Assessment of Nebulizer Performance for Delivery of Dual and Triple-Combination Formulations

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INTRODUCTION

The use of nebulizers in inhalation therapy to continuously deliver larger doses of solutions and suspensions has been well-established for several decades. Nebulizers are capable of aerosolizing formulations to directly deliver medication into the airways, thus treating respiratory diseases. Their advantage relies on that they do not require patients to generate a peak inspiratory flow or coordinate device actuation to release medication like in the case of dry powder inhalers (DPIs) and metered dose inhaler (MDIs) [1].

Although combination therapy in nebulizers has not been intensively covered until more recently, there are studies showing that it may increase patients' compliance since this practice considerably reduces nebulization time [2]. Nevertheless, a careful analysis of the physico-chemical compatibility of the drugs being mixed is critical as well as understanding the effects these inhaled mixtures could have on the nebulized aerosol characteristics [1].

It has also been reported that the treatment of various respiratory diseases can benefit from combination therapy. Studies revealed that chronic obstructive pulmonary disease (COPD) was effectively treated by application of dual-combinations of long-acting beta2-agonists and inhaled corticosteroids (LABA/ICS), and dual-combinations of long-acting beta2-agonists and long-acting muscarinic antagonists (LABA/LAMA) [3]. Similarly, combination of ipratropium bromide, a short-acting muscarinic antagonist (SAMA), and salbutamol, a short-acting beta2-agonist (SABA), has also been proven to improve conditions for patients suffering from COPD and children with acute to severe asthma [4, 5].

This study analyzed the aerosol characteristics of a dual and a triple-combination formulation using four commercial nebulizers to evaluate delivery performance. Comparison of performance was focused on a jet nebulizer and three mesh nebulizers using formulations designed for use with jet nebulizers. The selected formulations were combinations of SAMA/SABA and SAMA/SABA/ICS, as the components in both mixtures are widely used [6].

METHODS

Four nebulizers were used to analyze delivery performance of the corresponding formulations. For comparison, PARI LC PLUS®/TurboBOY® was chosen as the jet nebulizer along with three mesh nebulizers: HCmed PulmogineTM, Omron NE-U22, and Yuwell HL100A.

In order to assess aerosol characteristics, a dual-combination formulation was selected using salbutamol sulfate (Ventolin®, GSK), 2.5 mL/5 mg, and ipratropium bromide (Atrovent®, Boehringer Ingelheim), 2 mL/0.5 mg. The triple-combination contained the same two drugs previously mentioned and the addition of budesonide (Pulmicort Respules®, AstraZeneca), 2 mL/1 mg. The entire content of each ampule was loaded into the devices to perform the tests.

Laser diffraction particle size analyzer, Spraytec (without an inhalation cell; 21±1˚C, 58±6% humidity), from Malvern was used to analyze mean volume diameter (DV50), fine particle fraction (FPF <5 μm), and geometric standard deviation (GSD). Three tests were conducted for each nebulizer. Additionally, output rate during the first minute and total nebulization time were recorded and the residual mass was weighed in the reservoir after nebulization.

UV-Vis spectrometer, Lambda 365, from Perkin Elmer was used to examine and compare the absorption profile pre- and post-nebulization from the collected aerosol in order to identify concentration of active pharmaceutical ingredients (APIs). Absorption peaks for salbutamol sulfate were observed at 276 nm, ipratropium bromide at 210 and 220 nm, and budesonide at 246 nm. Calibration curves were used to calculate concentration of the APIs at the cited peaks.

RESULTS

The average values for DV50, FPF, and GSD of all four devices obtained from Spraytec were recorded along with the standard deviations for the dual and triple-combination formulations and are displayed in Table 1.

Table 1.

Dual and triple-combination formulation aerosol characteristics.

	Dual Combination			Triple Combination		
Device	DV50 (μm)	FPF (%)	GSD	DV50 (μm)	FPF (%)	GSD
PARI LC/TurboBOY	5.34±0.07	33.00±1.69	2.25±0.05	4.54±0.07	54.74±0.70	2.12±0.03
HCmed Pulmogine	4.11±0.01	52.95±0.48	1.75±0.02	4.52±0.01	56.57±0.31	1.76±0.08
Omron NE-U22	7.46±0.12	26.83±0.79	2.39±0.01	5.93±0.24	38.89±2.74	2.46±0.01
Yuwell HL100A	7.65±0.32	27.17±1.82	2.81±0.12	6.70±0.08	32.92±0.65	2.94±0.10

The output rate and residual mass in the reservoirs were also recorded, while the total nebulization time was computed to compare treatment duration with each device (Table 2). Figure 1 displays the absorption spectra of both formulations pre- and post-nebulization. The spectra confirmed API presence as depicted by the absorption on the respective peaks that were marked for each drug. Table 3 summarizes the concentration for both formulations after nebulization with the devices.

Table 2.

Output rate, residual mass in the reservoir, and total nebulization time for dual and triple-combination formulation.

	Dual Combination			Triple Combination		
Device	Rate (g/mL)	Residue (g)	Total Time (min:sec)	Rate (g/mL)	Residue (g)	Total Time (min:sec)
PARI LC/TurboBOY	0.20	1.57	25:00	0.17	1.30	55:30
HCmed Pulmogine	0.46	*NA	13:00	0.47	0.18	20:00
Omron NE-U22	0.33	0.34	16:45	0.20	0.11	44:00
Yuwell HL100A	0.69	0.25	5:30	0.64	0.33	16:00

* Residual mass below 0.0001 g.

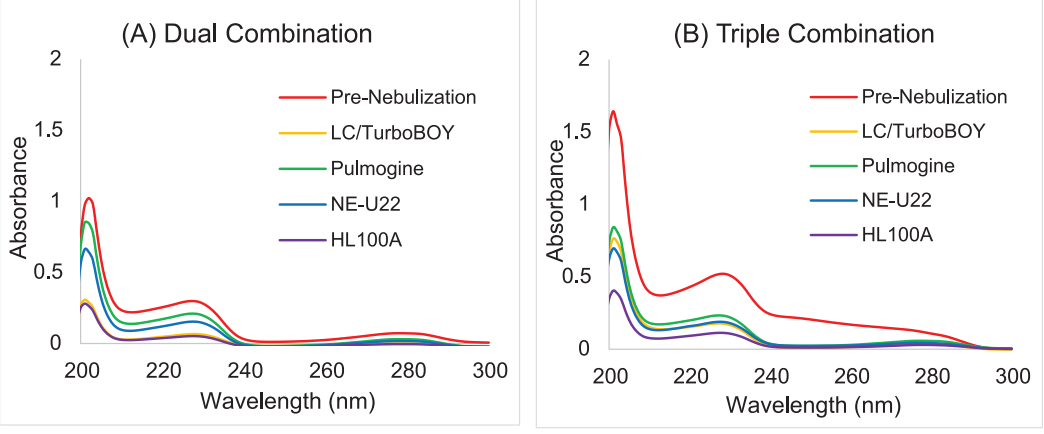

Figure 1. **Profile from UV-vis spectrometer pre- and post-nebulization (a) dual-combination formulation, (b) triple-combination formulation.**

Table 3.

API concentration for dual and triple-combination formulation post-nebulization.

	Dual Combination		Triple Combination		
Device	Ipratropium (mg/mL)	Salbutamol (mg/mL)	Ipratropium (mg/mL)	Salbutamol (mg/mL)	Budesonide (mg/mL)
PARI LC/TurboBOY	0.001	*NA	0.042	0.412	0.027
HCmed Pulmogine	0.045	0.317	0.056	0.628	0.064
Omron NE-U22	0.027	0.163	0.044	0.484	0.063
Yuwell HL100A	*NA	*NA	0.023	0.331	0.031

* Concentration below 0.0001 mg/mL.

DISCUSSION

Results obtained from laser diffraction analysis revealed that Pulmogine considerably surpassed the jet and other two mesh nebulizers when it comes to particle size distribution. Values for DV50 and GSD were lowest for Pulmogine during nebulization of both formulations, while the FPF was recorded at its highest.

Output rate and total nebulization time were faster with HL100A in both cases, although this nebulizer produced larger DV50 and lower FPF. LC/TurboBOY was the slowest performing device among the four. Residual mass was larger in the jet nebulizer for both formulations, whereas residue was negligible when nebulizing the dual combination with Pulmogine.

Absorption values for Pulmogine showed that concentration of APIs post-nebulization with this device were the highest among the four tested nebulizers in both formulations. With these positive results, an analytical protocol is currently under development to perform the test using HPLC. Therefore, the difference in API concentration could be further investigated to prevent overdose or underdose when using mesh nebulizers since all formulations in this study have been designed for delivery using jet nebulizers.

CONCLUSION

Originally intended dual and triple-combination formulations for jet nebulizers could be successfully delivered by the three mesh nebulizers used in this study. Performance assessment showed that the fastest mesh nebulizer that presented better aerosol characteristics was Pulmogine, nebulizing both formulations in less than half of the time required by the jet nebulizer. Implications of API concentration were assessed with UV-vis spectrometry but should be further investigated to identify values using HPLC and reassess delivered dose with mesh technology. Other types of combination formulations could also be explored in future studies.

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