Dose Proportionality in a Triple Therapy Cosuspension pMDI with Multiple Strengths of an Inhaled Corticosteroid

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Abstract

Clinical comparison of combination pMDI products for the treatment of asthma and COPD is complicated because *in vitro* aerosol performance of each active in the combination product may not be equivalent to that of the individual component products. In a multi-drug combination product, dose-ranging one or more active with others at fixed doses could complicate development further due to such non-equivalence.

Spray dried porous particles generate uniform and stable cosuspensions (1) with micronized APIs, across wide dose ranges for all principal classes of respiratory therapeutics in mono, dual and triple combinations (2), with aerosol performance of each API being independent of the number or type of cosuspended APIs.

Clinical experience with a LAMA and LABA combination demonstrates that Pearl's cosuspension technology enables fixed dose combination development without co-formulation driven performance in-equivalence (3).

Addition of an ICS to the LABA/LAMA combination requires aerosol performance equivalency at much higher strengths because of the larger corticosteroid doses. In this paper, we demonstrate in vitro dose linearity and aerosol performance equivalence of a triple formulation containing mometasone furoate in the range of 100-300 µg/actuation combined with a fixed LABA/LAMA combination.

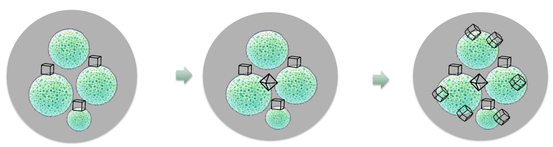
Materials and Methods

Pearl formulations are suspension pMDIs formulated with micronized actives, FF (X_{50} = 1.4 µm); at 4.8 µg/actuation), GP (X_{50} = 1.6 µm at 18 µg /actuation), and MF (X_{50} =1.6 µm at 100, 200 and 300 µg/actuation), cosuspended with spray-dried low density microparticles (i.e., porous particles) in a hydrofluoroalkane (HFA) propellant using off the shelf MDI cans and valve components.

Pearl porous particles are made by spray drying an emulsion feedstock containing phospholipid and calcium chloride in the molar ratio of 2:1. Porous particles are present in the product at a concentration of ~300 µg/actuation.

Aerodynamic particle size distribution (aPSD) is measured with a Next Generation Impactor using drug specific HPLC methods.

Mono cosuspension = Double cosuspension = Triple cosuspension

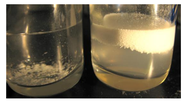


Spray-dried phospholipid/$CaCl_2$ porous particle

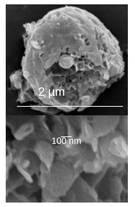
LAMA crystal LABA crystal ICS crystal

Results

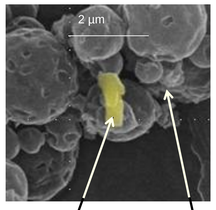
Porous particles associate with micronized drug crystals



Excipient free micronized GP (left vial) and micronized GP cosuspension with phospholipid porous particles (right vial) demonstrate formation of drug-porous particle cosuspensions



SEM Images of Phospholipid Microparticles (left top) and interior nanostructure (left bottom) and cosuspension upon actuation (right)

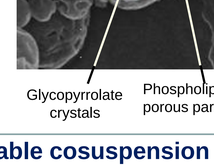


Porous particles form a stable cosuspension

pMDI with Micronized Active

0 seconds → 5 seconds

Cosuspension pMDI



0 seconds → 15 seconds → 30 seconds

Demonstrating dose proportionality in the high dose range; ideal to meet ICS dose requirements

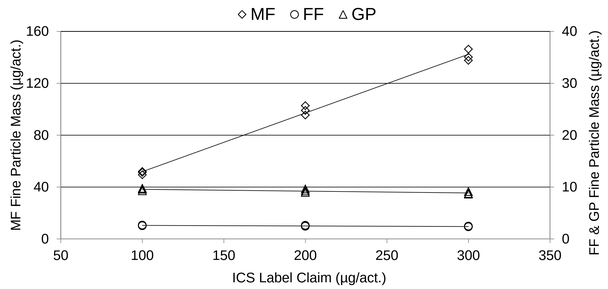


Figure 1. Fine particle mass (FPM) derived from the cascade impaction analysis of all active components in the triple combination cosuspension pMDIs at three MF strengths of (100, 200 and 300 µg/actuation) and fixed dose of 4.8 and 18 µg/actuation for FF and GP, respectively (n=3, all individual values shown)

Table 1. Physicochemical properties of compounds in cosuspension

Substance	Structure	HFA 134a Solubility (25 °C) (µg/g)	Dose (µg/act)	Density g/cm³
HFA 134a		NA	NA	1.296 ,1.226, 1.148 (0, 20, 40°C)
DSPC/$CaCl_2$		0.025	NA	1.066
Mometasone Furoate		3.2	50	1.383
Glycopyrrolate		0.16	36	1.369
Formoterol Fumarate Dihydrate		0.015	5	1.303

Cosuspension pMDI produces equivlaent aPSD of each of the components in the triple combination at the various strengths in the range of 100-300 µg/act

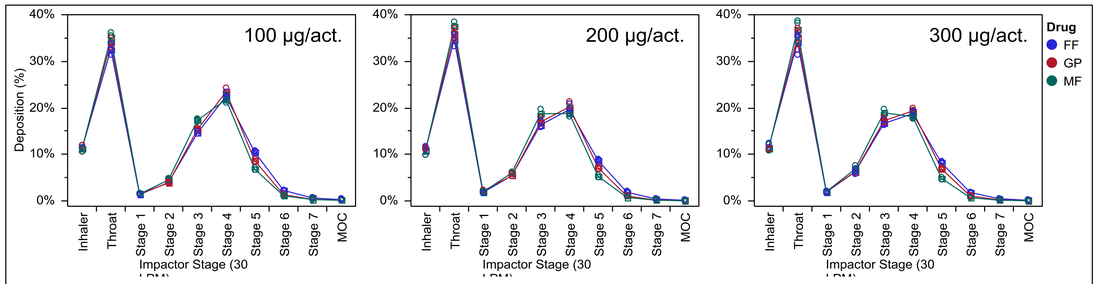


Figure 2. Aerodynamic PSD of MF, GP, and FF in Pearl Cosuspension pMDIs is equivalent within each strength of the triple cosuspension

Cosuspension pMDI enables consistent aPSD and FPM proportionality for ICS in a triple combination at strengths in the range of 100-300 µg/act

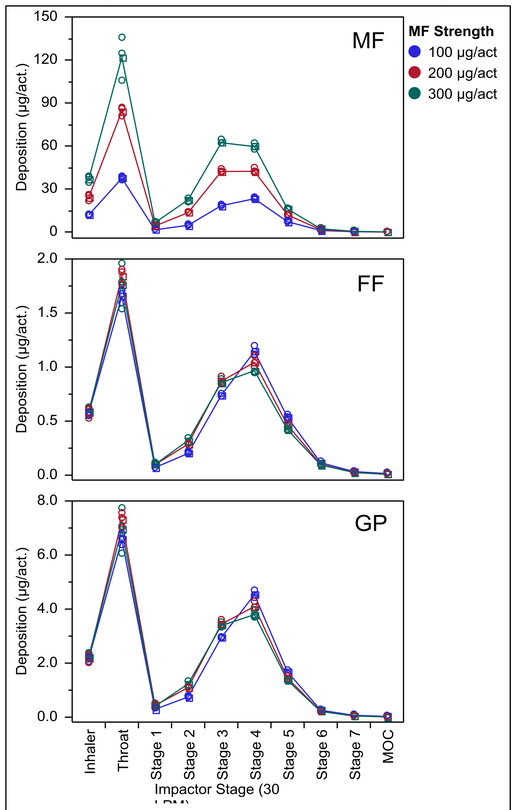


Figure 3:. Aerodynamic PSD of MF demonstrating dose linearity across 100-300 µg/act and showing fixed dose GP and FF similarity in the triple combination cosuspension pMDI

Conclusions

The Pearl cosuspension pMDI platform enables dose ordered delivery of high dose ICS in a triple combination product.

The triple cosuspension pMDI has demonstrated *in vitro* dose proportionality and comparable cascade impaction aerosol performance of the fixed dose combination across a three-fold range of corticosteroid doses, without the need to change either the CCS or formulation, while keeping the LAMA and LABA doses fixed.

Straightforward formulation technology, using Pearl porous particles and micronized drugs, is expected to enable rapid clinical development and regulatory review of a triple combination product from concept to safety and efficacy studies.

References

1. Vehring, R.; Lechuga-Ballesteros, D.,;Joshi, V.; Noga, B.; Dwivedi, S. K.. Langmuir ***2012, 28, 15015 -23***.
2. 2. Joshi, V.; Lechuga-Ballesteros, D.; Flynn, B.; Vehring, R.; Schultz, R. D.; Noga, B.; Cummings, H.; Speck, J. H.; Dwivedi, S. K., Development of mono, dual and triple combination pMDIs without co-formulation effect *Respiratory Drug Delivery Europe 2011* ***2011, 2, 383-6.***
3. Reisner, C.; Gotfried, M.; Denenberg, M. B.; Fernandez, C.; St Rose, E.; Fortner, P.; Kollar, C.; Orevillo, C. J., Low Doses of Pearl Therapeutics' LAMA/LABA Combination MDI (GFF MDI, PT003) Provide Superior Bronchodilation Compared to Components and to Open-Label Spiriva Handihaler in a Randomized, Double-Blind, Placebo-Controlled Phase IIb Study in Patients with COPD. *American Journal of Respiratory and Critical Care Medicine* ***2013, 187, A2433.***

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