliminate these adverse effects by utilizing the targeted action of nanostructures. It appears that these side effects are caused by DTX's lower transport effectiveness to cancer cells. After Compritol® 888 ATO was used as the primary source material, DTX was added to the SLN. A component-based SLN known as SLN-DOX demonstrated 86% efficiency in supporting DTX. SLN-DOX effectively induced both the arrest of the G2/M phase of the cell cycle and apoptosis in the cancer cells in the in vitro experiment. Furthermore, SLN-DOX treatment stopped mice from developing metastatic LC in vivo.

In order to transport DOX to specific LCs, transferrin was also added to SLN, much like lipid micelles. Stearic acid and injectable soy lecithin were used to make SLNs. Plasmids expressing enhanced green fluorescent protein (pEGFP) were co-delivered to cancer cells with DOX, and the expression of EGFP was used to assess the delivery efficiency. The EGFP plasmid transfection efficiencies utilizing SLN in the in vitro experiment were greater than 80%, and the released DOX concentration in the A549 cells was also greater than 80%. Transferrin decorating in SLN, which reveals the transferrin receptor's specific targets, led to a significant enhancement of the DOX-mediated anticancer activity in the A549 xenograft tumor model in mice.

Moreover, polyvinyl pyrrolidone k15-based SLNs and hydrogenated soybean phospholipids have been used to treat LC. After PTX and curcumin were added to this SLN, it was known as PC-SLN. In contrast to the combination of PTX and curcumin, which improved circulation time, PC-SLN extended the residence time and half-life. In the xenograft tumor model, PC-SLNs demonstrated a significantly stronger inhibitory effect on tumor growth than the combination treatment of PTX and curcumin.

Herbal medicine that has been traditionally utilized has also been administered via SLN. Yuxingcao has long been utilized in Chinese medicine to treat lung conditions like pneumonia and respiratory infections. But Yuxingcao was administered indiscriminately, which resulted in a number of adverse drug reactions (ADRs), some of which were fatal.65 In an attempt to address the issue of ineffective drug delivery within the sick lung, SLN was used to mitigate this side effect of Yuxingcao administration. The SLN was created using polyvinyl acetate and glyceryl behenate, and Yuxingcao oil was added. In 50 hours, the loaded Yuxingcao was completely released in the cultured media. Furthermore, Yuxingcao was successfully administered to the lung using intratracheal administration of SLN loaded with Yuxingcao. Despite the lack of in vivo outcomes

for LC treatment in mice, this study showed that SLN would be helpful in LC treatment since it might transport herbal medication to the lungs.

Characteristics of Lipid Nanoparticles (LNPs) as DDSs

Although the word "LNP" can be used to describe any type of nanostructure that contains lipids, its definition has slightly changed due to its application in the COVID-19 vaccine production process. Unlike liposomes, the LNP is made utilizing microfluidics and has lipids inside of it. A novel and potentially effective technique for producing LNPs in large quantities is microfluidic-mediated synthesis. Clinical trials can be conducted using this well-proven technology, which can be scaled up to Good Manufacturing Practice (GMP) production in the currently favored research lab. Furthermore, the application of microfluidics has the benefit of maintaining qualitative control, which is not possible with traditional techniques. LNPs have multiple unique compositions since they are primarily used as carriers for mRNA that can produce antigenic proteins. These circumstances include: a) cationic or ionized lipids with tertiary or quaternary amine heads to facilitate loading inside LNPs by negative conversion of nucleic acid molecules; b) phospholipids capable of forming hydrophilic membranes, like DSPC; c) cholesterol able to stabilize the lipid bilayer of LNP; and d) PEGylated-lipids to prevent LNP degradation in the blood and lengthen blood circulation time.

LNP-Mediated Treatment of LC

LNPs are frequently employed as carriers to transfer nucleic acids, in contrast to other lipid-based nanocarriers. This is most likely due to the COVID-19 vaccine's efficacy, which involved inserting an mRNA into the LNP. Research on delivering nucleic acids is more active than that on delivering anticancer medicines when it comes to LC treatment using LNPs. Moreover, immunotherapy employs LNP-delivered nucleic acid delivery to target immune cells. Cancer treatment was attempted by inserting the cancer antigen into the LNP, akin to the COVID-19 vaccine, which used mRNA capable of translating the SARS-CoV-2 antigen protein.68 Effective immunity against antigen-expressing malignancies was enhanced by experimental antigen ovalbumin-contained LNPs and LNPs carrying melanoma antigen TRP2 mRNA, since these therapies inhibited tumor growth.

T cell activation can be induced by dendritic cells (DCs), which are immune system core cells. Dendritic cells can activate T lymphocytes, which then locate and destroy antigen-expressing cells. Immune enhancers are chemicals that can promote the pattern that DCs recognize to activate themselves in response to infections. Moreover, activated DCs have surface expression of CD40 and exhibit increased activity as a result of T cells' binding of CD40. Pattern receptor stimulant R848 (toll-like receptor 7/8 agonist) and CD40 mRNA were loaded onto LNPs, also known as RAL2 CD40-LNP, to take advantage of this DC action. The extra anti-CD40 antibody treatment significantly increased the DCs' RAL2 CD40-LNP-induced activity. As a result, the administration of both RAL2 CD40-LNP and the anti-CD40 antibody together nearly entirely prevented the formation of tumors in mice in vivo.

The pattern recognition receptors of immune cells can be activated by a range of nucleic acid components of immune stimulatory drugs. Among them, it has recently been demonstrated that cyclic dinucleotide (CDN) molecules—which are STING ligands—have great immune stimulatory effects. Treatment with STING-LNP causes T cells and NK cells to infiltrate the lung in the mouse lung metastasis model.

Nanostructured Lipid Carrier (NLC)

Although they have certain drawbacks, lipid nanoparticles like SLN and LNP have long been considered viable carrier systems with prospective therapeutic applications. The NLCs' special qualities as intelligent, flexible systems that can boost drug loading, regulate release, and produce final dosage forms including creams, pills, capsules, and injectables make them a cutting-edge drug delivery technique for a range of pharmaceutical classes. Lipid-based formulations, or NLCs, are made up of a combination of liquid and solid lipid. Lipophilic actives can be trapped by the binary lipid-based nanocarriers, or NLCs, which slow down the deterioration of the actives and increase their stability. For drug therapy, it was shown that NLCs offered a few benefits over traditional carriers, including as increased permeability, better bioavailability, less adverse effects, longer half-lives, and tissue-targeted delivery. There has been a rise in interest in NLCs in recent years. Both lipophilic and hydrophilic drugs can be delivered with these nanocarriers. NLCs have become a feasible carrier system for the oral, parenteral, ocular, pulmonary, topical, and transdermal delivery of pharmaceuticals. NLCs have also been utilized recently for the administration of brain targeting, gene therapy, chemotherapy,

and cosmeceuticals and nutraceuticals. NLCs are a promising oral delivery medium that can capture both hydrophilic and lipophilic medications because of their enhanced stability during storage and ease of scalability without requiring sterile conditions. Several research works have been carried out on NLC-based drug delivery systems for various cancer treatments, and numerous scientists are examining the characteristics of NLCs to improve their performance. Using a modified vector, Yiqun Han and colleagues (2014) created a formulation based on NLC called "EGFP-loaded NLC" and transfected it into mice harboring A549 cell line and human alveolar adenocarcinoma cell line. The high transfection rate of NLC-based gene delivery systems makes them an effective technique for LC gene therapy, according to the results of both in vitro and in vivo experiments. Doxorubicin (DOX) and β-elemene (ELE) (DOX/ELE Hyd NLCs) were investigated for LC therapies in vitro and in vivo in 2019. By working in concert, the formulation efficiently suppresses the growth and proliferation of lung tumor cells.84 Shenghu Guo and colleagues conducted another trial based on NLC for the treatment of LC. To create the CET-PTX/DMN-NLCs formulation, they have loaded the drugs cetuximab (CET), paclitaxel (PTX), and 5-Demethylnobiletin (DMN) into NLCs. The formulation was tested in vivo (using lung tumor xenograft mice) and in vitro (using the A549 cell line). It was discovered that the drug and NLC work together to reduce the viability of cancer cells in a low-toxicity manner, suggesting that this could be a promising system for LC's synergistic combination therapy. A novel formulation known as "EtpP–CDDP-NLCs" was created in a recent study by conjugating the drugs etoposide (Etp) and cisplatin (CDDP) with NLC for the treatment of LC. The formulation demonstrated enhanced tumor-cell uptake, cytotoxicity, and tumor-inhibition efficacy when tested in vitro and in vivo.

Despite NLCs' great potential as drug delivery systems, there is still a dearth of preclinical and clinical research on them. Consequently, their applications must be expanded to include clinical trials in accordance with appropriate ethical standards.

Inhalation of Lipid-Based Nanocarriers for LC Treatment

Inhaling medication is one method used to treat lung cancer. After passing via the respiratory tract, the lungs are easily accessible tissues, and medications can directly target cancer by inhaling them. Drugs do not, however, normally flow through the respiratory track because it is a mucosal tissue. Drug-induced mucosal injury can also have major adverse effects. Thus, when treating lung cancer by inhalation, a stable and efficacious DDS is needed. A liposome is a lipid-based vesicle's transport system, as was previously discussed. The body is not harmed by the natural lipids employed in liposomes. Furthermore, liposomes are transporters that stably deliver medications to tissues by slipping through mucus with ease. Liposomes are being researched as inhaled medication delivery vehicles for the treatment of lung cancer because of these benefits.

A recent work by Khushaboo et al. on LC drug development showed that sorafenib tosylate-loaded LDP inhalers might be used as a vehicle for direct targeting of NSCLC via a pulmonary DDS. In the in vitro aerosol studies, the LDP inhaler exhibited higher lung deposition than the normal formulation. The created dry powder inhaler exhibited long-term release properties, as demonstrated by in vitro studies. Consequently, a customized distribution of sorafenib tosylate is anticipated from a slow systemic dilution after an LDP inhaler injection, which will reduce the frequency of doses and adverse effects associated with the medication. A liposomal curcumin dry powder (LCDP) inhaler was developed by Zhang et al. for use as a primary LC inhalation therapy. LCDPs were produced by freeze-drying the curcumin liposomes. Human A549 LC cells absorbed curcumin liposomes more easily than free curcumin. While the cytotoxicity of these liposomes was minimal in normal human bronchial BEAS-2B epithelial cells, it was substantial in A549 cells. The trachea of rats with lung cancer were used to spray curcumin powder, LCDPs, and gemcitabine directly into the lungs of the animals. In terms of the expression and pathophysiology of different cancer-related markers, LCDPs exhibit a higher more anticancer impact than the other two medications.

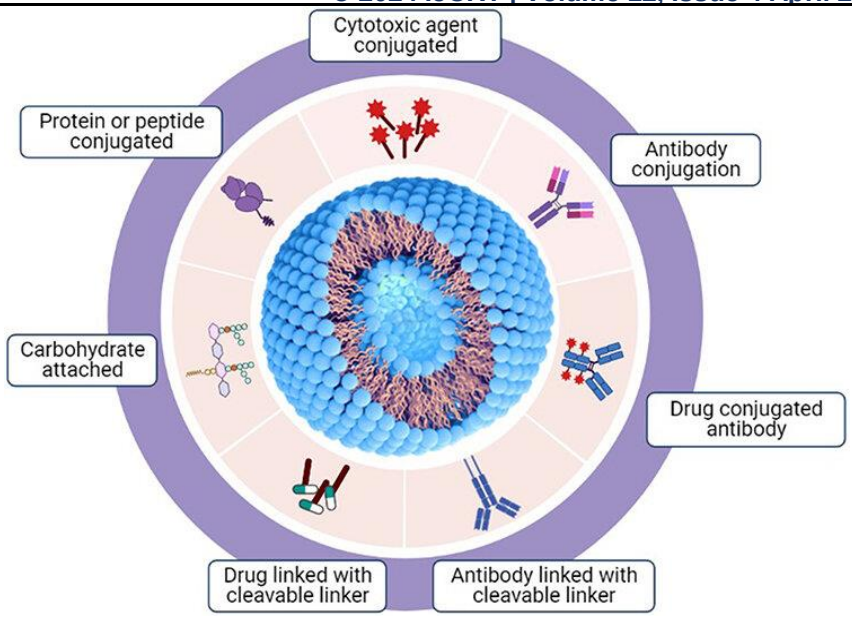

Figure 1. Limitations and challenges with DDSs using lipid-based nanocarriers

Adel et al. conducted additional research on the medication created with curcumin-liposomal in 2021. They produced spray-dried proliposomes loaded with curcumin for inhalation using a nano-spray drier. Cytotoxicity testing employing an MTT assay demonstrated lower IC50 values and improved growth inhibitory qualities on lung tumor A549 cancer cells as compared to curcumin powder and simple formulations.Parvathaneni et al.'s study suggested that inhalable liposomes loaded with pirfenidone (PFD) would be a viable therapy option for non-small cell lung cancer. Chen et al. investigated the function of nanocarriers in DDSs for LC and found that, in comparison to LBT-OA-PEG nanoemulsions (NEs), lycobetaine (LBT)-oleic acid (OA)-PEG liposomes could entrap more LBT and showed a slower drug release and longer circulation duration in pharmacokinetic experiments. When compared to free LBT, in vitro experiments on lung cancer cells revealed that LBT-OA-PEG liposomes had a stronger antitumor effect. Furthermore, LBT-OA-PEG liposomes with nRGD showed proficiency in the microenvironment-depletion of tumors as well as strong anti-lung cancer activity when nRGD was employed as a therapeutic adjuvant. Therefore, LBT-OA-PEG liposomes containing nRGD may be useful in clinical cancer treatment. Table 3 lists the several liposome-based bioformulations for the management and treatment of LC.

Table 3

Recent Studies Presenting Different Liposome-Based Bioformulations for Drug Delivery in LC Treatment

Liposome	Drug	Formulation Name	In vitro or in vivo/Model	Cancer Type	Result
Liposome	Doxorubicin (Dox)	SA-5-Dox-LP	In vivo/mice with lung tumors In vitro/BT-474, A549, Calu-3, and MCF-7 cells	NSCLC	Targeted SA-5-Dox-LP showed better anti-proliferative activity

Liposome	Drug	Formulation Name	In vitro or in vivo/Model	Cancer Type	Result
Chitosan oligosaccharide-modified liposomes	Paclitaxel (PTX)	PTX-loaded CP50-LSs	In vitro/A549 In vivo/mice	LC	CSO modification provides promising applicability for nanomedicine
RGD-modified liposomes	DOX	DOX-RGD-LPs	In vitro/A549 In vivo/Balb/c nude mice	LC	The DOX-loaded pH-sensitive liposome, which has been modified with 5% cRGD-lipid, could be used to enhance cancer therapy
Liposome	Lonidamine or Epirubicin	-	In vitro/A549 cells In vivo/Female BALB/c mice	NSCLC	The formulation used as an anticancer agent to treat drug-resistant LC
Folate-modified submicron-sized liposome (ssLip)	Rapamycin (RM)	RM/FA-ssLip	In vitro/KB and LL2 cells and A549 cells In vivo/Male C57BL/6NCr mice	LC	Administration of this formulation extended the survival of LL2 cell tumor-bearing mice
pH-sensitive liposomes (PSL)	Thymoquinone (TQ)	TQPSL	In vivo/Swiss Albino Mice	LC	It shows potential of TQPSL as a LC therapeutic agent
PEGylated liposome	Lycobetaine Olic acid RGD	LBT-OA-PEG-Lipo + nRGD	In vivo/ mice xenograft	Lung carcinoma	Improved tumor penetration, and increased extravasation of formulations and antitumor efficacy

Liposome	Drug	Formulation Name	In vitro or in vivo/Model	Cancer Type	Result
PSL	Afatinib (tyrosine kinase inhibitor)	AFT loaded PSL	In vitro/human LC cells (H-1975)	NSCLC cells	AFT loaded-PSL prompted apoptosis in H-1975 cells
Liposome	Betulinic parthenolide, honokiol and ginsenoside Rh2	Drug-loaded liposome	In vivo/mice In vitro/A549 cells	LC	Cocktail liposome systems could offer a more efficient and safer treatment for LC
PEGylated cationic liposomes	PTX	MLV-PEG-PTX	In vivo/Female C57BL/6 mice In vitro/A549 and the murine lung carcinoma cell line LL/2	LC	MLV-PEG-PTX exhibited biocompatibility and anticancer activity against CSCs
DSPE-PEG2000-PFV	Daunorubicin and Dioscin	Daunorubicin and dioscin co-delivery liposomes	In vitro/A549 cells In vivo/Male BALB/c nude mice	NSCLC	Increased the cellular uptake facilitated by PFV cell-penetrating peptide; augmented inhibitory effects on vasculogenic mimicry formation and tumor metastasis from the inclusion of dioscin
Liposome	Docetaxel and CD133 aptamers	CD133-DTX LP	In vitro/A549 tumor mice In vivo/mice xenograft	LC	CD133-DTX LP significantly decreased cell proliferation and improved the therapeutic efficiency

Liposome	Drug	Formulation Name	In vitro or in vivo/Model	Cancer Type	Result
Folate-modified liposomes	Metallothionein 1D pseudogene (MT1DP) Erastin	Erastin/MT1DP@FA-LPs (E/M@FA-LPs)	In vitro/A549 and H1299 cells In vivo/BALB/c nude mice	NSCLS	The combination increased the bioavailability and effectiveness of the drug/gene
Folate-modified liposome (F-PLP)	Plasmid BIM	F-PLP/pBIM	In vitro/LL/2 and A549 LC In vivo/Female C57BL/6 mice	NSCLS	Developed formulation considerably blocked tumor growth by inducing apoptosis in tumor cells, and inhibited proliferation and angiogenesis
Liposome	Curcumin	Liposomal curcumin dry powder inhaler (LCD)	In vitro/A549 cells	Primary LC	Formulation having notable anticancer effects compared with the other two medications with reference to the pathology
Liposome	Inhalable Pirfenidone (PFD)	PFD-loaded liposomes	In vitro/H4006, A549 cell lines	NSCLC	PFD-loaded liposomes induced cell migration, apoptosis, and angiogenesis assays
Cationic liposome	PTX and Survivin siRNA	L-PTX-PSur	In vitro/NCI-H460 LC cells	LC	Developed formulation synergistically inhibits cancer cell growth
Liposome	PTX Curcumin	RGD- PTX-CUR LPs	In vitro/A549 LC cell lines In	LC	The present formulation shows the

Liposome	Drug	Formulation Name	In vitro or in vivo/Model	Cancer Type	Result
	(CUR) RGD		vivo/BALB/c nude mice		antitumor effect in vivo, compared with the non-modified LPs
Liposome	PTX	LP (liposomal paclitaxel)-in-*E. coli* (LPE)	In vitro/A549 LC cell lines	LC	LPE significantly down-regulated the VEGF and HIF-1α in rat primary LC, and exacerbated apoptosis in the same cells

Conclusions

Because of their adaptability, lipid-based nanocarriers can be used in a wide variety of applications as DDSs. Their versatility in transporting different medications or genes, their simplicity of chemical modification, and their application through various ways make them very attractive. In addition, two other extremely significant features of lipid-based nanocarriers as DDSs are the capacity to use a trigger-based release and the safe transportation of drugs to their target areas. Lipid-based nanocarriers' potential harmful effects are impeding their successful commercial development. However, it is reasonable to have high hopes for the continued development of lipid-based nanomedicines as drug delivery systems in light of recent technological advancements. Lipid-based nanocarrier-based inhalable anticancer therapy is an intriguing and expanding field of study. In the fight against lung metastases and LC, this therapy approach shows promise. Lipid-based nanocarriers are becoming increasingly popular due to their special qualities, which include high drug loading, excellent biocompatibility, and customizable surfaces for controlled drug release and active targeting. The medications contained in these inhalable nanocarriers will target malignant cells by first diffusing into the bloodstream and lymphatic system, after which they will concentrate in the lungs, according to recent preclinical study results. Nebulizers and DPIs are the only pulmonary devices currently on the market that may be effectively used to deliver these nanoparticles. Due to their many benefits and potential to get around some of the drawbacks of this route, DPIs are a very attractive option for inhaled anticancer drug delivery systems packaged in lipid-based nanoparticles. New developments and opportunities arise when lipid-based nanocarriers, DPIs, particle engineering, and formulation sciences are combined. However, especially when it comes to in vivo and clinical investigations, this field's study is still in its infancy. In order to achieve effective lung deposition, drug delivery, and antitumor activity, the overall formulation strategy should focus on creating uni- or multifunctional lipid-based nanocarriers for active targeting, with good drugloading and sustained release properties, embedded in well-engineered microparticles made of safe and well-tolerated excipients of high FPF.

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