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Development of controlled-release cisplatin dry powders for inhalation against lung cancers

Vincent Levet[a,*], Rémi Rosière[a], Romain Merlos[a], Luca Fusaro[b], Gilles Berger[c], Karim Amighi[a], Nathalie Wauthoz[a]

[a] Laboratory of Pharmaceutics and Biopharmaceutics, CP207, Faculty of Pharmacy, Université libre de Bruxelles (ULB), Boulevard du Triomphe, Campus Plaine, B-1050 Brussels, Belgium
[b] Unité de Chimie des Nanomatériaux (CNANO), Université de Namur, 61 rue de Bruxelles, B-5000 Namur, Belgium
[c] Laboratoire de Chimie Pharmaceutique Organique, CP205/5, Faculty of Pharmacy, Université libre de Bruxelles (ULB), Boulevard du Triomphe, Campus Plaine, B-1050 Brussels, Belgium

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ABSTRACT

The present study focuses on the development of dry powders for inhalation as adjuvant chemotherapy in lung cancer treatment. Cisplatin was chosen as a potential candidate for a local treatment as it remains the main platinum component used in conventional chemotherapies, despite its high and cumulative systemic toxicities. Bulk cisplatin was reduced to submicron sizes using high-pressure homogenization, mixed with a solubilized lipid and/or PEGylated component and then spray-dried to produce controlled-release dry powder formulations. The obtained formulations were characterized for their physicochemical properties (particle size and morphology), aerodynamic performance and release profiles. Cisplatin content and integrity were assessed by electrothermal atomic absorption spectrometry and ^{195}Pt nuclear magnetic resonance spectroscopy. DPI formulations with cisplatin contents ranging from 48.5 to 101.0% w/w exhibited high fine particle fractions ranging from 37.3% to 51.5% of the nominal dose. Formulations containing cisplatin microcrystals dispersed in solid lipid microparticles based on acceptable triglycerides for inhalation and PEGylated excipients showed a controlled-release for more than 24 h and a limited burst effect. These new formulations could provide an interesting approach to increasing and prolonging drug exposure in the lung while minimizing systemic toxicities.
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1. Introduction

Lung cancer remains the most common type of cancer worldwide, with an estimated yearly incidence of 1.8 million new cases and a yearly mortality rate of 1.6 million deaths for both genders and is therefore the leading cause of cancer-related death (Ferlay et al., 2015). Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) account for approximately 85% and 15% of primary lung carcinoma, respectively (Johnson et al., 2008). Besides, secondary lung carcinomas caused by metastatic outgrowth from

Abbreviations: API, active pharmaceutical ingredient; d_{ae}, aerodynamic diameter; DMF, *N,N*-dimethylformamide; DPI, dry powder inhaler; DPPC, dipalmitoyl phosphatidylcholine; DSC, differential scanning calorimetry; DSPE-mPEG-2000, distearoyl phosphoethanolamine polyethylene glycol 2000 sodium salt; ETAAS, electrothermal atomic absorption spectrometry; FDA, food and drug administration; FPD, fine particle dose; FPF, fine particle fraction; FSI, ast-screening impactor; HPH, high-pressure homogenization; HPMC, hydroxypropyl methylcellulose; HSH, high-speed homogenization; IPA, isopropanol; IV, intravenous; MMAD, mass median aerodynamic diameter; NSCLC, non-small cell lung cancer; MOC, micro-orifice collector; MsLI, multistage liquid impinger; mSLF, modified simulated lung fluid; NMR, nuclear magnetic resonance; PSD, particle size distribution; SEM, scanning electron microscopy; SCLC, small cell lung cancer; SLM, solid lipid microparticle; TGA, thermogravimetric analysis; TPGS, alpha-tocopheryl polyethylene glycol 1000 succinate; TS, tristearin.

* Corresponding author at: Laboratory of Pharmaceutics and Biopharmaceutics, Faculty of Pharmacy, ULB, Boulevard du Triomphe-CP207 Campus de la Plaine, B-1050 Brussels, Belgium. Tel.: +32 2 650 52 21; fax: +32 2 650 52 69.
E-mail address: vincent.levet@ulb.ac.be (V. Levet).

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cancerous tissues are also frequently encountered (Kaifi et al., 2010). Because only 16% of lung cancers are detected at early loco-regional stages, the 5-year survival rates for lung cancer are among the lowest for all cancers, from 59% for localized NSCLC to 5% for distant NSCLC, and from 27% for localized SCLC to 3% for distant SCLC, as reported for the USA (Howlader et al., 2015). Cancer recurrence is also a prominent issue for survivors—regional recurrence is, for instance, encountered in up to 45% and 55% of stage I and II NSCLC, and up to 63% of limited-disease SCLC due to loco-regional lymph node involvement (Kelsey et al., 2009; Xu et al., 2014).

Lung cancer treatment generally involves surgery, radiotherapy and chemotherapy, which are often combined depending on the stage and progression of the illness. Adjuvant chemotherapy is administered after resective surgery at stage II or IIIA. It is associated with radiotherapy at later stages IIIB to IV in NSCLC and in all stages in SCLC (National Comprehensive Cancer Network, 2014a, 2014b).

Guidelines for first-line regimens against lung cancer rely on platinum-doublet chemotherapy. This administers platinum derivatives – predominantly cisplatin – in combination with other antineoplastic agents, such as etoposide for SCLC or taxane derivatives, vinorelbine, vinblastine, gemcitabine or pemetrexed for NSCLC. The most recent targeted agents aimed against tyrosine kinase (tinibs) or specific growth factors (bevacizumab, cetuximab), in addition to being costly, show only a modest outcome improvement. Moreover, they are indicated only in small groups of advanced disease NSCLC patients facing therapeutic failure with conventional chemotherapy and bearing specific tumor mutations. All these chemotherapeutic agents, which are currently administered through intravenous (IV) infusion or occasionally by the oral route, are usually associated with numerous systemic and dose-limiting side effects (National Comprehensive Cancer Network, 2014a, 2014b). Only a low pulmonary uptake is obtained after distribution from a systemic administration, with typically 5–10% of the administered that effectively reaches the lungs, let alone the tumor, which is a major determinant of treatment failure (Minchinton and Tannock, 2006). New adjuvant therapy regimens that are able to increase drug exposure in the target organ, the tumor and local lymph nodes, which is concomitant with an overall decrease in systemic toxicities, are therefore highly desirable. Such therapies include the local administration of well-known cytostatic drugs.

Cisplatin or *cis-dichlorodiammineplatinum*(II) was discovered in 1965 (Rosenberg et al., 1965) and subjected to its first clinical trial as early as 1972 (Lippman et al., 1973). It remains involved in first-line regimens against many cancers such as lung, head and neck, ovarian, cervical, osteosarcoma, lymphoma, bladder or testicular cancer (Boulikas and Vougiouka, 2003; Jamieson and Lippard, 1999). The potent antitumor activity of this class of compounds mostly rely on their ability to be aquated in the low-chloride intracellular medium, having one or its two chloro ligands replaced by water molecules (Jamieson and Lippard, 1999). The positively charged mono-aqua and di-aqua cisplatin complexes formed are then able to bind DNA in the cell nucleus and proteins in the cytoplasm, inducing apoptosis (Alderden et al., 2006; Boulikas and Vougiouka, 2003; Jamieson and Lippard, 1999). Despite its potent antitumor properties, clinical use of cisplatin is strongly hindered by its side effects. These are essentially dose-limiting nephrotoxicity, but also ototoxicity, myelosuppression, anemia, electrolyte disturbances and gastrointestinal reactions. Because cisplatin is preferentially excreted through urine (>90%) and is accumulated in proximal and distal nephrons at up to 5 times the plasma concentration, it can cause severe tubular damage and acute and chronic renal insufficiency in up to 36% of patients (Yao et al., 2007). Cisplatin, currently administered through IV infusion at doses ranging from 30 to 100 mg/m^2 of body surface area, is therefore administered cautiously in cycles every 3 weeks in SCLC or at days 1, 8 and 21 or 28 in NSCLC to limit kidney and other sensitive organ exposure. It is always supplemented by high hydration regimens including significant volumes of saline, potassium, magnesium and nephroprotective mannitol before and after administration (British Columbia Cancer Agency, 2013; National Comprehensive Cancer Network, 2014a, 2014b). Consequently, pulmonary administration of cisplatin could stand as an interesting approach as neoadjuvant and adjuvant chemotherapy for the treatment of lung tumors in both SCLC and NSCLC at later stages, but also specifically at early stages against lymph node involvement and cancer recurrence.

Aerosol therapy has been used since the early 20th century and has many advantages against respiratory diseases. It can avoid the first-pass metabolism, increasing treatment efficacy, while decreasing systemic exposure, systemic side effects and drug–drug interactions. Pulmonary delivery of chemotherapy has been investigated since the 1960s (Shevchenko and Resnik, 1968), but its development has been limited by drug-induced pulmonary toxicity as reported for some antineoplastic agents, such as taxanes or gemcitabine, during or shortly after IV administration. These side effects were, however, not observed when these drugs were delivered by the pulmonary route (Dulohery et al., 2016; Gagnadoux et al., 2008). Aerosol chemotherapy can thus provide a higher therapeutic index for systemically toxic drugs by limiting total body exposure while increasing drug concentration at the tumor site and in loco-regional lymph nodes; keeping in mind that these advantages can be counterbalanced by potential direct local toxicity to the lungs linked to higher local exposure, which depends directly on the considered drug (Gagnadoux et al., 2008). The ability of aerosol chemotherapy to deliver a systemically toxic drug slowly – allowing smoother concentration profiles and thus limiting peak concentration in sensitive organs – is therefore critical. This could allow an effective drug concentration to be maintained at the site of action between administrations while limiting systemic exposure and lowering the risk of acute pulmonary toxicity and the ensuing adverse effects. It can also greatly help decrease patient discomfort by lowering the strain of repeated administrations.

The ability of long-lasting particles to remain in the lungs and diffuse drugs locally can be hindered by clearance systems, including the mucociliary escalator and phagocytosis by alveolar macrophages. PEGylation of particle surface has been shown to provide an effective “stealth” shield for microparticles by preventing phagocytosis by macrophages (Wattendorf and Merkle, 2008). Inhalation of PEG has been demonstrated as safe (Klonne et al., 1989), and PEGylated excipients derived from vitamin E such as tocopheryl polyethylene glycol succinate (TPGS) or from endogenous phospholipids such as distearoyl phosphoethanolamine polyethylene glycol 2000 (DSPE-mPEG-2000) are of low potential pulmonary toxicity (Gill et al., 2011; Shah and Banerjee, 2011; Yan et al., 2007).

Herein we disclose the development of DPI formulations composed of cisplatin-based solid lipid microparticles (SLM) with good dispersion properties and a high theoretical lung deposition fraction, even under lower inspiratory flows. Controlled-release using lipid excipients and potential stealth properties using PEGylated excipients were sought to maintain drug concentration inside the lungs between administrations.

2. Materials and methods

2.1. Materials

Cisplatin was purchased from Shanghai Jinhe Bio-technology Co., Ltd. (Shanghai, PRC). Tristearin (TS) was purchased from Tokyo

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