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Emerging inhalation aerosol devices and strategies: Where are we headed?☆

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ABSTRACT

Novel inhaled therapeutics including antibiotics, vaccines and anti-hypertensives, have led to innovations in designing suitable delivery systems. These emerging design technologies are in urgent demand to ensure high aerosolisation performance, consistent efficacy and satisfactory patient adherence. Recent vibrating-mesh and software technologies have resulted in nebulisers that have remarkably accurate dosing and portability. Alternatively, dry powder inhalers (DPIs) have become highly favourable for delivering high-dose and single-dose drugs with the aid of advanced particle engineering. In contrast, innovations are needed to overcome the technical constrains in drug–propellant incompatibility and delivering high-dose drugs with pressurised metered dose inhalers (pMDIs). This review discusses recent and emerging trends in pulmonary drug delivery systems.
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Contents

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1. Introduction

Therapeutic applications of respiratory drugs have rapidly expanded beyond conventional indications such as asthma and chronic obstructive pulmonary diseases (COPDs), to include inhaled antimicrobials, vaccines, and anti-hypertensives. The physico-chemical properties and dose regimen of these newer therapies may vary significantly, thereby necessitating new formulation techniques and device designs. As a result, innovative technologies in aerosol medicine are emerging in parallel with these new therapeutic indications to ensure optimal aerosolisation performance, therapeutic efficacy and patient adherence. This review covers emerging aerosol device innovations and the evolving roles of nebulisers, dry powder inhalers (DPIs) and pressurised metered dose inhalers (pMDIs), as well as their impact on patient adherence.

2. Nebulisers

Nebulisers generate an inhalable drug aerosol from a solution or suspension. They are useful for treatment of respiratory diseases as asthma, COPD and cystic fibrosis (CF) [1]. The most common nebuliser type is the jet nebuliser, which generates aerosols from the liquid medicament using a source of compressed gas. Although relatively inexpensive, treatment with jet nebulisers has long treatment time, the air compressors are bulky and noisy, and expensive medications are wasted in considerable residual volumes [2]. Many of the pitfalls are addressed by more recent vibrating-mesh nebulisers which have much greater portability and operate silently. The low velocity plume and minimal residual volume greatly enhance drug delivery to the lungs [3,4]. However, these new devices may have a much higher upfront cost and there is a lack of open literature demonstrating equivalent dosing of existing products to the more commonly used jet nebulisers. Other types of liquid aerosol generation systems include the Respimat® SoftMist™ Inhaler and AERx® systems, which generate liquid aerosol by mechanically forcing a drug solution through a nozzle array [5,6].

Optimisation of this existing nebuliser technology has focused on maximising aerosol lung deposition with each breath. Nebulisers typically generate aerosols throughout the entire respiratory cycle of the patients, leading to a significant loss during expiration. Thus mechanical regulation of aerosol generation has been implemented in breath-enhanced (Pari LC® Star) or breath-actuated (e.g. Trudell AeroEclipse® II) jet nebulisers. These limit aerosol loss by mechanically restricting the majority of aerosolisation to the inspiratory phase [1,7,8] and have been shown to shorten treatment time whilst minimising wastage of expensive medications [9,10]. However, these are relatively crude compared to the more recent integration of digital control systems with nebulisers, which provide much more precise regulation of aerosol delivery. These electronic systems further reduce treatment time by personalising aerosolisation to an individual patient's breathing pattern, thereby maximising lung drug deposition. Here we provide an update on the Activaero AKITA® and Philips Respironics I-Neb® adaptive aerosol delivery (AAD) systems.

2.1. Integration of software control

Originally designed to be coupled with a jet nebuliser (AKITA® JET), the AKITA® system – a stand-alone SmartCard electronic control unit with an air compressor – can now also coordinate with newer mesh nebulisers (AKITA® APIXNEB and AKITA2® APIXNEB) [4]. The software directs the compressor unit which utilises positive air pressure to control the patient's entire inhalation manoeuvre [2]. By controlling the aerosol flow rate, delivery volume and timing, the AKITA® system can optimise aerosol release at specific periods of a patient's inspiratory phase to target certain regions of the lungs and maximise aerosol delivery [11].

The AKITA® system has been particularly useful in gaining valuable lung deposition and clinical trial data. To refine imaging techniques used to assess lung deposition, Fleming et al. [12] used AKITA® system-controlled mesh nebulisation to generate radiolabelled human serum albumin with a variety of different lung deposition patterns. These were used to show that the combination of single photon emission computed tomography and X-ray computed tomography was superior to planar imaging, for the analysis of aerosol lung deposition. With application to clinical efficacy, Bakkar et al. [13] demonstrated that the AKITA® system can aid in determining optimal regional deposition profiles of inhaled drugs in specific disease states. Specifically, nebulised dornase alpha was directed to either the smaller or larger airways of patients with CF. Deposition in the smaller airways demonstrated greater improvement in therapeutic efficacy. Such data can allow formulation and device improvements to enhance clinical response to inhaled medications, and minimise unwanted side effects. The technology also opens up new opportunities for efficacy testing and clinical trials. For example, Moller et al. [14] showed that lung deposition of lipopolysaccharide, an endotoxin that can trigger airway inflammation and exacerbations in patients with COPD, can be well-controlled using an AKITA® system coupled with jet nebulisation to limit the risk of adverse effects. This could allow safe testing of new treatments for COPD by using an AKITA® system controlled lipopolysaccharide challenge test. Therefore, the AKITA® system has established new avenues in inhaled delivery such as regional targeting of nebulised drugs and in refining clinical trials.

Similarly, the I-Neb® consists of an AAD software control unit and a mesh nebuliser but combined into a single handheld device [15]. The I-Neb® software has two modes of operation — a tidal breathing mode and a targeted-inhalation mode. Whilst tidal breathing mode adapts device aerosolisation to a patient's regular tidal breathing patterns, the latter uses a unique vibratory feedback mechanism to guide the patient towards an optimal breathing pattern that maximises aerosol deposition for a shorter treatment time.

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