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Delivery strategies for sustained drug release in the lungs ☆

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ABSTRACT

Drug delivery to the lungs by inhalation offers a targeted drug therapy for respiratory diseases. However, the therapeutic efficacy of inhaled drugs is limited by their rapid clearance in the lungs. Carriers providing sustained drug release in the lungs can improve therapeutic outcomes of inhaled medicines because they can retain the drug load within the lungs and progressively release the drug locally at therapeutic levels. This review presents the different formulation strategies developed to control drug release in the lungs including microparticles and the wide array of nanomedicines. Large and porous microparticles offer excellent aerodynamic properties. Their large geometric size reduces their uptake by alveolar macrophages, making them a suitable carrier for sustained drug release in the lungs. Similarly, nanocarriers present significant potential for prolonged drug release in the lungs because they largely escape uptake by lung-surface macrophages and can remain in the pulmonary tissue for weeks. They can be embedded in large and porous microparticles in order to facilitate their delivery to the lungs. Conjugation of drugs to polymers as polyethylene glycol can be particularly beneficial to sustain the release of proteins in the lungs as it allows high protein loading. Drug conjugates can be readily delivered to respiratory airways by any current nebulizer device. Nonetheless, liposomes represent the formulation most advanced in clinical development. Liposomes can be prepared with lipids endogenous to the lungs and are particularly safe. Their composition can be adjusted to modulate drug release and they can encapsulate both hydrophilic and lipophilic compounds with high drug loading.

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1. Introduction

Drug delivery to the lungs by inhalation offers a targeted drug therapy for respiratory diseases. The local route of drug administration allows one order of magnitude-lower drug doses to be delivered, compared to systemic administration by the oral route or by injection. The low dosing locally reduces systemic exposure to the drug, and thereby systemic side effects, and increases drug therapeutic index. In addition, portable inhalers make this route of drug administration convenient for the patient. Inhalation aerosols are developed for drug administration to the systemic circulation as well. The large absorptive surface area of the alveoli, the very thin diffusion path from the airspaces into the blood and the elevated blood flow make the lung a port of entry to the systemic circulation. Drug molecules are absorbed more efficiently from the lung than from any other non-invasive routes of drug administration. As a result, a continuously increasing number of inhaled drugs are becoming available on the market to treat various diseases [1].

However, the therapeutic efficacy of inhaled drugs is limited by their rapid clearance in the lungs [2]. Small solutes delivered to the lungs quickly diffuse across lung epithelia and penetrate the bloodstream within minutes. Peptides are rapidly transported to the systemic circulation as well, but are significantly metabolized locally [3,4]. Although macromolecules can be absorbed into the systemic circulation over several hours, they can be rapidly taken up by alveolar macrophages, they can be removed by the mucociliary escalator and they can be metabolized locally as well. For instance, recombinant human deoxyribonuclease I is a 37 kDa glycoprotein which cleaves the DNA in respiratory secretions of cystic fibrosis patients and thus, lowers their viscosity [5]. This glycoprotein is the mucolytic agent most widely used in the symptomatic treatment of cystic fibrosis. However, it is rapidly cleared from the human lungs: when the daily dose of 2.5 mg is inhaled, a concentration of 3 μg/ml is measured in sputum immediately after inhalation and it is reduced to 0.6 μg/ml after 2 h. Therefore, its once to twice daily administration provides limited therapeutic coverage to the patients. The short residence time of drugs within the lungs can also imply frequent dosing and this can jeopardize patient compliance. It is for instance recommended to inhale corticosteroids twice daily and short-acting β2-agonists up to 4-times daily.

Carriers providing sustained drug release in the lungs could improve therapeutic outcomes of inhaled medicines. Their objectives are to retain the drug load within the lungs for an extended period of time and to progressively release the drug locally at therapeutic levels. Sustained therapeutic drug concentrations should improve local therapeutic efficacy and further decrease systemic side effects as the biodistribution throughout the systemic circulation is minimized. In addition, a sustained-release inhaled formulation could avoid peaks in local drug concentrations that could be toxic to the pulmonary tissue. This is particularly relevant for chemotherapeutic agents. Sustained drug release in the lungs could also benefit to systemically-acting drugs by controlling the rate of drug release and transport into the systemic circulation.

Although sustained-drug release in the lungs presents high potential to improve the therapeutic efficacy and safety of inhaled drugs, there is not yet any sustained-release formulation available in the market. Only a few sustained-release formulations are in clinical development and all are in the form of liposomes (Table 1). In recent years, tremendous efforts in the area have focused on the development of new inhaler devices and new formulations with the goal to increase pulmonary deposition and its reproducibility. However, a further degree of sophistication in inhalation aerosols could be reached through the development of controlled-release formulations.

This review will present the main parameters involved in the local availability of inhaled compounds as well as the different strategies developed to control drug release in the lungs including microparticles, insolubilization and the wide array of nanomedicines.

2. Factors affecting the local availability of inhaled compounds

Several factors affect the local availability of drugs following delivery to the lungs. First, the ability of an aerosol particle to settle in one or another region of the respiratory tract depends on its aerodynamic diameter. Second, the pulmonary fate and rate of clearance of a drug from the lungs are determined by its physico-chemical and biological properties. Third, if the drug formulation is not merely the drug molecule but involves a carrier, the latter must avoid its own pathways of clearance within the lungs.

2.1. Mechanisms of particle deposition in the lungs

The site of deposition of an aerosol particle within the lungs depends on its aerodynamic diameter (d_{aer}) and on the breathing pattern of the patient. The aerodynamic diameter of a particle is equivalent to the diameter of a unit density (ρ_0) sphere that has the same terminal velocity

Table 1
Clinical status of liposome formulations for sustained drug release in the lungs.

Active, registered trade name if any	Phase of clinical development	Indication	Ref
Amikacine, Arikace®	III	Cystic fibrosis patients with *Pseudomonas* lung infection	[6,7]
Ciprofloxacin, Pulmaquin®		Management of chronic lung infections with *Pseudomonas aeruginosa* in patients with non-cystic fibrosis bronchiectasie	
Amphotericine B, Ambisome®	III	Lung transplant recipients	[8]
Amphotericine B, Ambisome®	II–III	Prophylaxis of invasive pulmonary aspergillosis in neutropenic hemato-oncologic patients	[9]
Fentanyl, AeroLef®	II	Moderate/severe acute pain in post-surgical setting in adults	[10]
9-Nitro-20-S-camptothecin	II	Non-small cell lung cancer	[11]
Ciclosporine	I	Chronic rejection in lung transplant recipients	[12]

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