Solution-based pressurized metered dose inhaler formulations using HFA134a, HFA152a and HFO1234ze(E) propellants: Analysis of size, aerosolization performance and particle morphology

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INTRODUCTION

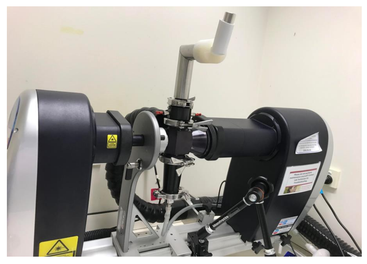
- There is currently an increasing demand for transition from conventional pressurized metered-dose inhaler (pMDI) propellants with high global warming potential (GWP) such as HFA134a and HFA227ea towards lower GWP "greener" pMDIs [1].
- While the newer generation propellants such as HFA152a and HFO1234ze(E) will largely reduce the GWP of pMDI products, their thermodynamic and physicochemical properties are different from the traditional HFA propellants which may affect the aerosol performance and subsequent pMDI therapeutic efficacy [2].
- A thorough understanding of the newer propellants on pMDI performance is therefore needed.

AIMS

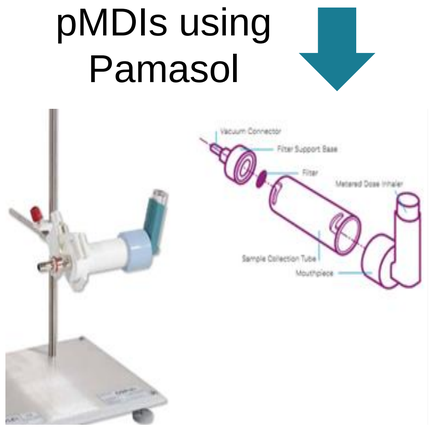
- To evaluate the impact of new propellants, HFO1234ze(E) and HFA152a along with traditional HFA 134a on aerosol performance in a solution-based pMDI formulations prepared at a fixed corticosteroid concentration of 2 mg/mL and ethanol co-solvent concentration of 8% w/w using a 0.4 mm actuator.

METHODS

Manufacturing of pMDIs using Pamasol



A. Size distribution analysis (Spraytec)



B. Delivered Dose Uniformity Analysis (DUSA)

C. Aerodynamic size distribution using Andersen Cascade Impactor (ACI)

D. Morphological analysis of matured particles by scanning electron microscope (SEM)

RESULTS

- Delivered dose uniformity of the pMDI formulations were not impacted by propellant type, where the mean delivered dose was found to be within ± 15 % of the target value of 500 µg after five shots.
- In general, the HFO1234ze(E) pMDI formulation produced the smallest droplet size followed by formulations made in HFA134a and HFA152a.
- Aerodynamic particle size distribution measured by Anderson Cascade Impactor (Figure 1B) showed that a large fraction of the delivered dose (approx. 50%) was deposited in the throat (USP induction port), whereas approximately 10% and 3% of the drugs were retained in the actuator and mouthpiece adaptor (MPA), respectively.
- The fine particle dose produced from all pMDI formulations was between 167 to 177 µg (representing 38 to 40% of the delivered dose).
- All pMDI formulations regardless of propellent-type showed matured particles that are a mixture of smooth and irregular spherical size and shape (Figure 1).

CONCLUSIONS

- Solution-based pMDI formulation prepared with HFO1234ze(E) showed similar characteristics to that of a comparative HFA134a formulation in terms of drug dose uniformity, droplet size and aerodynamic properties, with both pMDI formulations also showing similar particle morphology of the matured particles after actuation.
- Our data support the need for more detailed studies on the influence of new 'greener' low GWP propellants on pMDI performance for the design of the next-generation of pMDI products.

REFERENCES

[1] Zhu, B.; Traini, D.; Chan, H.-K.; Young, P. M. *The effect of ethanol on the formation and physico-chemical properties of particles generated from budesonide solution-based pressurized metered-dose inhalers*. Drug Dev. and Ind. Pharm. 2013, *39* (11), 1625-1637.

[2] Zhu, B.; Traini, D.; Lewis, D. A.; Young, P. *The solid-state and morphological characteristics of particles generated from solution-based metered dose inhalers: Influence of ethanol concentration and intrinsic drug properties*. Colloids Surf A Physicochem Eng Asp. 2014, *443*, 345-355.

Table 1. ***Post-throat droplet size distribution of pMDIs prepared with different propellants as measured by laser-diffraction technique (Average, n=3 ± SD).***

	DV10 (µm)	DV50 (µm)	DV90 (µm)	Span
HFA134a	0.63 ± 0.0	1.4 ± 0.1	3.6 ± 0.6	2.1 ± 0.3
HFO1234ze(E)	0.64 ± 0.0	1.3 ± 0.0 *	2.8 ± 0.2*	1.6 ± 0.1*
HFA152a	0.59 ± 0.1	1.8 ± 0.1*	6.5 ± 0.8*	3.3 ± 0.5*

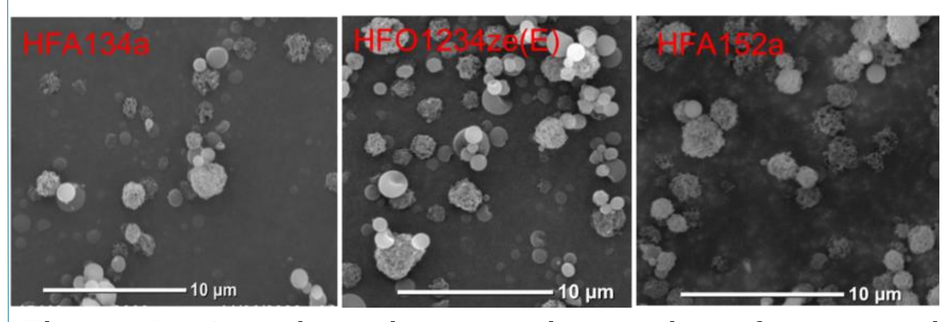


Figure 1. ***Scanning electron micrographs of maturated particles on stage 5 of the Andersen cascade impactor, produced from HFA134a (magnification ×3000), HFO1234ze(E) (magnification ×2700) and HFA152a (magnification ×3000) formulations after deposition at a flow rate of 28.3 L/min.***

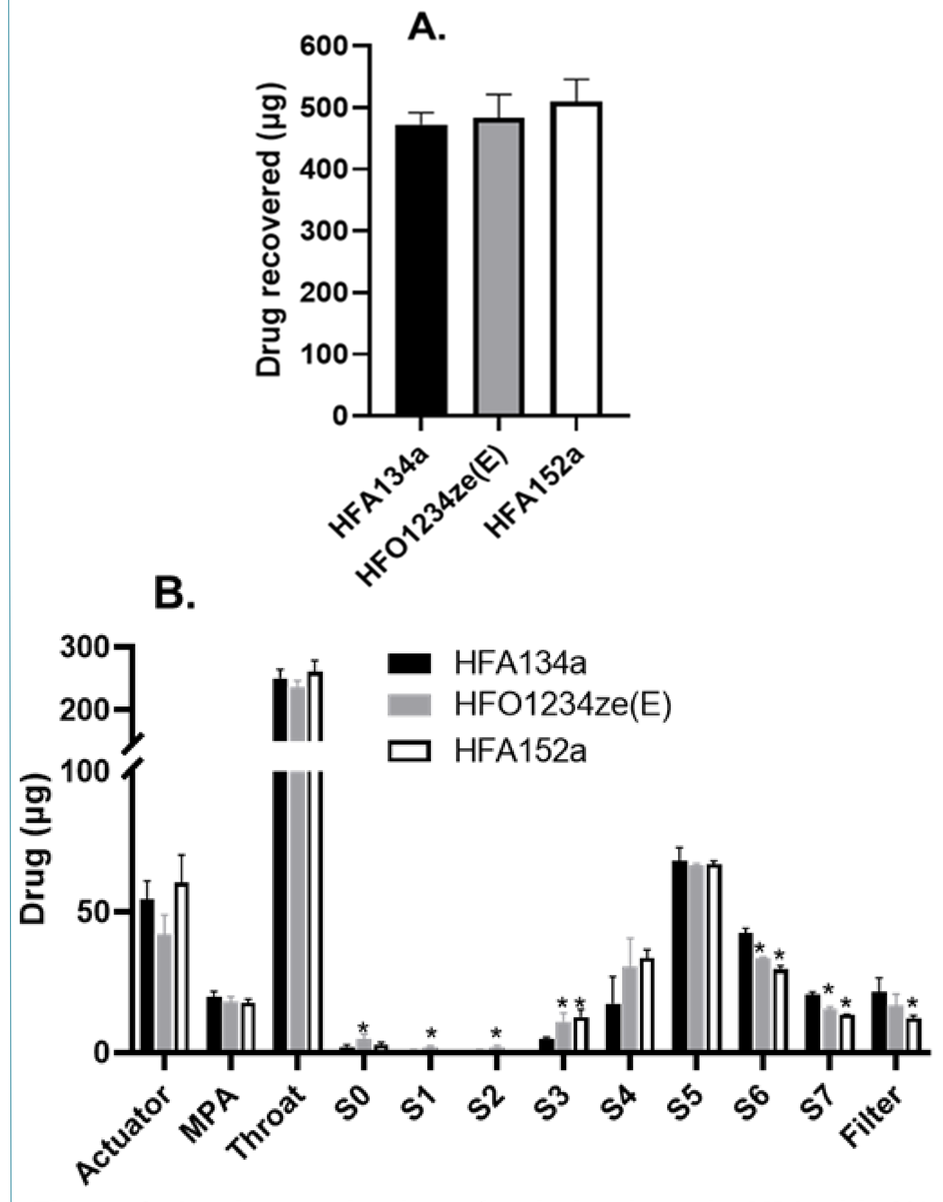


Figure 2. ***In vitro evaluation of solution-based pMDI with 8% w/w ethanol and 2 mg/mL dissolved drug after five shots. A. Delivered dose uniformity (DDU) and B. Drug deposited in the actuator, mouthpiece adaptor, and various stages in the ACI at 28.3 L/min. Results are reported as average ± SD from three independent replicates. MPA=Mouthpiece adaptor.***

Table 2. ***Summary of the key aerosol performance parameters generated from solution based corticosteroid pMDI formulations, containing 8% w/w ethanol and 2 mg/mL drug, based in different propellants (Average, n=3 ± SD).***

Aerodynamic parameters	HFA134a	HFO1234ze(E)	HFA152a
Emitted dose [µg]	450 ± 15	439 ± 5	450 ± 25
Fine Particle dose, <5 µm [µg]	177 ± 10	177 ± 14	167 ± 6
MMAD [µm]	0.8 ± 0.04	0.9 ±0.04	1.5 ± 0.05*
GSD	2.3 ± 0.3	2.6 ± 0.2	1.84 ± 0.03*

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