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Review article

Inhalable particulate drug delivery systems for lung cancer therapy: Nanoparticles, microparticles, nanocomposites and nanoaggregates

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ABSTRACT

There is progressive evolution in the use of inhalable drug delivery systems (DDSs) for lung cancer therapy. The inhalation route offers many advantages, being non-invasive method of drug administration as well as localized delivery of anti-cancer drugs to tumor tissue. This article reviews various inhalable colloidal systems studied for tumor-targeted drug delivery including polymeric, lipid, hybrid and inorganic nanocarriers. The active targeting approaches for enhanced delivery of nanocarriers to lung cancer cells were illustrated. This article also reviews the recent advances of inhalable microparticle-based drug delivery systems for lung cancer therapy including bioresponsive, large porous, solid lipid and drug-complex microparticles. The possible strategies to improve the aerosolization behavior and maintain the critical physicochemical parameters for efficient delivery of drugs deep into lungs were also discussed. Therefore, a strong emphasis is placed on the approaches which combine the merits of both nanocarriers and microparticles including inhalable nanocomposites and nanoaggregates and on the optimization of such formulations using the proper techniques and carriers. Finally, the toxicological behavior and market potential of the inhalable anti-cancer drug delivery systems are discussed.

1. Introduction

Lung cancer, a highly fatal disease with mortality to incidence ratio of 0.87, became the major cause of all cancer-associated deaths all over the world by the end of the twentieth century. In 2012, an estimated 1.8 million new cases were recorded and a 1.6 million lung cancer-related deaths occurred worldwide which is approximately 19% of all cancer-related deaths. By 2035, the number of lung cancer-related deaths is expected to hike up to 3 million worldwide [1,2]. Histologically, two types of lung cancer could be distinguished; small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC) with the latter accounting for 85% of lung cancer cases. Three subtypes of NSCLC were further identified; large cell lung cancer, squamous-cell carcinoma and adenocarcinoma. Despite the advances in the field of oncology, NSCLC is usually diagnosed at a late stage and shows poor prognosis with a 15% overall 5-year survival [3].

Treatment modalities for lung cancer include surgery, chemotherapy, radiotherapy, and/or targeted therapies depending on the cancer stage. However, surgery is usually deemed ineligible due to diagnosis of patients at an advanced stage. Despite the enormous efforts for developing new biomarkers that aid early diagnosis, this goal has not yet been achieved. Whether alone or combined with other therapeutic strategies, chemotherapy is the major key player in the treatment of lung cancer [3–5]. Despite the several theoretical advantages offered by inhalation chemotherapy of lung cancer, intravenous (i.v.) administration (systemic chemotherapy) is still the mainstay. Many

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Table 1
Inhalable polymeric nanocarriers for targeted drug delivery to lung cancer.[a]

Polymeric nanocarrier	Drug	Preparation method	Key outcome	Ref.
Gelatin NPs	CIS	Desolvation	Enabled active targeting of EGFR-overexpressing cancer cells.	[18–20]
HSA NPs	DOX + TRAIL	Self-assembly	DOX and TRAIL showed synergistic antitumor activity *in vivo*.	[22]
CS/PLGA NPs	OMR	Emulsion–diffusion	Enhanced uptake and good tolerability of the NPs.	[43,44]
BIPCA NPs	DOX	Emulsion polymerization	A secondary cytotoxicity was achieved by alveolar macrophages.	[10]
PEGylated PAMAM dendrimers	DOX	Chemical conjugation	Temporal and spatial (pH-sensitive) release of DOX.	[45]
Hyaluronan conjugates	CIS	Covalent bonding	5.7-fold increase in CIS accumulation in lungs compared to i.v.	[26]
PEI polyplexes	p53	Electrostatic complexation	Effective inhibition of lung metastases	[46]
SDA-PEI polyplexes	PDCD4 + shAkt1	Electrostatic complexation	Derivatization with SDA increased the biocompatibility of PEI.	[47]
Glucosylated PEI polyplexes	PTEN	Electrostatic complexation	Down-regulation of Akt signaling pathway.	[31]
UAC polyplexes	PDCD4 PTEN	Electrostatic complexation	UA enhanced endolysosomal escape of complex via proton sponge mechanism	[32,48]
SPE-GPT polyplexes	shAkt1	Electrostatic complexation	SPE-GPT showed lower cytotoxicity than PEI and comparable transfection	[40]
SPE-PEG polyplexes	PDCD4	Electrostatic complexation	SPE-PEG showed higher transfection when compared to PEI or Lipofectamine	[49]
CHI-g-PEI polyplexes	shAkt1	Electrostatic complexation	CHI-g-PEI showed lower cytotoxicity than PEI.	[38,39]
Polylysine/protamine polyplexes	P53	Electrostatic complexation	Higher transfection and better stability during aerosolization than complexes based on PEI or cationic lipids.	[50]
PEI-alt-PEG polyplexes	Akt1 siRNA	Electrostatic complexation	80% reduction in Akt1 expression	[51]
PEI polyplexes	DOX + Bcl2 siRNA	Electrostatic complexation	pH-sensitive DOX release was achieved	[41,42]

[a] EGFR: Epithelial growth factor receptor, PAMAM: poly(amidoamine), PLGA: Poly(lactic-co-glycolic acid), p53: tumor suppressor gene, SDA: Sorbitol diacrylate, PDCD4: cDNA of programmed cell death protein 4, PTEN: Phosphatase and tensin homologue deleted on chromosome 10 gene, UAC: Urocanic acid–modified chitosan, SPE-PEG: Spermine-alt-poly (ethylene glycol) polyspermine, OMR: Antisense oligonucleotide, 2′-O-Methyl-RNA.

lung barriers need to be overcome first before inhalation treatment gets a foothold in the lung cancer therapy avenue. The upper airways are made of columnar epithelial cells that are ciliated and mucus-producing which both collectively make the mucociliary escalator system. This is the main cleaning system in the upper airways which efficiently sweeps any insoluble particle that gets deposited on it. Deeper in the alveolar sacs, macrophages take the responsibility of getting rid of any insoluble particles that deposit on the alveoli. Chemotherapeutics first need to be inhaled efficiently and deposit deeply in lungs to reach their target regions. The drugs then have to bypass the barriers of mucociliary escalation and macrophage clearance, and lastly to get taken up efficiently by the cancerous cells for them to be effective in treating lung cancer [6].

2. Inhalable chemotherapy of lung cancer

Compared to systemic chemotherapy, inhalation treatment locally delivers the chemotherapeutic agent to tumor tissues thereby enhancing its efficacy and lowering its systemic side effects. Moreover, inhalable therapy avoids first pass metabolism and increases patients' comfort towards treatment since being needle-free. Also, systemic chemotherapy has been associated with side effects and drawbacks that are not even chemotherapy-related. For instance, i.v. paclitaxel (PTX) has been associated with hypersensitivity reaction and neurotoxicity attributed to the solubilizing mixture of Cremophor EL and dehydrated alcohol. Such toxicities are dose-limiting and could lead to therapy failure.

In 1993, Tatsamura et al. published one of the first clinical studies regarding the pulmonary administration of a chemotherapeutic (5-fluorouracil, 5-FU) solution in the treatment of NSCLC [7]. Results have shown that only trace amounts of 5-FU were detected in plasma with no local or systemic adverse effects being detected during the study. Intriguingly, lung tumor tissues showed 5- to 15-fold higher drug concentrations than normal lung tissues. In another investigation, celecoxib (CXB) solution was effectively nebulized to treat lung tumor combined with i.v. docetaxel (DTX). Aerosolized CXB was therapeutically as effective as oral CXB, but at a lower dose, thus showing great potential for treating lung cancer [8].

3. Inhalable particulate DDSs for lung cancer therapy

Unfortunately, inhalable lung cancer therapy is hampered by several potential drawbacks that have hindered its clinical applications. Inhalation of chemotherapeutics increases their concentration locally in the lung which increases the risk of pulmonary toxicity. Also, elimination of the therapeutic agent is immediately initiated once it has been deposited in the lung. This rapid decay often requires multiple daily inhalations, which inevitably affects the patient compliance. Furthermore, traditional inhalation therapy does not enable drug targeting to specific lung tumor sites. To overcome these drawbacks associated with “conventional” inhalation therapy of chemotherapeutic drug solutions, “intelligent” pulmonary drug delivery systems have emerged [9,10]. In the following sections, we will thoroughly discuss the outcomes brought by different micro- and nano-size drug delivery systems.

3.1. Inhalable nanocarrier-based lung cancer therapy

Pulmonary delivery of chemotherapy via inhalable nanocarriers has gained more attention in recent years due to their ability to highly associate with drugs and sustain their release, in addition to their ability to target cancer tissues in the lungs. They also have the ability to be efficiently transferred into aerosols, and highly endure nebulization forces [11]. Moreover, nanocarriers can avoid mucociliary clearance and lung phagocytic mechanisms, thus prolonging the residence of the therapeutic agent within the respiratory tract.

3.1.1. Polymeric nanocarriers

Cancer nanotechnology research is greatly progressing in the last years. Polymers either synthetic or natural have been extensively utilized for tumor-targeted drug delivery [12–17]. Polymeric nanoparticles (NPs) have been widely utilized for the aerosol delivery of chemotherapeutics, genes, or their combinations for lung cancer therapy (Table 1).

i. Pulmonary delivery of chemotherapeutics

Chemotherapeutic drugs could be physically entrapped within inhalable biodegradable polymeric nanocarriers. Gelatin-based NPs (GNPs) have demonstrated powerful anti-tumor activity against A549 lung adenocarcinoma cells (IC_{50} = 1.2 μg/mL) via the pulmonary delivery of cisplatin (CIS) compared to free CIS solution (IC_{50} = 2.54 μg/mL). The droplet of nebulized aerosol of GNPs demonstrated mass median aerodynamic diameter (MMAD) of 0.5–5 μm thus suitable for