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Targeted nanocarriers for lung cancer therapy: lipids for pulmonary drug delivery

J. Patel [a,c], M. Dastjerdi [b], Z. Abbasi Radmoghaddam [b], S. Akbari [a,b], P. Mobarezjou [a], A. Akbari [c*]

[a]*NanoSciTec GmbH, Hermann Weinhauser str. 67, Munich, 81867, Germany*
[b]*BioMedEx GmbH, weyringerg 37 Stiege 1, 1040, Wein, Austria*
[c] *GreenNanoTech Kft, Király Utca 80, Budapest, 1068, Hungary*

Abstract

Lung cancer is one of the leading causes of cancer-related mortality worldwide. The lung cancer treatment strategy includes surgery, high doses of intravenous chemotherapeutic medications, radiation therapy, etc. Chemotherapy, as one of the most essential treatment methods, can increase a patient's survival rate. However, there are serious side effects, systemic toxicity, and poor selectivity associated with the use of chemotherapeutic agents. A combination of nanotechnology and delivery systems has been used as a novel approach to developing cancer therapies, and its global profile is widely growing. Hence, among various nanocarriers, lipid-based nano-delivery systems could potentially circumvent these issues due to their unique properties. The purpose of this study was to investigate the effects of lipid-based nanocarriers for lung cancer therapy by considering a targeted approach. Due to its characteristics, including its small diameter, low toxicity, high biocompatibility, hybrid structure, ability to provide controlled and sustained release, etc., which are mentioned in this research, it could be used by lung cancer sufferers owing to its efficacy and lack of severe side effects because of its targeted function.

Keywords: *Lung cancer, Drug targeting, Lipid nanocarriers, Nanostructured lipid carriers*

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* Corresponding author: A. Akbari. Tel.: +36-20-453-7574 *E-mail address*: armita.akbari@greennanotec.com

1. Introduction

Bronchogenic carcinoma or lung cancer refers to malignancies developing in the lung parenchyma or bronchi [1]. In the United States, it is one of the top causes of cancer-related fatalities. Since 1987, lung cancer has been the leading cause of mortality among women, surpassing breast cancer. An estimated 225,000 new instances of lung cancer are diagnosed yearly in the United States, with around 160,000 deaths attributable to lung cancer [2,3]. A survey based on literature showed patients diagnosed with lung cancer had significant five-year survival rates with the typical three types of cancers including non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), and lung carcinoid tumor. World Health Organization (WHO) has subdivided NSCLC into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma [4]. Non-small cell lung cancer is the most prevalent subtype of lung cancer diagnosed in non-smokers [5]. The only way for fruitful treatment is preferred toward nanotechnology advanced drug delivery systems because of the scope of significant concern and major applications toward the border area of scientific diagnosis and treatment of the above-mentioned types of commoner cancers.

The treatment strategy for lung cancer is determined by the stage of the disease and the state of the patient. Surgery, large doses of intravenous chemotherapeutic drugs, radiation therapy, targeted treatments, immunotherapy, and photodynamic or laser therapy are some of the standard treatment options now available [6,7]. Often, surgery is reserved for the earliest stages of LC and is accompanied by other routes of treatment to eliminate malignant tissue [7,8]. Utilizing chemotherapies such as cisplatin, paclitaxel, and gemcitabine in patients with a late diagnosis is regarded as one of the most promising global lung cancer treatment strategies [9,10]. However, the constitution of these chemotherapeutic agents is typically lipophilic. Consequently, there is an imperative need to develop and expand these therapeutics to improve their curative efficacy and reduce their adverse effects on normal cells. In this regard, the modification of drug formulations, the reduction of macromolecule diameters, the modification of drug charges, and the possible conjugation of therapeutic agents with biodegradable materials could increase the bioavailability of the drugs [11,12]. First, nanotechnology can be used to characterize the potential control of matter between 1 and 100 nanometers in size. In recent decades, this cancer research technology has undergone significant advancements. Moving into this field is strongly recommended for biomedical applications [13,14]. However, proper delivery faces several challenges, such as enhancing the pulmonary clearance mechanism with an increasing nanoparticle diameter directly into the sites of lung cancer cells via both systemic and localized forms of treatment [15]. The anatomy of the lungs provides potent characterization, enabling nanoparticles to optimize their reactions effectively. In general, nanoparticles represent moieties that may interact with one or more monomers to produce structures with colloidal suspension characteristics. Based on their size, net charge, chemical structure, and functionalization, substances can either be toxic or safe for biomedical applications. Its biodegradability and cross-linking largely determine the toxicity of nanoparticles [16]. For this reason, scientists have devoted a great deal of attention to this issue, and today, a significant number of biodegradable nanoparticles have been manufactured that some of them already being used in clinical studies and offered on the industrial market [12]. Most insoluble particulates with diameters greater than 6 mm can be phagocytosed [12,13]. Different

nanocarriers have found great success in turning drugs into aerosols and creating nebulization forces that last for a long time. These have recently been used to treat lung cancer [12]. Because of this, numerous nanoparticles, including liposomes, micelles, solid lipid nanoparticles, and polymeric nanoparticles, have been devised and developed as lung cancer treatment [17-21]. In fact, lipid-based nanoparticles and polymeric nanoparticles (PNP) are regarded as effective delivery systems. These assemblies have been approved by the Food and Drug Administration (FDA) of the United States [22]. Liposomes, solid lipid nanoparticles, and hybrid polymeric lipid nanoparticles are subcategories of lipid-based nanocarriers [23]. As a result, liposomes or targeted nanocarriers are widely employed to localize chemotherapeutic agents within the lungs. As lung cancer has the highest incidence rate compared to any other type of cancer, there have been extensive research studies aimed at finding a better treatment for curing this disease. One of the many approaches is to improve the delivery of anticancer drugs to cancer cells using advanced technologies.

Therefore, in this review, we will aim to investigate the benefits, avenues, and challenges of targeted lipid-based nanoparticle drug delivery systems for lung cancer treatment.

2. Nanotechnology-Mediated Pulmonary Drug Delivery

Due to the inability of lung cancer treatments to reach Due to the inability of lung cancer treatments to reach specific tumor sites, nearly two million people worldwide die from lung cancer [24]. There is an urgent need to enhance the targeted delivery of cancer medications to cancer cell surfaces and targeting moieties using nanocarriers. Specific nano-encapsulated drugs target EGF receptors, Folate receptors, transferrin receptors, and sigma receptors or other target receptors on the surface of lung cancer cells and deliver anticancer drugs, resulting in cancer cell regression [25-37].

It is possible to optimize nanoparticle-based drug delivery systems by decreasing their diameters, controlling their release, and developing improved imaging and diagnostic instruments for the earlier detection of cancerous cells in biological systems [38]. Functionalized nanoparticles can contribute to advancing targeted therapies by optimizing both active and passively targeted treatments [16]. Passive targeting results in the enhancement of the permeability and retention (EPR) effect, which is distinguished by a prominent tumor vasculature and minimal lymphatic drainage [39]. EPR can enhance the distribution of encapsulated payload molecules, whereas nanoparticles accumulate well in tumor tissues due to their ability to reach a specific location with a higher concentration than other formulations [16]. Meanwhile, active targeting can be developed by conjugating medications to specific ligands with a high affinity for binding receptors overexpressed in tumor tissues. Therefore, drugs function as prodrugs until they are identified by the active sites of tumor cells. Pulmonary drug delivery systems offer an excellent opportunity to deliver therapeutic molecules directly to the sites of lung cancer cells via systemic and localized treatment [12,16]. Lung anatomy provides potent characterization, allowing nanoparticles to effectively optimize their reactions. In addition, nanoparticles have been functionalized to have a high solute exchange capacity due to their large surface area and ability to circumvent first-pass metabolism [40]. In general, nanoparticles represent moieties that are capable of interacting with one or more monomers to form structures that have colloidal suspension properties. Based on their size, net charge, chemical structure, and functionalization, substances can be toxic or harmless for biomedical applications. Nanoparticle toxicity is primarily determined by biodegradability and cross-linking [41]. In addition to reducing the cytotoxicity of the chemotherapeutic agent, this decreases the effect of systemic dilution by increasing the likelihood of accumulation at the tumor site [16]. This has enhanced the patient's compliance and quality of life. However, their effective delivery presents some difficulties, such as improving the pulmonary clearance process with an increasing nanoparticle diameter and delivering them [42] directly into the locations of lung cancer cells using both systemic and localized methods of treatment [43].

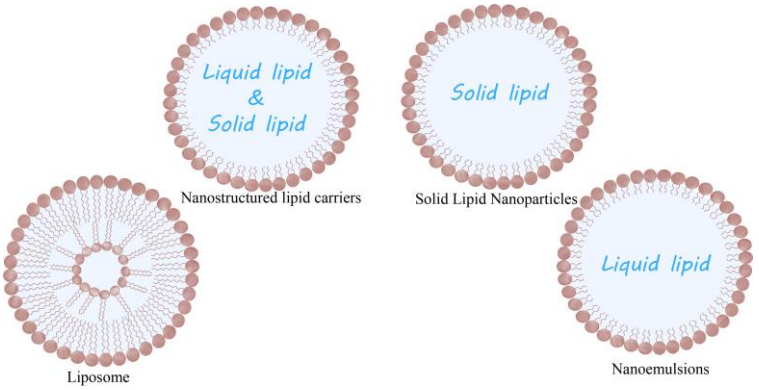

Figure 1. Main types of lipid-based nanoparticles

3. Tpes of lipid-based nanoparticles:

Based on the characteristics and structures outlined below, nanocarriers for pulmonary drug delivery consist of lipid-based nanocarriers (Liposomes, Solid-Lipid Nanoparticles, Nanostructured Lipid Carriers, and Nanoemulsions) or polymer-based nanocarriers. (e.g., micelles, polymeric nanoparticles, nanogels) [44-46] (Figure 1).

3.1 Liposome

Liposomes were authorized in 1965 and are regarded as the first encapsulated microscopic phospholipid bilayer nanosystem [47]. They are spherical vesicles made mostly of unilamellar or multilamellar phospholipids. Their average size ranges from 20 nanometers to more than 1 micrometer [48]. Typically, a liposome has a hydrophilic center and a hydrophobic phospholipid bilayer. Based on the pharmacokinetic properties of the drug [49], this type of structure allows for the entrapment of both hydrophilic and hydrophobic medications. The typical structure of liposomes encapsulates hydrophilic drugs in the aqueous interior and hydrophobic drugs in the lipid bilayer. In the human bloodstream, drugs encapsulated within the central cavity of the liposome are protected against environmental degradation [50]. The size and number of bilayers are two essential factors that affect how much a drug can be loaded and how long it stays in the body; Therefore, unilamellar vesicles and multilamellar vesicles can be distinguished based on these two conditions [51]. Unilamellar vesicles are further subdivided into small unilamellar vesicles (SUV) and large unilamellar vesicles. In multilamellar liposomes, an onion-like structure is formed, and several unilamellar vesicles can form within other vesicles to produce multilamellar concentric phospholipid spheres separated by water molecules [52]. According to extensive research on nanocarriers, modern liposomes exhibit many unique properties and areas encompassing functional characteristics; consequently, novel applications based on liposome materials have emerged [53]. These characteristics imply advantages such as breaching biological barriers or covering the membrane with proteins, peptides, polymers, or other molecules, which significantly enhance the ability to escape from the cells of the mononuclear phagocyte system and thus contribute to longer liposomal half-lives [48].

In pulmonary drug delivery, nanocarrier systems provide several advantages for reducing patient side effects, including uniform dose distribution, drug protection from degradation, increased drug solubility, and enhanced cell penetration [54]. Another method is sustained drug release, which reduces the dosing frequency, improves patient compliance, reduces severe side effects, and applies to all liposomal nanocarrier varieties [55]. Therefore, it is evident from the available literature that liposomal nanocarriers must be evaluated to improve their performance. Each form of lipid-based carrier has a distinct structure, so liposomes used for pulmonary drug delivery have a special structure [56]. One of the most extensively

studied systems for the controlled delivery of pharmaceuticals to the lungs is liposomes [57,58]. Because liposomes can be prepared from compounds endogenous to the lungs, such as the components of lung surfactant, these vesicles appear to be particularly suited for therapeutic agent delivery to the lung. These properties make liposomes desirable candidates as drug delivery vehicles [44]. These vesicles are composed of one or more phospholipid bilayers with an aqueous core, giving them the ability to enclose amphiphilic, lipophilic, and hydrophilic drug molecules within the phospholipid bilayer or at their core [59,60]. There are two forms of lipid-based medications: liquid and powdered granules [61]. Adel, I.M., et al. created spray-dried pro-liposomes for the pulmonary delivery of curcumin as a lung cancer treatment [59]. Vyas SP, Kannan ME, et al. developed a liposomal aerosol for enhanced delivery of rifampicin to alveolar macrophages to treat tuberculosis infection [62]. Stern, Ulrich, et al. expanded the capacity of liposomes as gene carriers [63]. In 2004, to decrease the systemic toxicity of cisplatin, Boulikas developed Lipoplatin, a liposome-based cisplatin drug [64]. Liposomal formulations have long-term instability, which is a significant drawback. Thus, liposomes can be freeze-dried or spray-dried to improve stability and can be formulated as liposomal dry powder for inhalational pulmonary delivery [65].

Due to their strong biocompatibility, liposomes are becoming increasingly popular as ways to deliver anticancer drugs. Liposomes also serve as a biodegradable pulmonary reservoir that enhances pulmonary residence time, decreases the mucociliary clearance of drugs, prevents local irritation, and increases drug potency, which makes them suitable for lung cancer therapeutic purposes [66,67].

3.2 Nanostructured lipid carriers (NLCs)

Bangham initially created nanostructured lipids (NLs) in 1961, which consist of a phospholipid bilayer with a diameter of tens to hundreds of nanometers [68,69]. Nanostructured lipid carriers (NLCs) have been created by transforming NLs into spherical structures with a mixed solid-liquid matrix and an aqueous core surrounded by a lipid bilayer. NLCs are more efficient in trapping, loading, and stability [70]. They are regarded as a new generation of lipid-based nanoparticles used in cancer therapy methods [71-73]. The use of nanostructured lipid carriers as gene carriers has garnered much interest recently. In contrast to SLN and other lipid carriers, NLCs have a larger loading capacity due to the combination of a liquid lipid and a solid lipid, which may be attributed to increased drug accumulation and decreased drug release during storage [74,75]. NLCs loaded with PTX and DOX were presented by Wang et al. for their potential synergistic impact on the treatment of lung cancer. Cytotoxicity tests performed in vitro on NCL-H460 large cell lung cancer cells revealed that the IC_{50} of NLCs loaded with both anticancer drugs at a weight ratio of 1.1 PTX/DOX was three times lower than PTX-NLC and DOX-NLC for single drug administration and ninefold less than the free drug formula. An in vivo investigation on a mouse model of non-small cell lung cancer revealed that the simultaneous administration of both chemotherapeutic treatments increases the potential to target tumors and the inhibitory impact of both medications [76]. In a separate investigation, Makeen et al. (2020) evaluated the cytotoxicity of gefitinib-containing NLCs (GEF-NLCs) against human colon cancer cell lines (HCT 116). Against HCT-116 cell lines, the IC_{50} values for GEF and GEF-NLC were 20.88 M and 4.58 M, respectively. This drug is also used to treat lung cancer [77]. Cetuximab (CET), paclitaxel (PTX), and NLCs coated with 5-Demethylnobiletin (DMN) demonstrated synergistic treatment for advanced lung cancer in a separate investigation [78].

3.3 Solid lipid nanoparticles (SLNs)

SLNs are colloidal drug carriers with sizes between 50 and 1000 nm [79]. They are made by dispersing melted solid lipids in water with an emulsifier (or several emulsifiers). This form of NPs, which came out in 1991, is more advanced than colloidal vehicles like emulsions, polymeric NPs, and liposomes [80]. Most SLNs are made up of solid lipid particles suspended in water or an aqueous solution of an emulsifier [81]. The core, which is typically composed of a solid hydrophobic core and a monolayer or multilayer of phospholipid coating (an emulsifier), contains the dissolved or dispersed substance. Due to the incompatibility of hydrophilic molecules with lipids and the high leakage of the laden drug into the ambient

aqueous environment, the encapsulation of hydrophilic pharmaceuticals in a conventional SLN is challenging [82]. Methods such as the double emulsion technique and the incorporation of various types of lipids were used to produce SLNs with the capacity to load hydrophilic pharmaceuticals, with varying degrees of success as reported in the scientific literature [80,83].

Docetaxel (DCX), for example, is a highly effective chemotherapeutic agent used to treat various forms of cancer, which include NSCLC [84]. The tumor microenvironment may contribute to resistance to DCX via the paracrine amplification loop of multiple cytokines and growth factors generated by the stroma and cancer cell adhesion to the extracellular matrix. The presence of overexpressed growth factors, such as vascular endothelial growth factor, and the efficacy of solid lipid nanoparticles in the drug delivery system are additional factors in the tumor microenvironment that contribute to drug resistance [80,84].

3.4 Nanoemolsions (NEs)

Nanoemulsions are emulsions with a droplet size of about 100 nm, which usually contain oil, water, and an emulsifier (as a surfactant). Also, lipids and proteins can be used in the preparation of nanoemulsions [20,85-88]. Nanoemulsion has not yet been thoroughly investigated for pulmonary drug delivery, and few works and studies have been published in this field [89]. The formulation of inhalable NE is difficult due to the detrimental effects of lipids and surfactants on lung alveoli function [90].

Since they can dissolve a large number of hydrophobic medications within their lipophilic core, O/W NE is of great interest for their production [91-93] and can increase the drug's resistance to enzymatic degradation and hydrolysis, thereby enhancing its stability. NE may sustain pulmonary drug retention for extended periods, so frequency and dosage can be decreased. Furthermore, NEs are simple to produce [93,94] and can employ medications with varying hydrophilicity in a single formulation [94]. On the other hand, drug micro-suspension has several disadvantages, including significant heterodispersity in the concentration of the drug in the aerosolized particles, a brief drug residence time in the airways due to ciliary movement, and a non-optimized drug deposition pattern [94]. As a consequence, researchers are investigating NE as a potential alternative method for addressing these drawbacks.

4. Other nanocarriers-mediated drug delivery systems

4.1 Polymeric nanoparticles

Polymers are synthesized into polymeric nanoparticles as nano-drug delivery systems [95]. Recently several biodegradable polymers have been developed, such as poly(lactic acid) (PLA), poly(lactic-co-glycolic) acid (PLGA), gelatin, chitosan, albumin, poly-alkyl-cyanoacrylates, and polycaprolactone [96-105]. The popularity of using polymers has increased owing to their controlled and sustained release characteristics, subcellular size, and biocompatibility [106-108]. For the delivery of targeted chemotherapeutics for lung cancer, polymeric nanoparticles have been widely utilized. Tseng et al. created a system of gelatin nanoparticles decorated with EGFR-targeted biotinylated EGF (bEGF). These nanoparticles exhibited enhanced cellular uptake in EGFR-overexpressing cancer cell lines, indicating their potential as a targeted lung cancer therapy [109]. Jiang et al. recently studied various polymer-based nanoparticles composed of polycaprolactone (PCL) and surface-modified with chitosan polymer for oral administration of chemotherapy in lung cancer [110]. Polymers have mucoadhesive properties that enhance the therapeutic efficacy of anticancer drugs by interacting selectively with the elevated levels of mucin expressed by cancer cells relative to normal cells [111].

Because of poor solubility, poor bioavailability, a lack of targeted delivery, and numerous off-target effects, the majority of anticancer drugs frequently fail in clinical trials [112]. Polymeric nanoparticles provide controlled and sustained drug release, biocompatibility, and promising anticancer effects [113]. However, the route of administration, nanoparticle size, pharmacokinetic properties, immune clearance, and other factors limit the clinical applications of nanomedicines [114].

4.2 Micelles

Micelles have garnered interest in the delivery of medications with low water solubility [115]. They are formed when amphiphilic molecules self-assemble. Their structures include a hydrophilic/polar region (the head) and a hydrophobic/nonpolar region (the tail) [116]. In an aqueous solution, micelles are formed with the polar region facing the outer surface and the nonpolar region forming the nucleus. Micelles can transport hydrophilic and hydrophobic substances [117]. It is also possible to chemically alter the structure of polymeric micelles in order to design optimal delivery vehicles. This can be modified to enhance drug stability, regulate drug release, and facilitate targeted drug delivery [61]. Uniform distribution of drug dose among the target organ, enhanced solubility, a sustained drug release that consequently reduces the dosing frequency, improved patient compliance, decreased incidence of side effects, and the potential for drug-internalization by cells are all advantages of nanocarrier systems in pulmonary drug delivery [89].

4.3 Nanohydrogels

The term Hydrogel has been used to describe a synthetic or natural polymeric network chemical that is widely recognized as a highly absorbent material (over 90% water). Hydrogel has been widely used as a soft matter classified material for drug delivery and controlled release drug delivery [118].

Hydrogel is a self-healing polymer that transforms into a double network through copolymerization, and its individual superabsorbent properties have been investigated, as demonstrated by research [119]. The primary reason for using advanced lung cancer nanocarriers is that a less cost-effective sorbent material should often be used, such as in the case of regulating the excess of the chemotherapeutic agent towards a wider range of cancer cell treatment targets in single-dose functioning by selective nanohybrid carrier functioning based treatment to improve the quality and affordability of anticancer agents with minimal side effects. Moreover, based on the data, this enhanced nanocarrier-based nano hydrogel material could be advantageously used for lung cancer treatment or other emerging field applications and developments [120,121]. The properties of stimuli-responsive nanohydrogels mimic the effect of a drug molecule engineered for controlled delivery. The activation of double network polymerization is the hydrogel's primary mechanism of action [121,122]. Synthesizing double network nanohydrogels by polymerization from click-mediated biodegradable monomers is an alternative method for addressing issues [19,22,38].

Polyethylene glycol (PEG) and polyvinyl alcohol (PVA) are typical structural components of a nano hydrogel with a double network [123-125]. PEG and PVA are hydrophilic by nature, so click-mediated polymerization of vinyl alcohol or other biodegradable monomers can be used to design synthesis along with support for nano hydrogel-based liposomal nanocarriers for drug delivery. There are numerous reports in the scientific literature concerning the general synthesis of the double-network hydrogel polymerization process and the basic structure of click-mediated double-network nano hydrogel nanocarriers for applications involving linker and terminal proteins or chemotherapeutic agents [126].

5. Conclusion

Recently, nanotechnology has been utilized as a novel approach to developing cancer therapies. Using ligand-receptor conjugation to drive an optimal dose into a specific reaction, functionalized nanoparticles are intriguing in targeting lung cancer cells. Liposomes, solid lipid nanoparticles, and polymeric-based nanoparticles can overcome respiratory tract barriers and mucociliary clearance to deliver drugs into the deep lungs. Although many types of nanoparticles have been manufactured in recent years, liposomes have promising potential in biomedical applications. They are being tested in clinical trials due to their biodegradability, biocompatibility, and ability to undergo large-scale production. They can also be functionalized by PEGylation or layer-by-layer assembly, thereby extending the circulation half-life. In addition, their targeted systems have a small diameter, low toxicity, hybrid structure, the ability to provide controlled and sustained release, and the capacity to regulate the distribution of medications within the core and shell.

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