

Inhaled medical aerosols by nebulizer delivery in pulmonary hypertension

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The late 1820s saw the development of nebulizers.¹ Nebulized aerosols can be designed for oral inhalation to the lungs, nasal inhalation to the upper respiratory tract, or both though the use of sized face masks. The solvent can be aqueous or aqueous/alcohol, as the first nebulized product approved for human use contained 50% ethanol as an aqueous/alcohol cosolvent. The physicochemical properties of the inhalation formulation and interactions with the nebulizer device directly impact aerosol properties and ultimately efficacy following nebulization.² Dual-drug combination formulations are available for nebulization where one inhaled aerosol formulation contains two drugs from two different therapeutic classes with pharmacological mechanisms of action. Inhaled therapeutics by nebulization can be done in the outpatient setting, inpatient setting, and in the intensive care unit setting in mechanically ventilated intubated patients. Currently, many different disease states are treated by nebulization³ with marketed pharmaceutical products including asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, pulmonary infections, and pulmonary hypertension.^{4–6}

Nebulizers have been increasing in growth, as exemplified by the increase in marketed nebulizer pharmaceutical products. Nebulizers create the aerosol independent of the patient's inspiratory force. Hence, they are used successfully in niche patient populations such as infants, pediatrics, geriatrics, and in patients with advanced stage lung disease. In 2018, the global pulmonary drug delivery market is expected to hit \$43.9 billion.⁷ The nebulizer market reached \$685.7 million in 2013 and in 2018 is expected to reach \$893.5 million.⁷

Nebulizers are drug-device combination products. As such, the interactions between the inhalation formulation and nebulizer device directly influence aerosol properties, targeting, and efficacy. The three main nebulizer classes are air-jet, ultrasonic, and vibrating mesh. Ultrasonic nebulizers are also known as electronic nebulizers. Air-jet nebulizers are also known as standard nebulizers. All three classes require a power supply that is provided externally

to the device or within the device via a battery. New nebulizers have been developed that are hand-held and these tend to be the ultrasonic nebulizers and the vibrating mesh nebulizers. Constant output (i.e. unvented), breath-enhanced (i.e. vented), and breath-activated are the subtypes existing within the main classes of nebulizers.³

Inhalation delivery of therapeutics has been demonstrated in pulmonary hypertension (PH).^{4–6} The Adaptive Aerosol Delivery[®] (AAD) nebulizer device that is used in the PH treatment inhaled pharmaceutical product Ventavis[®] is a vibrating mesh nebulizer device.^{5,8} The Optineb[®] nebulizer device that is used with PH treatment inhaled pharmaceutical product Tyvaso[®] is an ultrasonic nebulizer device.⁶ In the paper by Hajjar et al.,⁹ the authors investigated the safety and efficacy of nebulized gene delivery.

Inhaled gene delivery in a large diseased animal model of PH was achieved in pigs by nebulization. In addition, four months after aerosolized gene delivery, follow-up was performed. Promising results were reported.⁹ Pulmonary vascular resistance was lowered and long-term survival was increased. Imaging showed the distribution of the aerosol in the lungs. Sheep and pigs are well-known and generally recognized to be good large animal models of human lung diseases.

Inhaled recombinant human DNase for use in cystic fibrosis delivered by nebulization has been on the market for several years. In 2018, the U.S. Food and Drug Administration recently approved an inhaled liposomal product delivered by nebulization. For decades, inhaled gene delivery and inhaled liposomal delivery have been active areas of promising research for the treatment and prevention of lung diseases. With innovations in inhalation formulations and inhaler devices, it is expected that this exciting targeted drug delivery area will continue its tremendous growth. This targeted delivery approach has great potential in the treatment and prevention of PH.



Conflict of Interest

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