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Review Article

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Nebulization as A Route for Salbutamol Delivery: Current System, Future Directions & Emerging Trends

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Abstract: Nebulization has emerged as a valuable alternative to hand-held inhalers for delivering medications like salbutamol, especially in cases involving patients who face difficulties using conventional inhalation devices, such as children, the elderly, and critically ill individuals. This review explores the current systems of nebulization for salbutamol delivery, focusing on the challenges and advancements in nebulizer technology. Although nebulization offers numerous benefits in emergency and critical care settings, there are gaps in the knowledge surrounding best practices, and existing national guidelines on nebulization are outdated. Salbutamol, a short-acting β2-agonist, is widely used for managing acute bronchospasm, though overuse may contribute to adverse effects, including increased airway inflammation. The article also discusses emerging trends in inhaled drug delivery, highlighting the potential of new technologies to address unmet medical needs in pulmonary and systemic drug therapies. Future research should focus on refining nebulization techniques, improving equipment efficiency, and establishing comprehensive, evidence-based guidelines to ensure safe and effective use in diverse clinical settings.

Keywords: Nebulization, obstructive airway diseases (OADs), asthma and chronic obstructive pulmonary disease (COPD)

1. Introduction

Inhalation therapy is currently a cornerstone treatment for obstructive airway diseases (OADs) such as asthma and chronic obstructive pulmonary disease (COPD), and is also widely used for various pulmonary and even non-pulmonary conditions (1). However, hand-held inhalation devices can be challenging to use, particularly for children, the elderly, or patients who are debilitated or distressed. In such cases, nebulization therapy presents a valuable alternative, offering significant benefits in home care, emergency rooms, and critical care settings (2).

With the rapid advancements in nebulizer technology, the availability of diverse drug formulations, and the expanding applications of this therapy, healthcare professionals, including medical practitioners, respiratory therapists, and other caregivers, face the challenge of selecting the most appropriate inhalation devices and drug formulations for different clinical situations (3). Additionally, proper maintenance of nebulizer equipment, including disinfection and storage, is essential but often overlooked. Improper use and poor maintenance of nebulizers can result in serious health risks, including nosocomial infections, transmission of disease, and other adverse outcomes (4).

Given these challenges, there is a pressing need for national guidelines on nebulization practices to address knowledge gaps among healthcare providers (5). These guidelines would also serve as a vital educational and

scientific resource for healthcare professionals and encourage future research by highlighting overlooked areas within the field. Currently, no comprehensive national guidelines exist, and the only available international guidelines were issued in 1997 and have not been updated in over two decades, despite significant advancements in technology. Consequently, many current nebulization practices may not be evidence-based, and some approaches may be ineffective or even harmful (6).

Inhalational therapy is now a cornerstone treatment for obstructive airway diseases (OADs) such as asthma and chronic obstructive pulmonary disease (COPD), and it is also widely used for a range of other pulmonary and non-pulmonary conditions (7). Beyond bronchodilators and inhaled corticosteroids (ICS), many other medications are now administered via the inhaled route, including mucolytics, various antimicrobials, insulin, prostacyclin, surfactants, and non-steroidal anti-inflammatory drugs. This method also enables systemic drug delivery through the large alveolar epithelial surface, facilitating rapid absorption and providing benefits for treating some systemic disorders (8).

In addition to pressurized metered dose inhalers (pMDI) and dry powder inhalers (DPI), nebulizers serve as aerosol generators, converting drug solutions or suspensions into droplets for effective delivery (9). This makes nebulization particularly valuable in emergency and critical care settings, as well as for some patients using it at home. Nebulization also plays a crucial role in pediatric care. National and international guidelines for managing asthma, COPD, and other pulmonary conditions frequently recommend nebulization for drug delivery to the lungs (10).

However, it is increasingly recognized that much of the current practice in nebulization may not be evidence-based, and some approaches could be ineffective or even harmful. Additionally, it has been shown that the dose delivered to the lungs can vary dramatically—sometimes increasing more than tenfold—simply by switching from a poorly performing nebulizer system to one that is highly efficient (11).

2. Salbutamol

Salbutamol, the first selective short-acting β2-agonist (SABA) introduced in 1968, has become a cornerstone in clinical practice. It is a selective β2-adrenergic receptor agonist used to manage acute bronchospasm episodes associated with asthma and other chronic bronchopulmonary disorders. Salbutamol provides effective symptomatic relief and prevents bronchospasm due to its potent smooth muscle relaxant properties (12). The World Health Organization (WHO) recognizes salbutamol as one of the most effective and safest essential medicines for healthcare systems worldwide. It is known to improve daytime symptoms, though a subtle decline in asthma control may occur over time (13).

However, salbutamol should not be used as monotherapy; it is typically recommended in combination with inhaled corticosteroids (ICS) or as an alternative in certain conditions (14). Regular use of salbutamol may have a pro-inflammatory effect, as noted by Gavreau et al., potentially explaining the increased risk of exacerbations. This finding is supported by Ritchie et al., who suggest that β-agonists may elevate the levels of inflammatory mediators, leading to airway obstruction and hyperresponsiveness. Excessive use of bronchodilators may, therefore, contribute to exacerbations (15).

3. Chemistry

Salbutamol is a chiral drug with both (R)- and (S)-isomers. The pharmacological activity of salbutamol is primarily associated with the (R)-enantiomer, which binds to the human β2-adrenoceptor. The role of the (S)-enantiomer remains a subject of debate. While it is generally considered inert in humans, Patel et al. have reported experimental evidence suggesting that the (S)-isomer may cause clinically significant adverse effects. Interestingly, non-racemic (R)-salbutamol has been shown to provide beneficial effects. Gumbhir-Shah et al. found that the pharmacokinetics (PK), pharmacodynamics (PD), and safety profile of this enantiomer are similar, whether administered as a single enantiomer or in a racemic mixture via inhalation to patients with mild to moderate asthma. However, several well-conducted studies indicate that the (R)-enantiomer does not show clear clinical superiority over racemic salbutamol (16-17).

4. Salbumatol Mechanism of Action

The respiratory tract smooth muscle contains a high density of β2-adrenergic receptors. The activation of these receptors leads to the production of cyclic adenosine monophosphate (cAMP), a second messenger that plays a key role in the process. As an agonist, salbutamol binds reversibly to the β2-receptors, which in turn activates adenylate cyclase (18). This enzymatic activation leads to the conversion of ATP to cAMP. Elevated cAMP levels trigger a series of intracellular events that ultimately inhibit bronchial smooth muscle contraction, promoting relaxation and bronchodilation, which is the desired therapeutic effect (19).

Additionally, salbutamol has an inhibitory effect on the release of mediators involved in immediate hypersensitivity, particularly from mast cells. Due to its high selectivity, salbutamol exhibits minimal action on β1-adrenergic receptors, reducing potential side effects related to the heart (20).

The β2-adrenergic receptor is activated by salbutamol, leading to the activation of adenylate cyclase and the subsequent conversion of ATP to cAMP. This cascade results in bronchodilation, providing relief from symptoms during an acute asthma episode (21).

5. Emerging Trends in Inhaled Drug Delivery

Inhaled therapy is ideally tailored to meet the specific needs of disease management, where lung biology interacts with inhaler performance to enable optimal delivery of therapeutic agents. Inhalation aerosol products are composed of the therapeutic agent, formulation, and device. The manufacturing specifications for each component, as well as their integration, ensure precise control over quality measures and in-vitro performance. These product variables, in conjunction with patient factors such as inhaler coordination skills, lung biology, disease state, and pulmonary function, all play crucial roles in determining drug safety and efficacy outcomes (22).

Given the complexity of pulmonary drug delivery, predicting biological outcomes from fundamental principles has been a challenging endeavor. However, ongoing research continues to provide new insights that may eventually allow for more accurate predictions of drug behavior in the lungs. Disruptive innovations characterized inhaled drug delivery research at the close of the last century. Although the first decade of the new millennium saw relatively few new inhaled products, it became clear that the early phases of exploration laid the foundation for commercially successful technologies (23).

In the past decade, the field has experienced a significant surge in the launch of new and generic products, alongside emerging trends in technology, regulation, and disease management. Some of these advancements can be traced back to earlier periods of creativity, while others are driven by progress in basic sciences, computer technology, and engineering. This article highlights select biological and technical advances, with a focus on their potential to shape future clinical and regulatory landscapes (24).

Over the past seventy years, high-quality, pharmacologically targeted inhaled therapy has become the cornerstone of pulmonary disease management. Many of these modern therapies can trace their roots to the early use of inhaled natural products in India and China. In the last decade, the innovative technologies developed over the previous twenty-five years have matured into commercial products or have been refined to meet the evolving needs of development, quality, safety, and efficacy (25).

As inhaled medicines have progressed, much of the traditional space for innovation in conventional pulmonary disease treatments has been explored. However, future breakthroughs are likely to emerge from addressing unmet medical needs. In this context, rare and infectious lung diseases are gaining increasing attention, while the field of systemic drug targeting via pulmonary delivery remains in its early stages.

6. Conclusion

Nebulization remains a vital and often underutilized method for delivering salbutamol, particularly in populations that struggle with traditional inhalation devices. While recent advancements in nebulizer technology have improved treatment delivery, there is a clear need for updated national guidelines to standardize practices and ensure safety and efficacy. Given the complexities surrounding nebulizer use, such as equipment maintenance and variation in drug delivery, continued research and refinement of both technology and clinical protocols are crucial. Furthermore,

as salbutamol continues to play a pivotal role in managing obstructive airway diseases, attention must be given to the long-term effects of its use and the potential for combination therapies. Looking ahead, the future of inhaled drug delivery will likely be shaped by innovative technologies that address both pulmonary and systemic disease management, offering new opportunities for improved patient outcomes.

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