

In Vitro Comparative Assessment and Characterization of Glycopyrronium Nebulizing solutions with Mesh Nebulizer: New Generation Impactor Study

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Abstract

Background: Inhalation therapy involving nebulization remains important modality of therapy for severe or high-risk obstructive airway diseases including bronchial asthma. The likely incremental factors for the translational impact of this delivery strategy includes fine particle dose (FPD), fine particle fraction (FPF), mass median aerodynamic diameter (MMAD), and respirable fraction (RF) of the pharmaceutical aerosols playing a key role in site-specific delivery to the lungs. The new generation active vibrating mesh nebulizers (VMNs) offer a convenient, portable strategy in above clinical cases without compromising the delivery efficiency for improved therapeutic outcomes.

Aim: This *in vitro* study was conducted to validate the improved efficiency and aerodynamic effect of glycopyrronium solution nebulization with novel patented active and passive VMN devices.

Materials and Methods: A *in vitro* lung deposition study was conducted using drug samples of glycopyrronium bromide (25 mcg/2 ml and 1 ml) using new generation cascade impactor at a flow rate of 15 L/min at Glenmark R&D Center, Sinnar, India.

Results: Three samples of glycopyrronium nebulizing solution were analyzed using next generation impactor at a flow rate of 15 L/min for aerodynamic aerosol parameters (FPF and RF) and total/active substance delivered (FPD and delivered dose) when loaded with active (NEBZMART*, 2 ml) and passive (E-flow*, 1 ml) VMN. The results demonstrated comparable aerodynamic aerosol, particle size, and total delivered dose as FPF (64.9% vs. 72.8%), FPD (16.4 vs. 14.2 mcg), MMAD (3.9 vs. 3.2), and GSD (1.8 vs. 1.62) for active and passive VMN, respectively. The nebulization time was observed as 3–5 min for both the devices demonstrating higher efficiency for active VMN.

Conclusion: The results showed comparable aerodynamic aerosol, particle size, and total delivered dose or RF for glycopyrronium nebulizing solution delivered by the VMNs.

Key words: Glycopyrronium, Aerodynamic particle size dimension, New generation impactor, Nebulization, Mesh nebulizer

INTRODUCTION

The global burden of obstructive airway diseases remains high with increased morbidity and mortality associated

with the above conditions including chronic obstructive pulmonary diseases (COPD). The latest figures highlight COPD as the second leading cause of death among the non-communicable diseases of India.

Despite the availability of inhalational therapies and strategies including pressurised metered-dose inhaler and dry powder inhaler, patient compliance, and adherence remains poor especially in elderly or high-risk patients with poor inspiratory flow rates. European Research Society^[1] guidelines recommend the use of nebulization strategy

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for patients with severe airway obstruction, repeated use of rescue medications and physical or cognitive deficit for their inability to operate the traditional inhaler devices that have been the cornerstone of therapy in bronchial asthma and COPD since yesteryears. The role has been again highlighted by the Irish Guidelines especially for patients with severe asthma, or acute exacerbation of COPD wherein the role of nebulization with short-acting beta-agonist (SABA) or SABA/short-acting muscarinic-antagonist has been envisaged before the patient can be hospitalized or following discharge.^[2]

Vibrating mesh nebulizers (VMNs) are the new generation inhaler devices that are compact, portable, noiseless offering optimal convenience, or compliance for patients in home or ambulatory settings in such cases. More importantly, they generate a gentle, soft mist aerosol with a droplet size distribution and acceptable respirable fraction (RF) suitable for central and peripheral lung deposition while offering short nebulization time for better patient compliance and adherence rate. The delivery of long-acting antimuscarinic agents remains an interesting prospect, especially for high-risk cases including COPD. Glycopyrronium nebulizing solution remains the only approved and available formulation for use in combination with the eflow* rapid nebulizer system involving active vibrating mesh for COPD and related phenotypes as long-term maintenance therapy.^[3]

However, the *in vitro* characterization including drug delivered dose or aerosol particle size dynamics remains unexplored especially with NEBZMART* that incorporates microbase

technology for aerosolization and deposition in smaller airways with negligible residual volume (0.1 ml) offering shorter nebulization time while avoiding sub-therapeutic clinical effects and related adverse outcomes.

The current study was, therefore, undertaken to explore further the *in vitro* characterization including aerosol particle size deposition and delivered dose kinetics for NEBZMART*, an active VMN that is widely available in the real-world outpatient settings of India when compared with the e-flow rapid system.

MATERIALS AND METHODS

The aerosol performance of the VMNs including NEBZMART* and eFlow Rapid CS nebulizer was analyzed utilizing aerosol droplet size distribution and delivered a dose that was determined by next generation impactor (NGI). Three samples each of Glycopyrronium nebulizing solutions manufactured by Glenmark and Sunovion* respectively were utilized in this study.

A set of dedicated eFlow CS and NEBZMART* VMNs were used for each glycopyrronium drug product lot. Each device was tested in single measurement for NGI and duplicate measurements for delivered dose with reference values for lung deposition as 80% of the delivered dose when an aerosol with a mass median aerodynamic diameter (MMAD) of 3 µm was produced by the VMNs.

The procedure was completed as per the US Pharmacopoeia 2007 guidance. The characteristics of the aerosol were determined and assessed using several parameters including fine particle fraction (FPF), MMAD, and fine particle dose (FPD). The definitions included FPF: Fraction of the aerosol that is in a size range with the potential the fine particle (<5 m) dose divided by the total delivered dose; MMAD: Diameter of drug particles at which 50% of particles by mass is larger and 50% are smaller; FPD is the quantity of drug with fine particle size and related to drug deposition in the lung,^[4-6] and Aerodynamic particle size dimension (APSD) involves the determination of the total mass emitted from the inhaler and is, in essence, an indirect measurement of “delivered” dose.

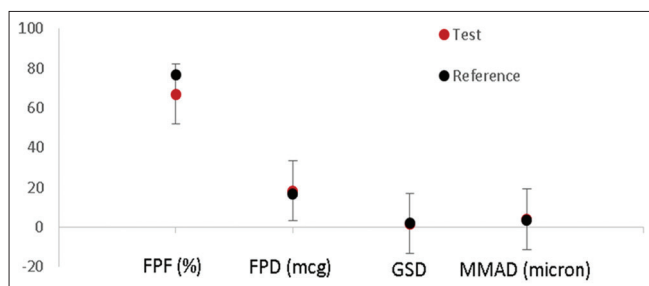


Figure 1: Comparison of drug deposition profile aerodynamic particle size dimension of the test (Glenmark's glycopyrronium nebulization solution) and reference (Sunovion's glycopyrronium nebulization solution)

Table 1: Glycopyrronium nebulizing solution particle characteristics demonstrated by Fine Particle Fraction (FPF), Fine Particle Dose (FPD), Geometric Standard Deviation (GSD) and Mass Median Aerodynamic Diameter (MMAD)

Type	FPF (<5 µm, %)	FPD (<5 µm, mcg)	GSD	MMAD (micron)
Reference GLY Formulation – (Lot no. UG162 with E-flow*)	72.91–75.55%	14.21–15.83 mcg	1.62–1.81	3.40–3.58
Test GLY Formulation (Lot no. SGLYA-02/1703011 and SGLYA-02/1703012 with Nebzmart*)	64.87–66.31%	16.36–17.67 mcg	1.80–1.82	3.91–3.92

FPD: Fine particle dose, FPF: Fine particle fraction, MMAD: Mass median aerodynamic diameter

RESULTS

Three samples of glycopyrronium nebulizing solution were analyzed using NGI at a flow rate of 15 L/min for aerodynamic aerosol parameters (FPF and RF) and total/active substance delivered (FPD and delivered dose) when loaded with test (NEBZMART*, 2 ml) and reference (E-flow*, 1 ml) VMN. The results demonstrated comparable aerodynamic aerosol, particle size, [Table 1] and total delivered dose as FPF (64.9% vs. 72.9%), FPD (16.4 vs. 14.2 mcg), MMAD (3.9 vs. 3.2), and GSD (1.8 vs. 1.62) for active and passive VMN, respectively [Figure 1]. The nebulization time was observed as 3–5 min for both the devices demonstrating higher efficiency for active VMN.

DISCUSSION

Mesh nebulizers provide increased portability, convenience, improved drug delivery efficiency compared with a conventional compressor or jet nebulizers. Although the VMNs offer larger MMAD >3 μ m, scintigraphic aerosol and lung deposition studies suggest improved lung deposition with the reduced oropharyngeal loss. This suggests that the mesh nebulizer is as effective as a jet nebulizer in producing aerosol particles suitable for inhalation, with high deposition in the lungs.^[7]

The results from the current study demonstrate comparable results or bioequivalence for glycopyrronium nebulizing solution dispersed with active VMN (i.e. NEBZMART* and eFlow* devices) for FPF, FPD, and APSD as per specifications laid down by USP 601.^[8]

The performance characteristics of the eFlow CS vibrating membrane nebulizer support its use for the administration of glycopyrronium drug solution as a potential maintenance treatment for COPD. The specifically engineered eFlow vibrating membrane technology, and the uniquely designed CS ampoule of the eFlow CS nebulizer produces glycopyrronium aerosols with optimized acceptable RFs and dose uniformity under routine laboratory and simulated stressed-use conditions.

The results in the current study with active VMN (NEBZMART*) for fine particle dose (FPD) and Fine particle fraction (FPF) from APSD testing with mean values being well within the specified limits including 85 to 115% of the emitted dose from eFlow* CS nebulizer.

Similarly, the FPF was well over the prescribed limit of 50% for inhaler devices and comparable to the results published by Pham^[3] in this line

Study Limitation

The results are limited by small sample size and need to be reproduced by large scale studies, and represent first of its kind study to compare the APSD or FPD for glycopyrronium nebulizing solution with a conventional compressor (Jet) or small volume nebulizers (SVNs) including active VMN (NEBZMART*). At the same time, the results are suggestive of the likely potential and benefits of SVNs in showing greater versatility in highlighting the dispersion of both nebulizing suspension and solution.

CONCLUSION

The results showed comparable aerodynamic aerosol, particle size, and total delivered dose or Fine particle fraction (FPF) for glycopyrronium nebulizing solution delivered by the VMNs.

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