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Review

Targeted Lipid-Based Drug Delivery Systems for Lung Cancer Therapy

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Abstract: The aim of this study was to review the literature to explore the lipid-based drug delivery systems that have been investigated for improved treatment of lung cancers. Such lipid-based drug delivery systems include microemulsions, liposomes, transferosomes, niosomes, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). In order to minimise the side effects of chemotherapeutic active pharmaceutical ingredients, surface modification with various ligands has been introduced so that the delivery system will attach only to specific receptors which are overexpressed in lung cancer cells. This review briefly explored cancers and their aetiologies and risk factors, especially lung cancer. It then discussed different modifications that have been performed on the drug delivery systems to successfully treat lung cancer. The use of different ligands has also been investigated in this review. The particle size of drug delivery systems after the attachment of the ligand remained small, varying from 75 to 189 nm, which was the most significant physicochemical property during development as it affected the delivery of particles to specific sites in the lungs. Overall, evidence suggests that surface modified lipid-based drug delivery systems have significant potential to revolutionise the treatment of lung cancer, leading to reduced side effects from chemotherapy.

Keywords: lipid-based drug delivery systems; lung cancer; surface modification; targeting moiety; receptors; ligands

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1. Introduction

Cancer now causes millions of deaths every year worldwide, while lung cancer is being responsible for 1 in 5 of these deaths, making it the cancer with the highest mortality rate [1]. In 2020, 19.3 million people were diagnosed with cancer worldwide [2] and around 10 million people died of cancer in the same year [1]. While the incidence (new cases) of breast cancer has increased such that it is now the leading cancer type being diagnosed, with 2.26 million cases in 2020, lung cancer is still the leading cause of cancer deaths [1].

Depending on the stage of cancer, treatment may involve chemotherapy, radiotherapy or surgery followed by chemotherapy and/or radiotherapy. Unfortunately, current therapies are largely inadequate, as they are generally invasive and the cytotoxic drugs used adversely affect the human body in the process [3]. New and better approaches are, therefore, being developed, with a view to reducing the side effects of existing therapies. In this regard, novel drug delivery systems have been developed, optimised and employed for various cancer treatments, such as liposomes, transfersomes, SLNs and NLCs.

The purpose of this study was to review the literature on lipid-based drug delivery systems aimed at improving lung cancer treatment. To reduce the side effects of chemotherapeutic agents, surface modifications with various ligands have been introduced and discussed within this review paper to ensure that the delivery system targets only specific receptors that are overexpressed in lung cancer cells.

2. Cancer

Cancer is initiated in body cells because of a genetic mutation (carcinogenesis). There is an established cell cycle that controls cell growth and cell division. Cells divide based on specific cell cycle signals, and two classes of genes link cell cycle control to tumour formation and development. Oncogenes are mainly associated with the conversion of normal cells to tumour cells, while tumour suppressor genes are basically responsible for blocking cancer development [4]. Various regulatory checks also ensure that a balance is maintained between cell proliferation and cell death. However, cells may grow and divide at a different rate to the normal rate (abnormal rate, usually excessive proliferation) due to a loss-of-function or gain-of-function mutation. Any of these regulatory signals or processes may be wrong, deficient or missing. This can lead to the development of a tumour, which could take on malignancy to become a cancer.

However, not every change (mutation) leads to cancer or is characterised as cancer. A few changes might happen in healthy cells which are usually easily treated and are therefore unlikely to result in cancer, although if not successfully treated they might eventually progress to cancer. One example is hyperplasia, whereby cells divide at a faster rate than the normal rate, thus leading to an increased number of cells in a tissue or in an organ, but the cells look normal under the microscope. Another example is dysplasia, where there is a small change to the morphology of the cells. The more abnormal the appearance, the more chances that cancer can eventually result from it [5]. Hyperplasia and dysplasia are not characterised as cancers and can be easily treated, but if not successfully treated they might lead to cancer [5].

There are solid cancers, where a lump develops, and liquid tumours, where the cancer cells build up in the bone marrow or the blood [6]. There are five major categories of cancer based on their histological characteristics (type of cell they start from) [7]:

- Carcinomas start in the epithelial tissues of the skin or other internal organs of the body such as the liver or the kidneys, such as squamous cell carcinoma, adenocarcinoma or small and large-cell carcinoma.
- Leukaemia starts in the white blood cells.
- Sarcoma is a rare type of cancer which starts in the connective tissues, such as primary pulmonary sarcoma.
- Lymphomas and myelomas start in the immune system cells.

2.1. Risk Factors for Cancer

The various risk factors for developing cancer include age, family history, workplace conditions, environment and/or lifestyle of individuals (e.g., diet, exercise and smoking) [8]. Increasing age is one of the most significant and perhaps the biggest risk factor for the development of cancer. Some cancers are associated with a family history of cancer, although this is not always the case. Regarding workplace and environment, exposure to certain chemicals and carcinogens can potentially increase chances of acquiring cancer; these include asbestos, a few active pharmaceutical ingredients (APIs) such as mirtazapine, an antidepressant drug specifically in high doses [9] or colours in the dye industry (e.g., azo dyes such as E133 "Brilliant blue") whose carcinogenicity is related to the presence of benzidine [10]. A few viruses and bacteria have also been linked with the development of cancer, including human papilloma virus, Hepatitis B and C and Human Immunodeficiency Virus, which are associated with cervical cancer, liver cancer and lymphomas or sarcomas, respectively [11].

Some key lifestyle choices could be risk factors for cancer. For example, smoking is a major risk factor for the development of lung cancer, being responsible for over 65% of lung cancer deaths around the world [12]. Overweight could also increase the risk of developing cancers of the bowel, kidney, womb and oesophagus [13]. Maintaining a healthy body weight requires following a balanced diet. Foods with high fibre levels can reduce the risk of developing bowel cancer [12,14], while red meat is associated with a higher risk of bowel and prostate cancer [15]. Exercise and being physically active can also enhance body health

and food processing and disposition within the body, which in turn can reduce exposure to various ingredients that could cause cancer [16]. Moreover, limiting to certain (moderate) levels the amount of alcohol consumption could reduce the risk of various cancers such as breast, bowel and mouth cancers [17], while avoidance of excessive exposure to ultraviolet rays could reduce the risk of developing skin cancer [18].

2.2. Cancer Heterogeneity and Phenotype Variability

Manifestations of the same cancer can be different from person to person or gender to gender, based on several reasons. One reason could be related to the site of origin: there are various cell types in which cancer can develop within tissues or organs such as lungs, bones, eyes, skin, etc. A cancer that develops in the same organ in two different individuals can be expressed in different cell types in those individuals and therefore manifest different phenotypes. For example, in the case of lung cancer, it could be an adenocarcinoma (begins in glandular (secretory) epithelial cells) or a small cell lung cancer (lung cell types affected appear small and round under a microscope). These different types of lung cancer are treated using different approaches [19]. Cancers are also different in their survival rates, which are assessed based on the chances that a cancer patient stays alive, usually after five years of diagnosis. Some skin cancers like non-melanoma skin cancer have a 99.9% five-year survival rate, meaning that less than 1 person in 100 diagnosed with this cancer type will die within five years of the diagnosis. On the other hand, there are a few cancer types, such as liver and lung cancer, which have high mortality rates and therefore extremely low five-year survival rates, especially in older people [19].

Staging and grading are used to determine the size or severity of a cancer. The stage of a cancer describes the tumour size as well as how far it has spread from where it originated, and different staging systems are used for different cancers, for example the TNM system, which is used for many types of cancer, where T relates to tumour size, N relates to the lymph node and M relates to metastasis. The lower the stage number, the higher the five-year survival rate and also the higher the chances that the cancer can be treated successfully [19]. The grade of a cancer, usually between 1 and 4, is based on how the cells appear under a microscope (lower-grade cancer is slower-growing, and higher-grade cancer is faster-growing). For example, in Grade 1, the cancer cells which have already formed a tumour look like normal cells and their rate of division is slow, while in Grade 4 the morphology of the cells has already changed significantly, and the cell division is much quicker than in their healthy counterparts. The higher the grade, the lower the possibility of long-term survival [19].

2.3. Cancer Treatments

When cancer is detected, several treatment approaches can be adopted based on the type and the stage of the cancer. The cancer type and stage will determine how aggressive the treatment should be. When metastasis has not occurred (cancer is still localised to the origin), surgery is a major treatment [20]. However, surgery is invasive and could have a few negative effects on the patient, including on their appearance. For example, following breast cancer surgery, additional plastic surgery may be required to improve the appearance of the breasts. Where surgery cannot successfully remove all the cancer cells, post-surgery chemotherapy or radiotherapy is usually required to eliminate the remaining cancer cells. However, radiotherapy and chemotherapy also have their own negative effects, as they usually do not only affect the cancer cells but also kill healthy cells either surrounding the cancer cells (in radiotherapy) or actively dividing (in chemotherapy) [3].

2.4. Lung Cancer and Particle Deposition

There are mainly two different types of lung cancer: the small cell lung cancer (SCLC) and the non-small cell lung cancer (NSCLC). NSCLC, being the most common, is responsible for 80–85% of the lung cancer cases [21]. SCLCs are acquired from the hormonal cells of the lung and are the most dedifferentiated cancers, and generally occur as central

mediastinal tumours. SCLCs comprise 10–15% of all lung cancers, and they spread rapidly into submucosal lymphatic vessels and regional lymph nodes and are always present without a bronchial invasion. SCLCs remain one of the deadliest malignancies with a 5-year survival rate of less than 7% [22].

NSCLC is further classified into three types: squamous-cell carcinoma, adenocarcinoma and large-cell carcinoma. Squamous-cell carcinoma comprises 25–30% of all lung cancer cases. It occurs from early versions of squamous cells that are present in the airway epithelial cells of bronchial tubes in the centre of the lungs. This subtype of NSCLC is mainly caused by smoking cigarettes. Adenocarcinoma is the most common type of lung cancer and comprises around 40% of all lung cancers [23]. Adenocarcinoma is the most prevalent type of lung cancer in both male and female smokers and non-smokers. It generally occurs in the periphery of the lungs and prevents the entry of large particles into the lungs. In comparison to other types of lung cancers, adenocarcinoma tends to grow slower and has a significant chance of being detected in the lungs before spreading to other parts of the body from the lungs. Large-cell (dedifferentiated) carcinoma generally accounts for 5–10% of lung cancers. The central part of the lungs is significantly affected by large-cell carcinoma, which sometimes extends into nearby lymph nodes, the chest wall and distant organs. Large-cell carcinoma tumours are strongly associated with smoking [24]. However, the identification of genetic changes in NSCLC and a better understanding of the composite biology of molecular subtypes of the disease has changed the diagnosis and treatment of advanced lung cancer [25]. Early screening of lung cancer is considered a significant step in improving patient survival [26].

There are various therapies for lung cancer, including surgery, chemotherapy and radiotherapy, depending on the stage of the cancer [27]. During drug administration for pulmonary delivery, the deposition of drug particles in the different parts of the lung depends on the particles' size, shape and density. The right lung consists of three lobes and the left lung of two lobes. The lungs further comprise the bronchi and small airways, the alveoli, lymph tissues and blood vessels [28].

There are three mechanisms by which particles can deposit in the lungs:

- Inertial Impaction: The deposition of the particles near the surfaces of the airways during the air flow changes [29]. Most of the particles deposit at the oropharynx and the primary bronchi and this is usually observed for dry powder inhalers, metered dose inhalers and nebulisers with particle sizes larger than 5 μm [28]. This may be responsible where particles fail in manoeuvrability and hence deposition occurs in the upper respiratory tract.
- Sedimentation: The deposition of the particles is highly affected by the breathing process and gravitational forces. Particles within the size range of 1 and 5 μm deposit to the smaller airways and the bronchioles (secondary bronchi) [28].
- Brownian Diffusion: The deposition of the particles in areas where they can be dissolved in the alveolar fluid. Particles smaller than 1 μm are deposited in the area of the lung and particles with a size less than 0.5 μm are exhaled [28]. Deposition of formulation in this region can be further improved by holding breath for a few seconds.

3. Drug Delivery Systems

In chemotherapy, the most important step is that the drug reaches the desired site of action successfully with minimal adverse reactions. A variety of drug delivery systems have been developed, trialled and used in order to deliver anticancer APIs to specific sites of action, i.e., the lungs, in order to avoid high-dose delivery and therefore reduce associated side effects (Figure 1). Drug delivery systems are also important because they avoid affecting the healthy cells or tissues surrounding the targeted area. The maximum efficacy with the minimum side effects of a drug delivery system can be achieved via controlling the physicochemical properties of the formulation; these include the particle size, shape and distribution, drug loading, entrapment efficiency, surface properties and charge as well as release profile of a drug [30].

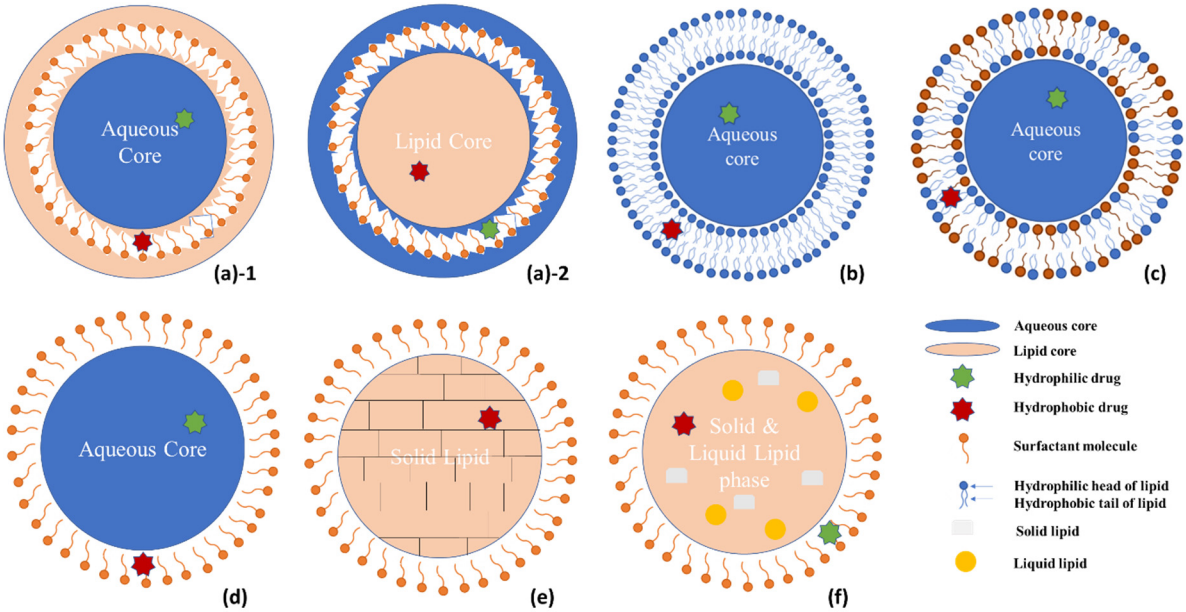

Figure 1. (**a**)-1,(**a**)-2 Microemulsion consisting of water, oil and surfactant; (**a**)-1 is water in oil emulsion and (**a**)-2 is oil in water emulsion. (**b**) Liposome containing of phospholipids and an aqueous core. (**c**) Transfersome comprising phospholipids, surfactant and an aqueous core. (**d**) Niosome consisting of neutral lipids like cholesterol and surfactant. (**e**) Solid lipid nanoparticle comprising of solid lipids and surfactant. (**f**) Nanostructured lipid carrier structure, consisting of solid lipids, liquid lipids and surfactant.

There are three major categories of these lipid-based drug delivery systems that have been widely trialled in cancer treatment: (a) emulsions, which include micro and nanoemulsion [31], and self-emulsifying drug delivery systems [32]; (b) vesicular systems, which include liposomes/proliposomes [33], niosomes/proniosomes [34], transfersomes/protransfersomes [35]; and (c) lipid particulate systems, which include SLNs [36], NLCs [37] and lipid/drug conjugates (Figure 1).

A comparison of the susceptibilities of cancer cell lines and normal cell lines is essential during assessment of any formulation in the early stages of development; this is completed ahead of any animal testing in order to identify whether the formulation is able to selectively target cancer cells to be an effective chemotherapeutic agent. Cytotoxicity studies are employed to assess the cell death that is caused by a test material and the parameter measures, and compare cell number in the absence of and following exposure to the specific material [38]. The following terms are used in Table 1.

- Cell viability: This term refers to the number of healthy, alive cells [39].
- IC50: This term refers to the concentration of a tested material, i.e., active pharmaceutical ingredient or formulation, that is required for 50% inhibition [40].
- Antitumour/cytotoxic effect: This term refers to the ability of any tested material to stop abnormal cell growth or kill (cancer) cells via various mechanisms such as cell apoptosis [41].

3.1. Microemulsions

Microemulsions have been introduced by Hoar and Schulman [42] and they consist of oil, water and surfactant (Figure 1a). They have been majorly employed for topical delivery, but have also been used for lung cancer therapy [43]. They are classed as self-aggregated systems and in contrast to conventional emulsions, they are more stable thermodynamically. They also offer better permeability due to their lower viscosity. Their disadvantages include the usage of toxic organic solvents for their preparation and a complex manufacturing procedure involving high-cost equipment and long processes [44]. Some drugs which have

been entrapped within microemulsions for lung cancer therapy as shown in Table 1 are etoposide [45], gemcitabine [43] and simvastatin [46]. Pharmacokinetic studies have shown that a microemulsion containing paclitaxel exhibited a significantly higher area under the curve (AUC), a much smaller elimination rate constant (K10) and reduced circulation time in rats compared to the plain paclitaxel [47].

3.2. Liposomes/Proliposomes

Liposomes (Figure 1b) were discovered by Bangham et al. [48]. They consist of a lipid bilayer consisting of phospholipids, cholesterol and an aqueous phase which is enclosed in the lipid bilayer [49]. Phospholipids are commonly obtained from natural or synthetic sources and are called amphiphilic molecules as they have a hydrophilic head group and a hydrophobic tail group. When these phospholipids come in contact with aqueous medium (above their phase transition temperature), they tend to self-assemble into vesicles, where, based on alike-likes-alike, the lipophilic moiety of phospholipids attracts the lipophilic part (tail–tail), and the lyophobic part towards the lyophobic moiety (head–head) [50,51]. Their advantages include low toxicity and high biocompatibility, and entrapment of both hydrophobic and hydrophilic drugs. However, liposomes are associated with stability issues like vesicles aggregation, vesicles fusion and leakage of drugs. For this reason, proliposomes offer a better, more stable alternative, which is the dry formulation of liposomes, and it can be achieved by spray drying, freeze drying or rotary evaporation [52,53]. Proliposomes also have an additional component called a carbohydrate carrier (i.e., sorbitol, mannitol, lactose or sucrose) [52]. Some drugs which have been entrapped within liposomes for lung cancer therapy as shown in Table 1 are paclitaxel [33], docetaxel [54] and triptolide [55]. A pharmacokinetic study revealed that the mean maximum concentration in the pleural fluid ($C_{max,IP}$), the disposition half time ($T_{1/2}$) and the area under the concentration–time curve in the pleural fluid ($AUC_{0\rightarrow96,IP}$) were approximately two times higher compared to free paclitaxel. Additionally, the area under the concentration–time curve in plasma during 96 h ($AUC_{0\rightarrow96,Pla}$) was significantly greater than that of free paclitaxel. However, the excretion rate in urine over 24 h was lower than that of free paclitaxel [56]. Immune responses included increased selectivity, site-specific delivery or co-delivery of APIs with different mechanisms of action [57]. Intravenous and intratracheal delivery have also been investigated for the delivery of docetaxel for lung cancer treatment, with the latter being more effective, showing a higher peak concentration and reduced clearance [58].

3.3. Transfersomes/Protransfersomes

Transfersomes were introduced by Cevc and Blume [59] (Figure 1c). These vesicles comprise phospholipids and neutral lipids such as cholesterol and surfactants. A surfactant is a single-chain molecule (containing both hydrophilic and lipophilic moiety) that destabilises the lipid bilayers of vesicles and enhances their deformability, and therefore they are called elastic or deformable vesicles. Examples of surfactants used in formulating transfersomes are Span 60, Span 80, Tween 20, Tween 80 and sodium cholate. The selection of the type of surfactant in transfersomes directly affects the physicochemical properties of the vesicles. They offer sustained release and higher entrapment efficiency compared to liposomes [60]. Their disadvantages include high production cost and low drug incorporation due to possible leakage and they might undergo oxidation which would lead to degradation [61]. Protransfersomes refer to the dry formulations of transfersomes [35] and they are prepared similarly to the proliposomes with the addition of a carbohydrate carrier. Paclitaxel has been successfully entrapped within transfersomes intended for lung cancer therapy [35] (Table 1). The intravenous route has been explored; however, they have mostly been studied for transdermal delivery due to their flexibility; enhanced pharmacokinetic parameters, such as AUC and $T_{1/2}$, have also been observed for the latter one [62].

3.4. Niosomes/Proniosomes

Niosomes (Figure 1d) were introduced by L'Oreal in 1989 [63] and they consist of neutral lipids, for example, cholesterol and surfactants [64]. They have proven more successful for skin penetration and are more stable due to the surfactant used instead of a phospholipid used in liposomes, as they can be easily oxidised [65]. The presence of cholesterol also increases the stability of the encapsulated drug, which in turn increases the entrapment efficiency [66]. Even though niosomes exhibit very good chemical stability, they lack physical stability and, like liposomes, there might be issues like vesicle aggregation, vesicle fusion and hydrolysis of the encapsulated drug, which in turn could lead to shelf-life shortening [67]. For this reason, proniosomes offer a better, more stable alternative. Some drugs which have been entrapped within niosomes for lung cancer therapy as shown in Table 1 are vinblastine [68] and co-delivery of gemcitabine and cisplatin [69]. Intravenous niosomal delivery of ofloxacin demonstrated higher Cmax, AUC and t1/2 values compared to the commercially available intravenous ofloxacin product, suggesting that the investigated floxacin niosomes could be a potential carrier system to improve patient compliance and reduce side effects [70]. Other routes of administration for niosomes include transdermal [71], oral [72] and ocular [73].

3.5. Solid Lipid Nanoparticles (SLNs)

SLNs were pioneered by Eldem et al. [74] (Figure 1e). SLNs consist of solid lipids such as fatty acids and surfactants. The combination ratio of lipids and surfactants used in preparing SLNs affects the particle size, particle size distribution, long-term storage stability, drug loading and release rate. Various types of lipids that are used in formulating SLNs include fatty acids, steroids, waxes, monoglycerides, diglycerides and triglycerides, and are present in a solid state at room temperature. Similarly, various surfactants can be employed based on their hydrophobic–lyophobic balance in SLN formulation. In SLNs, solid lipids are used in order to increase the control over release kinetics of encapsulated drugs and also enhance the stability of chemically sensitive lipophilic excipients [75]. Their advantages include low toxicity and high biocompatibility. However, they are not flexible due to the presence of solid lipids and cannot therefore incorporate high amount of a drug [76]. Some drugs which have been entrapped within SLNs for lung cancer therapy are paclitaxel [77], epirubicin [78] and docetaxel [79] (Table 1). Intravenous delivery of doxorubicin within SLNs was investigated and the pharmacokinetic studies showed that the SLNs exhibited a notably higher AUC, a lower clearance rate and a smaller volume of distribution compared to the commercial doxorubicin solution [80]. Ocular [81] and oral [82] delivery have also been studied for SLNs, showing positive results against the free respective drugs.

3.6. Nanostructured Lipid Carriers (NLCs)

To overcome the disadvantages of SLNs (i.e., to form a rigid crystalline or a perfect ordered core), NLCs (Figure 1f) were introduced by Muller et al. [83]. To create NLCs, liquid lipid was added to the preparation of the SLNs in addition to the already-used materials, i.e., solid lipid and surfactant. The lipid droplets were partially crystallised and had a less-ordered crystalline structure (or amorphous structure) [84]. Flexibility was increased and therefore higher drug loading was achieved when compared to SLNs [85]. For these reasons, a better stability for the encapsulated drug was accomplished [86]. On the contrary, the NLCs may become sensitisers and become irritants due to the surfactant presence; therefore, their concentration and selection during NLC preparation is significant for the cell type that the NLCs are intended to target [61]. The use of solid lipids in the preparation of NLCs previously led to larger-sized particles, but due to continuous increase in liquid lipid content the particle size decreased due to a decrease in viscosity and an increase in molecular mobility. Therefore, the amount of lipid content is important in NLC formulation [87]. Some model drugs like doxorubicin [37], sunitinib [88] and paclitaxel [89] have been incorporated in NLCs for lung cancer therapy (Table 1). NLCs can be delivered through the oral [90], pulmonary [87], intravenous [91] and percutaneous [92] routes.

Regarding pharmacokinetics studies, intraperitoneal delivery of curcumin-loaded NLCs has displayed a significantly higher Cmax and AUC, showing that the NLCs have improved the relative bioavailability of curcumin when entrapped within the delivery system [93].

Table 1. Representing lipid-based formulations used for lung cancer therapy, their size, polydispersity index (PDI), entrapment efficiency (EE) and cytotoxicity results.

Drug Delivery System	Drug	Particle Size (nm)	PDI	EE (%)	Cytotoxicity	Ref.
Microemulsions	Etoposide	44.3	-	94.3	The IC50 of etoposide-loaded microemulsion was 1.49 μg/mL against 5.03 μg/mL of the plain etoposide on A549 lung cancer cells.	[45]
	Gemcitabine	-	-	-	The cytotoxicity study revealed a low antiproliferative effect of plain drug against A549 lung cancer cells compared to drug-loaded water in oil microemulsion.	[43]
	Simvastatin	-	-	-	The microemulsion improved the antitumour effect of the drug against A549 lung cancer cells.	[46]
Liposomes	Paclitaxel	5350	3.32	95.45	The paclitaxel-loaded liposomes exhibited lower cell viability of 58% against MRC5-SV2-transformed human lung fibroblast cells.	[33]
	SiRNA and docetaxel	165.4	0.115	95	The IC50 of the siRNA/docetaxel-loaded liposomes was lower compared to the free docetaxel against A549 and H226 lung cancer cells.	[54]
	Osimertinib	100.91	0.200	77.89	The liposomes reduced the IC50 by 2.2-fold compared to the free drug in NCI-H1975 human adenocarcinoma cells.	[94]
Transfersomes	Paclitaxel	254.36–458.92	0.330–0.382	93–96	The paclitaxel-loaded transfersomes exhibited significantly lower cell viability of 60–68% against MRC5-SV2 transformed lung fibroblast cells.	[35]
Niosomes	Vinblastine	234.3	-	99.92	The IC50 of the niosomal formulation was 5.3 and 7.4 μg/mL after 48 and 72 h, respectively, against 10.4 and 13.3 μg/mL for the same incubation time for the free drug in TC-1 lung cancer cells.	[68]
	Gemcitabine (G) and cisplatin (CS)	166.45	0.16	74.37 for G and 85.44 for CS	The niosomal formulation was weakly toxic and moderately toxic to MRC5 lung cells and A549 lung cancer cells, respectively, against the plain drug which was very toxic to both cell lines.	[69]
SLNs	Paclitaxel	114.2	0.117	82.5	Plain paclitaxel showed a 20-fold lower cytotoxic effect than the SLN formulation in MXT-B2, a metastatic mammary carcinoma cell line.	[77]
	Curcumin	20–80	-	62–75	The IC50 of the curcumin-loaded SLN was 1/20 of that of the plain drug.	[95]
	Epirubicin	223.7	-	78.9	Cytotoxicity studies showed that the SLN formulation was more cytotoxic than the plain epirubicin against A549 lung cancer cells.	[78]
	Docetaxel	126	0.19	86	The IC50 for the SLN formulation was found to be 0.08 μg/mL and 0.01 μg/mL after 24 and 48 h incubation, respectively, and 10 μg/mL and 0.3 μg/mL for the plain docetaxel.	[79]
NLCs	Doxorubicin (D) and β-element (ELE)	190	0.2	91.8 for D and 86.9 for ELE	The cytotoxicity of the NLC formulation was higher than that of the combination of the plain drugs. Also, the in vivo anticancer activity showed that the tumour inhibition ratio was 24.1 for the combination of the plain drugs and 65.4% for the NLC formulation.	[37]
	Sunitinib	125.50	0.22	85.10	The IC50 of the NLC formulation was found to be 2.17 μg/mL while the plain sunitinib's IC50 was found to be 3.14 μg/mL.	[88]
	Paclitaxel	79	-	87	The NLC formulation showed significantly higher cytotoxic effect compared to the plain paclitaxel solution in NCI-H460 lung cancer cells.	[89]

4. Surface Modification

Targeted drug delivery is a kind of smart drug delivery system which delivers the drug to targeted parts of the body (e.g., organs/tissues/cells). The concentration of the drug in the desired targeted part of the body is increased and this improves the efficacy of treatment by reducing the side effects. By delivering the drug to the desired part of the body, the desired plasma concentration is maintained, and healthy cells/tissues are avoided in the case of cancer. When designing a targeted drug delivery system, the following factors should be considered: drug properties, side effects of drugs, route of drug administration, site of target and the disease [96]. In 1986, Matsumara and Maeda [97] found out that the solid tumours have defective architecture in their blood vessels. Large molecules with molecular mass over 40 kDa leak out from the tumour vessels and they are therefore accumulated in the tumour tissues, which does not happen in healthy tissues [98]. This is called the enhanced permeability and retention (EPR) effect. The EPR effect in combination with the rapid clearance of some anticancer agents and drugs in general from the bloodstream created the necessity of finding an additional way to maintain the successful targeted delivery of a therapeutic drug. Surface modification of the drug delivery systems was then identified that can help in overcoming these issues [99].

Surface modification may be achieved by using various targeting ligands such as proteins, antibodies, peptides, carbohydrates or other small molecules in order to improve the selectivity process. Binding these ligands onto the surface of a drug delivery system can bind them to specific receptors in order for them to be accumulated locally, and as a consequence the therapeutic outcome is enhanced and a lower dose might also then be required [98,99]. Other advantages of surface modification include decreased side effects with improved patient compliance, controlled biodistribution as well as increased localisation [100].

4.1. Passive and Active Targeting

Drug delivery systems may achieve their objective, i.e., delivery of the drug to the desired site of action via various mechanisms. These include passive and active targeting.

Passive targeting is highly associated with the inflammation caused by a tumour. APIs with a size larger than 40 kDa can easily permeate through the endothelium of the blood vessels that are created during tumour growing—the EPR effect [101]. An important disadvantage is that smaller molecules cannot be retained within the vessels and therefore cannot treat the newly created cancer cells; in these cases active targeting is preferable [102]. Another alternative is the PEGylation of these anticancer drugs which gives them a bigger size and total molecular mass and also an increased solubility as well as increased stability [103]. Due to the EPR effect, the anticancer drugs that are PEGylated have more chances to be more easily accumulated within the cancer cells and consequently kill them rather than the plain drugs themselves.

The mechanism involved with passive targeting involves the circulation of the prepared drug delivery system within the human bloodstream. The targetability of the drug delivery system is directed through various factors such as molecular shape, temperature or pH and the targets include receptors or lipid components found on cancer cell membranes or antigens and proteins that can be found on cancer cell surfaces [104].

Active targeting occurs when a moiety that is capable of targeting is attached directly to the delivery system in order to identify and connect to specific cancer cells; the main reason for the attachment is the difference in the surface biology that the cancer cells have compared to the surrounding healthy ones. The surface biology of the cancer cells is different due to the overexpression of some receptors, which only occurs in the presence of cancer; these receptors do not overexpress in healthy cells. Once the cancer cells are targeted and the moiety is attached to these specific overexpressed receptors, the drug delivery systems allow the release of the encapsulated drug [105].

The mechanism regarding the active targeting varies depending on the receptor attached to the drug delivery system. Receptors which are overexpressed in cancer cells are not developed on healthy cells; this is the reason why ligands are used on the drug

delivery system's surface in order to be attached onto the overexpressed receptors of cancer cells [106].

4.2. Lung Cancer and Targeting

When trying to target lung cancer cells, it must be taken into account that there are some receptors which are overexpressed in these cells. Some typical examples are described below.

- Epidermal growth factor receptor (EGFR): EGFR mutations have been identified to be associated with some lung cancers, more specifically responsible for non-small cell lung cancer [107]. This type of lung cancer is highly associated with higher mortality rates as well as metastatic behaviour [108] and poor chemosensitivity [109].
- Transferrin receptor: Cancer cells require an increased amount of iron when trying to grow and divide. Proteins such as transferrin (Tf) have been used in multiple delivery systems for cancer therapy, as the Tf receptor is overexpressed widely in various cancer cells such as lung cancer cells [110]. Tf enables the binding of two atoms of iron, making it ideal for targeting cancer cells [111].
- Folate receptor: This receptor has shown an increased selectivity in lung adenocarcinomas, making it an excellent target for this type of cancer [112].
- Cluster of differentiation 44 (CD44): It has been found that this glycoprotein is highly overexpressed on the surface of lung cancer cells [113] and it is associated with Fas protein expression [114], and therefore the initiation of the cancer cells' apoptosis process.
- Other receptors such as $\alpha_v\beta_3$ integrin receptor [115], luteinising hormone-releasing hormone (LHRH) receptor [116] or tyrosine kinase Axl receptor [117].

Some typical examples of targeted moieties previously explored are shown in Figure 2 and include glycoproteins such as transferrin [110]; antibodies or antibody fragments to avoid the risk of inactivation of the antibody; aptamers such as A15 which has been identified as promising to target CD133 lung cancer cells [118]; and peptides such as CB5005 which inhibit the activation of transcription factor nuclear factor-κB [119]. Other types of ligands include hyaluronic acid, which has been used when targeting specific receptors (for example, glycoprotein CD44) that are overexpressed in most lung cancer cells [120], and folic acid, which has been widely used for functionalization when targeting folate receptors [121].

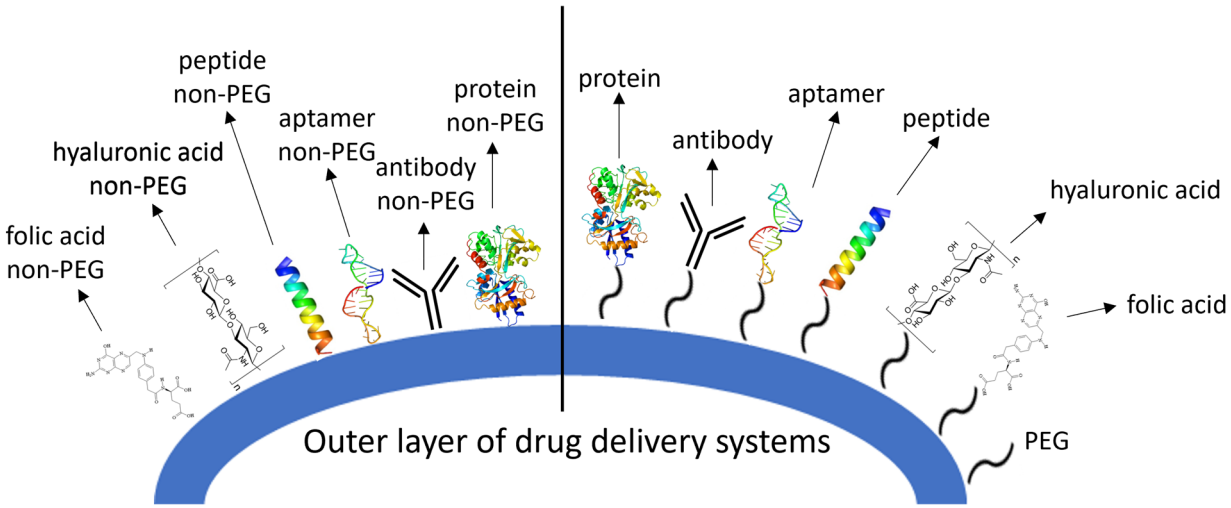

Figure 2. Different surface modifications for drug delivery systems which include PEGylation (**right** side) or not (**left** side).

Targeting any of these receptors can help in inhibiting lung cancer survival, any possible metastasis or tumour growth. During in vitro testing when developing a medicine,

a few different lung cancer cell lines have been employed. A549 is the most common of them, as there are many studies in which an active pharmaceutical ingredient of a drug delivery system has been tested in this cell line which was first isolated in 1972 from the lung tissue of a 58-year old Caucasian man who suffered from bronchioalveolar lung cancer [122]. Another cell line that has been employed is H460 which, in comparison with A549, grows almost two times faster than A549 cells [123]. It is unique for studies because it is characterised as aggressive, since it has increased capacity for metastasis [124]. Another cell line employed is the H1299 cell line, also known as NCI-H1299 cell line, which has been isolated from the lymph node [125]. These cell lines are related to NSCLC. With regard to SCLC, H69, H466 and SHP-77 cell lines can be used. Both H69 and H466 cell lines have been introduced in 1982 by Carney et al. [126], while SHP-77 has been isolated by Ohara and Okamoto [127] from the upper lobe of the left lung of a 54-year old man.

4.3. Application of Targeted Lipid-Based Drug Delivery Systems in Lung Cancer Treatment

Targeted drug delivery systems have shown enhanced tumour internalisation, diagnostic imaging and prolonged in vivo survival when compared to non-targeted drug delivery systems [128]. By surface functionalisation, key factors such as circulation time, cellular uptake, payload accumulation at the tumour site, bypassing lysosomal degradation and stimuli-responsive payload release at the desired site can be improved [129]. Most of the applications of surface modification for the treatment of lung cancer have been performed on liposomes and NLCs; however, similar approaches can be adopted to surface-functionalise other lipid-based formulations.

When trying to target specific cells, and more specifically lung cancer cells, it is important to select the correct targeting moieties to achieve high selectivity in combination with minimal influence on healthy cells. This is important for the patients because when healthy cells remain intact, then side effects are minimal. Therefore, the targeting moiety should only attach on and kill the cancer cells and not the healthy ones. This is the reason why during any initial study in the laboratory a comparison of the susceptibilities of cancer cell lines and normal cell lines is required ahead of any animal testing or human clinical trials. Regarding the confirmation of ligand attachment onto the surface, various techniques have been used, such as transmission electron microscopy (TEM) [118], atomic force microscopy (AFM) [130], Sodium dodecyl-sulfate polyacrylamide gel electrophoresis (SDS-PAGE) [131], proton nuclear magnetic resonance (H-NMR) spectroscopy [88] and Fourier-transform infrared (FTIR) spectroscopy [88]. However, in some cases, there has been no difference between the modified and the non-modified liposomes when observed via TEM [119].

There have been a few studies where the surface modification of liposomes and NLCs has been investigated (Table 2). Most of the studies have used a specific cell line, i.e., A549. They are characterised as hypotriploid human alveolar basal epithelial cells and they are generally used during in vitro studies mostly for type II pulmonary epithelial cells and for lung adenocarcinoma cells [132]. Other cell lines that are presented in the same table include the NCI-H460 cell line as well as the MRC5-SV2 cell line. The latter cell line was derived from the MRC5 lung cell line by transformation with the SV40 virus, a known oncogenic virus [133]. The responses of a cancer cell line should be compared with those of a corresponding healthy cell line, for example (in the case of the MRC5-SV2), the MRC5 cell line, which was derived from the healthy lung tissue of a 14-week old foetus which was removed from a 27-year old woman in 1966 as reported by Jacobs et al. [134].

There are some receptors which are overexpressed normally in lung cancer cells. These include the transferrin [89] receptor, folate receptor [135] as well as EGFR [136]. For these types of receptors, the cell culture studies are performed directly in the wide-type cell lines. However, in other cases, cells have to be engineered or have their growth conditions modified to overexpress the receptor of interest; an example is the carbonic anhydrase receptor, for which the cells have to be incubated under hypoxia in order for this receptor to be overexpressed [131].

Table 2. Targeted lipid-based drug delivery system. This table describes various drug delivery systems, i.e., liposomes and NLCs that have been investigated, the drug involved, the cell line tested, the surface modification (SM) materials, the ligands and the targeted receptors as well as the particle size and the test that has been performed to identify the attachment of the ligand on the outer surface of the delivery system.

System	Drug	Cell Line	SM Material	Ligand	Receptor	Size (nm)	Test	Ref.
Liposomes	Docetaxel	A549	DSPE-PEG2000	A15	CD133+ cells	116.5	TEM	[118]
	Triptolide	A549	DSPE-PEG-MAL	Anti-carbonic anhydrase IX antibody	Carbonic anhydrase IX	160.1	SDS-PAGE	[131]
	Docetaxel	A549	N/A	Aspartate-polyoxyethylene stearate	ATB0,+	99.5	AFM	[137]
	Paclitaxel	A549	Pluronic P123	Chitosan oligosaccharide with Pluronic P123 (CP50)	Not specified	75	TEM	[138]
	Tiptolide	A549	DSPE-PEG2000-MAL	Anti-carbonic anhydrase IX antibody and CPP33	Not specified	137.6	n/a	[55]
	Rapamycin	A549	DSPE-PEG2000-Folate	Folic acid	Folate receptor	122.9	n/a	[139]
	Doxorubicin	A549	DSPE-PEG2000-Mal	GE11 peptide	EGFR	124.0	TEM	[140]
	Irinotecan	A549	Mal-PEG3400-DSPE	CB5005	NF-κB	120	TEM	[119]
NLCs	Sunitinib	A549	Stearylamine	Biotin	Biotin receptor	125.50	H-NMR and FTIR	[88]
	Doxorubicin	H460	SA-PEG4000-COOH	Bombesin	Gastrin-releasing peptide receptors	128	IR and H-NMR	[141]
	Paclitaxel and siRNA	A549	DSPE-PEG2000	LHRH	EGFR	n/a	n/a	[136]
	pDNA	A549	PEG-DSPE	Transferrin/ Hyaluronic acid	CD44	189.1	TEM	[142]
	Paclitaxel and 5-Demethylnobiletin	A549	DSPE-PEG-Mal	Cetuximab	EGFR	130.0	TEM	[143]
	Doxorubicin/Paclitaxel and siRNA	A549	DSPE-PEG-COOH	LHRegH/Cy5.5	Plasma membrane of lung cancer cells	100	AFM	[130]
	Gemcitabine and paclitaxel	A549, NCLH1299, LTEPa2 and L929	PMAGP-GEM	N-acetyl-d-glucosamine	Glucose	120.3	TEM	[144]
	Paclitaxel and DNA	NCI-H460	Glycol-phosphatidylethanolamine	Transferrin	Transferrin receptor	133	H-NMR	[89]

4.4. Ligands Used for Liposome Surface Modification

Regarding the surface modification of liposomes, various ligands have been previously investigated as described in Table 2. According to Ma et al., the attachment of A15 aptamer has provided sustained release of doxorubicin, as well as a decreased growth in the cancer cells [118]. A15 has been identified as a promising ligand to bind onto CD133, which is a marker widely involved in the NSCLCs. It has also improved the therapeutic efficiency; this could be possibly due to the amount of drug delivered to the target cells. When the A549 cell line was used, a superior inhibition of cell growth was observed when the surface-modified liposomes were tested in comparison with the drug itself and the liposomes without A15 aptamer [118].

Another study showed that carbonic anhydrase IX, an antibody controlled by hypoxia-inducible factor, successfully improved the uptake of the surface-modified liposomes, leading to increased cytotoxicity by killing more cancer cells compared to free triptolide and non-modified liposomes. Cellular uptake from the A549 cell line was increased by the targeted liposomes compared to the non-targeted ones [131]. The delivery of triptolide via dual ligand modified liposomes consisting of anti-carbonic anhydrase IX and CPP33 was also investigated by Lin et al. [55]. The in vitro tests showed that the modified liposomes successfully inhibited cancer cell proliferation in the A549 cell line. Compared to endotracheal administration, pulmonary delivery exhibited higher anticancer efficacy without expressing any toxicity [55].

Aspartate-conjugated polyoxyethylene stearate has also been studied as a targeting moiety for ATB^{0+} and it has shown promising results. ATB^{0+} is an amino acid transporter which is suitable for targeting cancer cells. Compared to plain docetaxel, the modified liposomes exhibited higher delivery of docetaxel within the cells and increased antitu-

mour potency against the A549 cell line [137]. A new biomaterial consisting of chitosan oligosaccharide [145] and Pluronic P123 was attached on the surface of liposomes, which delivered paclitaxel successfully to the A549 cell line and inhibited its growth. Onodera et al. studied the delivery of rapamycin through folic acid modified liposomes [139]. The folate receptor is widely overexpressed in various cancer cells, including lung cancer cells. Folic acid can attach on the folate receptors, and this is why it can be chosen as a targeting moiety. The surface-modified liposomes showed increased cytotoxic activity against the A549 cell line. It has also been proved in animal studies that, compared to intravenous delivery, pulmonary delivery offered an extended survival rate [139].

Another significant receptor which is overexpressed in cancer cells is the EGFR. Cheng et al. investigated the modification of liposomes with GE11, a peptide which previously showed high selectivity for this receptor [140]. Doxorubicin was successfully delivered to the target A549 cell line and increased retention of the modified liposomes on the cancer cells was achieved [140]. Lastly, the attachment of CB5005, a peptide which has the ability to block nuclear factor κB, has been studied by Hu et al. [119]. This factor (NF-κB) is known to represent an obstacle in the treatment of cancer, as it promotes drug resistance and anti-apoptosis. The results showed that the surface modification of the liposomes with CB5005 enhanced the cellular uptake of irinotecan and induced the apoptosis process [119].

4.5. Ligands Used for NLCs Surface Modification

As for the NLCs and their functionalisation, many ligands have been attached on their surface to achieve active targeting (Table 2). The Biotin receptor is widely overexpressed in cancer cells, including those of lung cancer. Taymouri et al. used Biotin as a targeting moiety conjugated with stearylamine on the surface of NLCs which were carrying sunitinib, a tyrosine kinase inhibitor with antitumour activity [88]. When tested on the A549 cell line, the Biotin-modified NLCs showed enhanced cellular uptake in comparison to the free drug and the non-targeted NLCs. The cytotoxicity of the targeted NLCs was higher as well [88]. Du et al. explored another interesting aspect of functionalisation: the difference between pre- and post-decoration is that the pre-decoration carriers are developed with drugs that have targeting moieties and post-decoration carriers are the ones in which preparation of the carriers occurs first, followed by surface modification. Based on the results, they found out that post-decoration was preferable, as it offered better antitumour activity [141].

Another study was performed by Garbuzenko et al. who investigated the LHRH and its possible effect following surface modification [136]. LHRH can successfully target extracellular receptors which are overexpressed in lung cancer cells. The LHRH-modified NLCs had increased cytotoxicity and allowed the delivery of paclitaxel directly to the tumours. This study achieved dual, active and passive targeting [136]. LHRH was also used by Taratula et al. who found that paclitaxel or doxorubicin with siRNA were successfully delivered to the target. The results also showed that the healthy organs and cells were not affected compared to intravenous injection of the investigated drugs [130]. Two ligands, transferrin and hyaluronic acid, had successfully modified the NLCs surface that delivered plasmid DNA (pDNA) to the A549 cell line. The results showed that the combination of these two ligands improved the ability for targeting the cancer cells and decreased systemic cytotoxicity, making them a safe alternative in cancer therapy [142]. Transferrin was also investigated as a single ligand by Shao et al. [89]. Transferrin-decorated NLCs had successfully increased transfection efficiency and increased antitumour activity [89].

Dual delivery of paclitaxel and 5-demethylnobiletin via cetuximab-modified NLCs has been investigated by Guo et al. [143]. Cetuximab is an antibody which can be used to target EGFR and it has also been approved for colorectal cancer. Sustained release was achieved while cellular uptake by A549 was increased for the targeted NLCs. The delivery of both drugs exhibited decreased cell viability compared to single-drug NLCs and also showed excellent antitumour activity while inhibiting cell proliferation [143]. Lastly, another study which explored the efficiency of dual delivery was performed by Liang et al. where N-Acetyl-D-glucosamine was used as a targeting ligand to target glucose receptors which

were overexpressed in cancer cells due to hypoxic conditions. The combined targeted NLCs showed better cellular uptake in the A549 cell line than the free drugs [144].

4.6. Surface Modification for Other Lipid-Based Drug Delivery Systems

Other lipid-based drug delivery systems which have been modified to target lung cancer cells include chitosan nanoparticles [121] and microemulsion [146]. Li et al. investigated the delivery of temozolomide via folic acid-modified chitosan nanoparticles in order to target the folate receptor which is overexpressed in lung cancer cells [121]. The results showed that a higher amount of the modified nanoparticles accumulated in the lung tissues compared to the free drug and the non-modified nanoparticles. The particle size remained small, i.e., 93.81 nm, and, during the animal studies, a 100% survival rate was achieved for the treated mice. On the other hand, Zhang et al. investigated the dual delivery of β-elemene and celastrol via a transferrin-decorated microemulsion [146]. In the A549 cell line, the modified microemulsion showed increased cellular uptake and cell apoptosis was also increased. Another advantage was the avoidance of systemic toxicity that is normally encountered in celastrol treatments [146].

5. Conclusions

The aim of this study was to review the literature to explore the lipid-based drug delivery systems that have been investigated for improved treatment of lung cancers, as well as the surface modification methods that have been investigated. Overall, the functionalisation of the surface of a lipid-based drug delivery system has proven a promising tool in order to better treat lung cancer. More specifically and compared to intravenous or endotracheal administration, the pulmonary route of administration offers a less invasive alternative. The attachment of the targeting moieties inhibits the growth of cancer cells or induces their apoptosis. Also, since these receptors are not expressed in the normal, healthy cells, the chemotherapeutic ingredient should not impair them, thus reducing the potential for patients to experience side effects. As described in the literature, mostly liposomes and NLCs have been modified in order to achieve active targeting. The reported results have shown that the targeting moieties can successfully trigger the desired antitumour efficacy and therefore treat lung cancer with minimal unwanted (toxic) effects on the surrounding healthy cells.

Further research in all the drug delivery systems, including transfersomes, niosomes, microemulsion and SLNs can enhance the possibilities of identifying a better way to treat lung cancer due to the complexity of chemotherapies and the side effects that this type of treatment causes to patients. It is highly significant that novel types of therapies are discovered so that the mortality rate of lung cancer can be reduced and the number of patients suffering from invasive therapies can be minimised.

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