Co-suspension metered dose inhaler of a combination of glycopyrrolate and formoterol fumarate with no co-formulation effect even at sub-microgram doses

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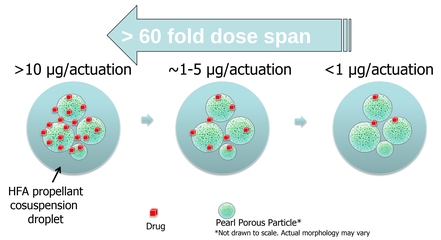
Introduction

Proper assessment of safety and efficacy of highly potent respiratory therapies necessitates clinical studies with very low doses. We report dose proportional and stable cosuspension pMDIs over a 300 ng to 18 µg range per actuation for glycopyrrolate (GP) and 480 ng to 9.6 µg range per actuation for formoterol fumarate (FF).
A challenge when formulating suspension pMDIs at very low doses is the potential instability resulting from changes due to temperature fluctuations during normal product handling. We report stable GP pMDIs at nanogram doses, even when subjected to several weeks of thermal cycling.

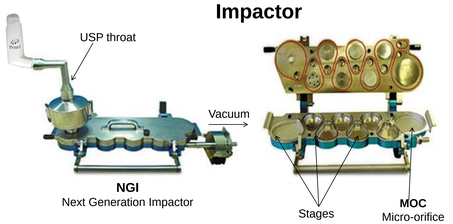


Consistent aerosol performance across doses

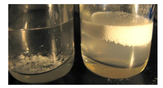
Materials and Methods

Cosuspension pMDI formulations were prepared by suspending micronized crystals of each drug in hydrofluoroalkane (HFA) propellant with spray-dried distearoyl phosphatidylcholine (DSPC) porous microparticles[1]. *In vitro* drug delivery characteristics were assessed by aerodynamic particle size distribution (aPSD) measurement using the Next Generation Impactor (NGI), and delivered dose uniformity through canister life (DDU), at a flow rate of 30 L/min. Fine particle mass (FPM) was calculated as the sum of stages 3 to Filter of the NGI. To assess impact of thermal cycling, MDIs were stored for 6 weeks in a chamber programmed to cycle from -5°C to 40°C, four times daily.

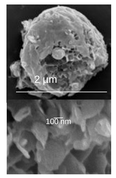
Determination of Aerosol Particle Size Distribution using a Pharmaceutical Cascade Impactor



Phospholipid microparticles associate with micronized drug crystals

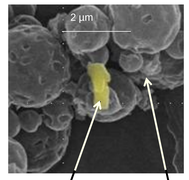


Excipient free micronized GP (left vial) and micronized GP cosuspension with phospholipid microparticles (right vial) .
Formation of drug - porous particle cosuspensions in right vial



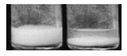
SEM Images of Phospholipid Microparticles (left top) and Interior Nanostructure (left bottom)

SEM Images of Cosuspension upon actuation (right)



Phospholipid microparticles form a stable cosuspension

pMDI with Micronized Active



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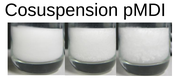
Cosuspension pMDI



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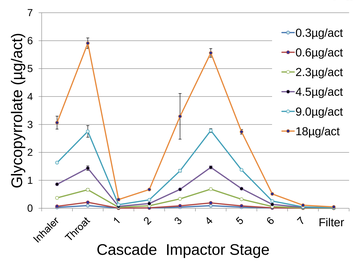
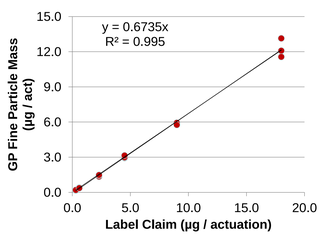
Results

Aerodynamic particle size distributions of Glycopyrrolate cosuspension pMDI (PT001) at strengths of 0.3, 0.6, 2.3, 4.5, 9.0, and 18.0 µg/actuation

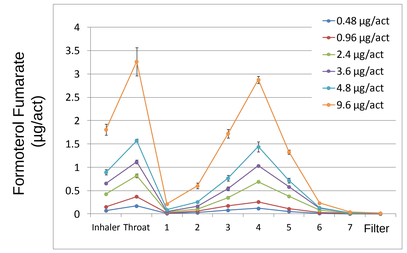


Glycopyrrolate cosuspension pMDIs: Dose independent aPSD with linear FPM (r^2 = 0.995) over a 60-fold dose range of 0.3-18 µg/actuation

Strength (µg/act)	FPM (µg)	MMAD (µm)	FPF (%)
0.3	0.2	3.0	63%
0.6	0.4	3.0	62%
2.3	1.4	3.1	64%
4.5	3.0	3.0	64%
9.0	5.8	3.0	65%
18.0	12.3	3.2	64%

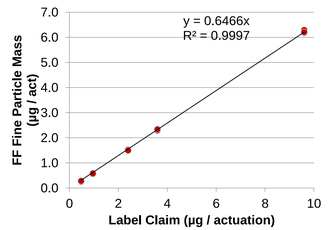


Aerodynamic particle size distributions of Formoterol Fumarate cosuspension pMDI (PT005) at strengths of 0.48, 0.96, 2.4, 3.6, 4.8 and 9.6 µg/actuation

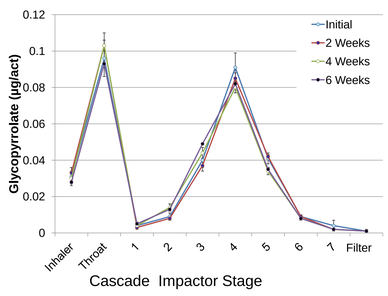


Formoterol fumarate cosuspension pMDIs: Dose independent aPSD with linear FPM (r^2 = 0.9997) over a 20-fold dose range of 0.5 - 10 µg/actuation

Strength (µg/act)	FPM (µg)	MMAD (µm)	FPF (%)
0.48	0.5	3.4	57%
0.96	1.0	3.5	56%
2,4	1.5	3.1	61%
3.6	2.3	3.0	64%
4.8	3.1	3.2	62%
9.6	6.2	3.3	60%



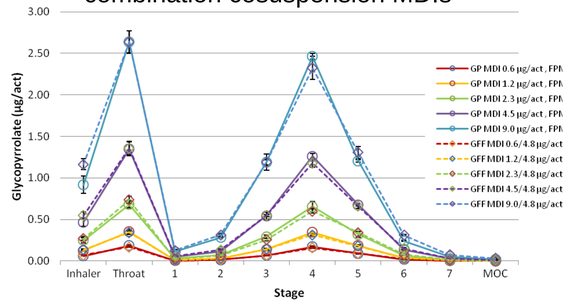
Nanogram strength (300 ng) Glycopyrrolate cosuspension MDI remains stable under thermal cycling between -5 to 40°C for six weeks



Time	FPM (µg)	MMAD (µm)	FPF (%)
Initial	0.2	3.0	63%
2 weeks	0.2	3.0	61%
4 weeks	0.2	3.2	58%
6 weeks	0.2	3.3	62%

No Co-formulation Effect

Equivalent API aerodynamic particle size distributions emitted from single or combination cosuspension MDIs



Aerodynamic particle size distributions of Glycopyrrolate cosuspension pMDI emitted from a single and a dual, with FF, cosuspension (PT001 and PT003) at indicated strengths

Conclusions

Pearl cosuspension technology is capable of generating stable pMDIs containing highly potent long acting muscarinic antagonist, GP, and long acting β2 agonist, FF, with the following characteristics:

- consistent *in vitro* aerosol performance,
- nearly ideal linear dose proportionality of fine particle mass, and
- excellent stability across a wide range of dose strengths, including nanogram doses.

This allows an opportunity to study the therapeutic response over an unprecedented range of doses for these drugs, potentially enabling the identification of non-effective, minimally effective and optimal doses, without formulation variability and manufacturability being limitations in such an effort.

Pearl Therapeutics' novel cosuspension pMDI formulation has enabled the conduct of a comprehensive Phase IIb LAMA/LABA dose ranging program, including assessments in the nanogram range.

References

1) C.J. Orevillo, C. Fogarty, L. Dunn, J. Parrino, E. St. Rose, C. Fernandez, J. Covino, T. Fischer, S. Strom, G. Vasilinin, J.F. Marier, C. Reisner. Pearl Therapeutics' Formoterol Fumarate MDI (FF-MDI, PT005) Demonstrates Pharmacokinetic Bioequivalence to Foradil® Aerolizer® In a Randomized, Double-Blind, Single Dose, Six-Treatment, Placebo-Controlled, Crossover Phase 2b Study In Patients With Moderate To Severe Chronic Obstructive Pulmonary Disease. Am. J. Respir. Crit. Care Med. 2012; 185: A2929