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EDITORIAL

Advances in Pulmonary Drug Delivery Systems and Inhalation Formulations

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Inhalation therapy has been popular for treatment of pulmonary diseases such as asthma and chronic obstructive pulmonary diseases (COPD). Recently, inhalation therapy has also attracted increasing interests in treatment of emerging pulmonary diseases including bacterial, viral and fungi infections in the respiratory tracts. For example, inhaled antiviral medications and vaccines have shown a great promise for COVID-19. However, there are many challenges to formulate these new substances or deliver these medications or vaccines into the targeted sites in the respiratory tracts. Novel pulmonary delivery systems and innovative formulations are urgently needed to address these unmet medical needs for emerging pulmonary diseases. Loo and Zhou *et al*. [1] review various antiviral agents and vaccines that have been recently developed for the treatment of respiratory viral infections. Key barriers for the development of the new antiviral therapies and vaccines are discussed, and strategies to circumvent the delivery barriers through nanoparticle formulations are proposed.

Inhaled biologics are a hot topic for both local and systemic efficacy. Mao *et al*. [2] provide a comprehensive review that discusses challenges in the systemic absorption of inhaled proteins and peptides, and potential strategies for enhancing pulmonary absorption of inhaled biologics for systemic effects.

Bacterial infections in the lower respiratory tracts are dangerous and difficult to treat. Pulmonary delivery of antimicrobials can generate high drug concentrations in the lower respiratory tracts and reduce systemic side effects. Due to the rapid resistance development for the traditional small-molecule antibiotics, novel biological antimicrobial agents such as peptides, RNAs and bacteriophages have emerged to treat deadly lung infections. Leung *et al*. [3] review recent development of emerging antibacterial agents as inhalation therapies. The barriers for clinical translation are discussed and potential solutions are proposed.

Among all pulmonary bacterial infections, multidrug-resistance tuberculosis (MDR-TB) remains a serious public health problem. Pulmonary drug delivery is an important strategy to improve the efficacy of anti-TB agents. Antimicrobial peptides have emerged to be promising candidate to combat MDR-TB. Lam *et al*. [4] report the development of inhaled powder formulations containing synergistic combinations of capreomycin and D-LAK antimicrobial peptides as potential new therapy against MDR-TB. This study provides insights on the development of inhaled antimicrobial peptides against respiratory infections.

Cannabidiol (CBD) is an interesting active ingredient found in cannabis, with the potential for treating many brain disorders such as epilepsy, pain, depression, anxiety, Parkinson's disease, and Alzheimer's disease. Kwok *et al*. [5] present a comprehensive review on the pharmacology and different routes of administration of CBD. The advantages of pulmonary and intranasal delivery over other routes of administration are also highlighted.

Dry powder inhalers (DPIs) are becoming popular for delivering biologics to the lung due to better stability. Particle engineering approach is commonly used to enhance aerosol performance. Spray freeze drying (SFD) has emerged to be an important particle engineering technique to produce DPIs. Its low-temperature processing conditions together with the ability to tailor particle properties make it particularly attractive for producing inhaled biopharmaceuticals. Henriques *et al*. [6] give a detailed explanation of fundamental principles of SFD. The different setups of SFD, their opportunities and challenges are also thoroughly discussed.

Thin-film freezing (TFF) is another emerging technology for producing powder formulation of inhaled biologics.

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Cui *et al*. [7] developed DPI formulation of plasmid DNA (pDNA) for pulmonary delivery using TFF. The produced dry powder formulations show excellent aerosol performance with MMAD around 1 – 2 μm, with pDNA activity preserved after TFF processing. The study demonstrates the feasibility to use TFF to manufacture pDNA powder formulation for pulmonary delivery.

Understanding the dissolution performance of dry powder is essential in the development of inhaled powder formulation as it affects the pharmacokinetic (PK) profile, yet there is no universally accepted method for assessing dissolution of inhaled products. Das *et al*. [8] present the use of an *in vitro* dissolution study together with modelling to predict plasma concentration-time profiles of inhaled dry powder formulations. This approach can be employed to assist the design of inhaled formulation to achieve the desirable PK profile.

Preclinical animal models are critical in evaluating the biological activity and immunogenicity of inhaled powder formulations of biopharmaceutical and vaccine. However, *in vivo* dry powder administration is challenging in murine models. To address this problem, Thompson *et al*. [9] developed different custom-made dosator designs for intratracheal dry powder delivery in mouse and their performance was compared. This study offers practical guidance on strategies to improve intratracheal delivery of dry powder formulation for use in animal studies.

It is challenging to assess the bioequivalence of inhalation products. Conventional PK studies may not consider potential difference in lung performance between reference and generic inhalation products. Hochhaus et al. [10] propose a population PK approach that could characterize the regional lung deposition by identifying and estimating the absorption of fluticasone propionate presumably from central and peripheral lung. Such approach could be useful to evaluate bioequivalence of inhalation products instead of clinical trials.

Although DPIs are attractive for the administration of inhaled medications, there is a critical challenge in the effective use of these devices by children due to low lung delivery efficiency and high inter-subject variability. Longest et al. [11] assessed the *in vitro* aerosol behavior of a dry powder antibiotic product that combined a highly dispersible tobramycin powder with an optimized air-jet DPI device for potential pediatric use. Data show that use of this product almost eliminated the drug deposition in the extrathoracic regions, with high lung delivery efficiency (~ 80%) and low variability in subject age and air volume. This research could lead to a new DPI product that is suitable for pediatric use.

We hope this theme issue will timely bring the latest updates in the development of pulmonary drug delivery systems and inhalation formulations with a purpose to provide insights in the development of new medications for treatment of life-threatening pulmonary diseases.

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