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Doxorubicin-loaded highly porous large PLGA microparticles as a sustained-release inhalation system for the treatment of metastatic lung cancer

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ABSTRACT

Doxorubicin-loaded highly porous large PLGA microparticles (Dox PLGA MPs) were prepared using a w/o/w double emulsification method using ammonium bicarbonate effervescent salt. The prepared Dox PLGA MPs were characterized by particle size analysis, scanning electron microscopy, and confocal microscopy. *In vitro* cytotoxicity to B16F10 melanoma cells and lung deposition in C57BL/6 mice were examined, and finally the anti-tumor efficacy of pulmonary administered Dox PLGA MPs was evaluated in a mouse model of B16F10 melanoma metastasis. Results showed that Dox PLGA MPs were highly porous, had high encapsulation efficiency, and good aerosolization characteristics. Doxorubicin was gradually released from Dox PLGA MPs over 2 weeks, and after pulmonary administration, Dox PLGA MPs were deposited in lungs and remained *in situ* for up to 14 days. Furthermore, exposure to Dox PLGA MPs killed B16F10 cells *in vitro* within 24 h. In particular, tumors in B16F10-implanted mice treated with Dox PLGA MPs were remarkably smaller in terms of mass and number than those in non-treated B16F10-implanted mice. We believe that doxorubicin-loaded highly porous large PLGA microparticles have great potential as a long-term inhalation agent for the treatment of lung cancer.

1. Introduction

Lung cancer is a leading cause of malignancy-related death in most developed countries, and the incidence of lung cancer in developing countries is rapidly increasing [1]. The lungs are a frequent site of metastasis, and >90% of deaths from lung cancer are attributed to the metastatic process [2,3]. Conventional modalities, such as, radiotherapy, chemotherapy, or their combinations, are considered to be the primary treatment choices for non-small-cell lung cancer patients [4]. However, the systemic administration of non-specific chemotherapeutic agents causes significant toxicities and undesirable side effects because the anti-cancer agents used act on normal cells as well as tumor cells [5,6]. Furthermore, the delivery efficiencies of intravenously administered agents to the lungs are low because they are diluted in the systemic circulation, and thus, therapies are often unsatisfactory and survival times are low [4,6].

Direct local delivery of chemotherapeutic agents to lung cancer sites offers an attractive alternative approach because it allows the concentrated delivery of anti-cancer drugs to tumor sites [5–7]. Moreover, high systemic levels of chemotherapeutic agents can be avoided when inhalatory delivery systems are used, because they reduce adverse systemic side effects. In addition, this form of delivery is non-invasive, and thus improves patient compliance, versus intravenous injections [8].

Nevertheless, the need for frequent administration can be a real hurdle to the establishment of a drug requiring pulmonary administration, and can be bothersome to lung cancer patients [9–11], in whom breathing is weak. Furthermore, frequent or failed inhalation of cytotoxic chemotherapeutics may induce higher risk to harm normal airway tissues from mouth to alveoli at the cellular level, when compared with fewer inhalations. Accordingly, the requirement for frequent inhalation should be avoided, which drives efforts to develop inhalatory systems that provide long-term sustained release type of active agents.

Porous microparticles (MPs) are viewed as useful tool for the delivery of drugs to the lungs because they are light and are inhaled deeply into the lungs [12–14]. Particles of low density

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