

A New Formulation Platform for Metered Dose Inhaler Combination Products: Cosuspensions of Engineered Phospholipid Microparticles with Micronized Actives

David Lechuga-Ballesteros, Reinhard Vehring, Vidya Joshi, Brian Noga, Harris Cummings, Robert Schultz, Jason H. Speck, and Sarvajna K. Dwivedi
Redwood City, California, USA



Abstract

Combination products of respiratory therapeutics have shown clinical benefits in the treatment of asthma and chronic obstructive pulmonary disease (COPD). Their development demands comparative *in vitro* and clinical testing versus the corresponding monotherapy products, across a range of doses. Clinical comparison is complicated because *in vitro* aerosol performance of each API in the combination product may not be comparable to that obtained from either the single component products or to that of the combination product in which the dose of one or more of the components is varied. A new formulation approach using spray dried phospholipid microparticles generates uniform and stable suspensions in hydrofluoroalkane propellants. The phospholipid microparticles act as a cosuspension agent for micronized APIs, enabling the preparation of cosuspension pressurized metered dose inhalers (pMDIs) with unique features, such as robust aerosol performance independent of particle size, density, propellant solubility, dose or number of actives in the cosuspension. The *in vitro* characterization of triple combination cosuspension pMDIs, containing a long acting muscarinic antagonist (LAMA), a long acting beta agonist (LABA) and an inhaled corticosteroid (ICS), and their corresponding double and mono pMDIs is presented, demonstrating remarkable aerosol performance and long term chemical and physical stability. Clinical experience with a LAMA and LABA combination demonstrates that Pearl's cosuspension technology has the potential of becoming a versatile and universal MDI product platform (1-3).

Materials and Methods

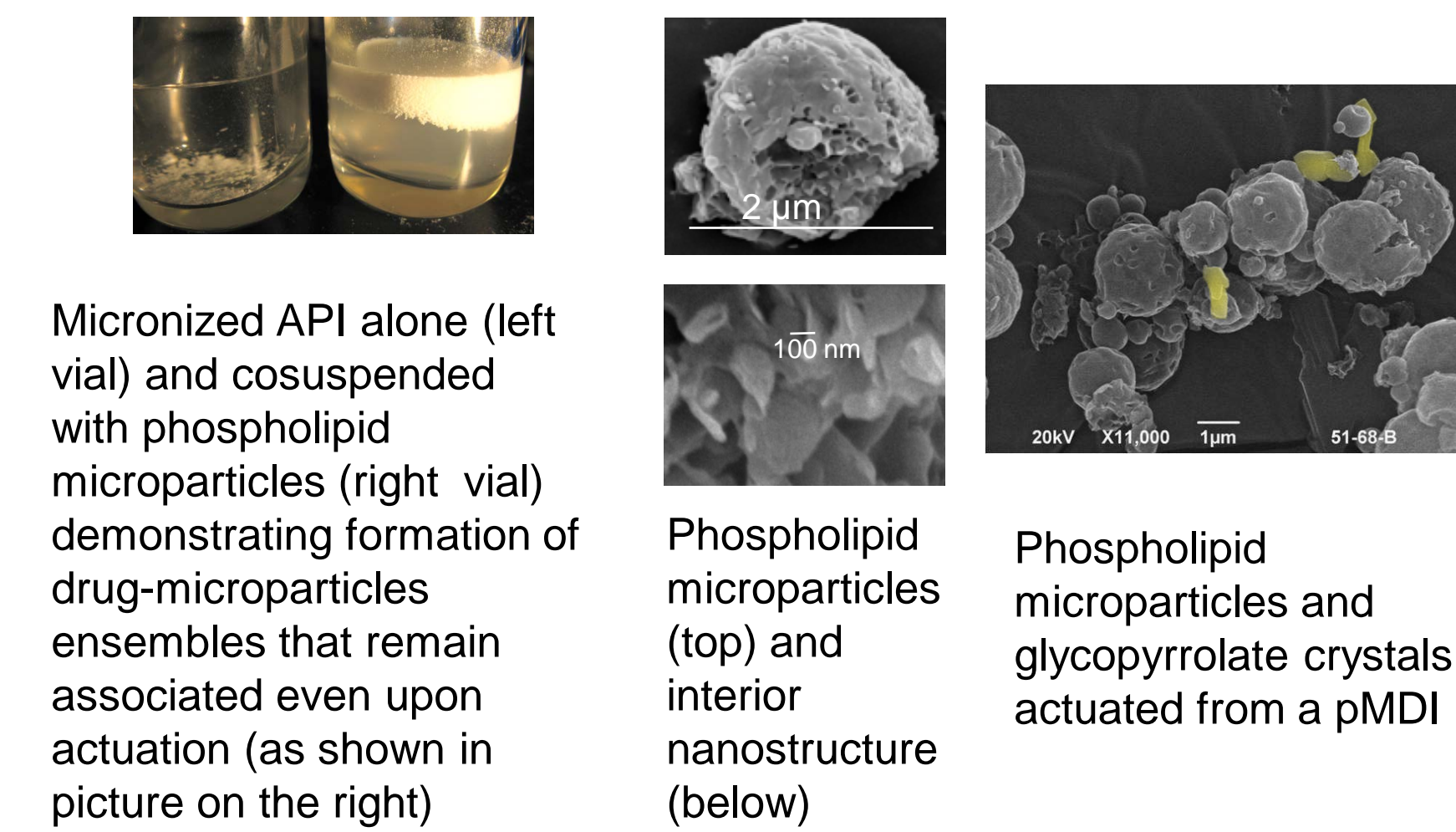
Cosuspension pMDIs were formulated with micronized actives such as formoterol fumarate (FF) (at ~5 µg/actuation), glycopyrrolate (GP) (at ~36 µg / actuation), and mometasone furoate (MF) (at ~50 µg/actuation), and spray-dried low density microparticles in a hydrofluoroalkane (HFA) propellant. These microparticles contain phospholipid and calcium chloride in a molar ratio of 2:1 and are present in the product at a concentration of ~300 µg/actuation. Aerodynamic particle size distribution (aPSD) profiles were obtained using the Next Generation Impactor (NGI). Drug content and degradation products were measured using reverse-phase HPLC. Stability was assessed by storing the triple combination MDIs at 40°C/75%RH, foil overwrapped with desiccant for 6 months, and testing the product for physical (particle morphology by scanning electron microscopy and aPSD) and chemical attributes (drug content and degradation).

Table 1. Physicochemical properties of compounds in cosuspension

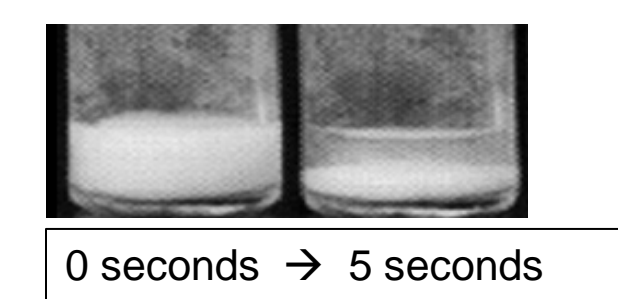
Substance	Structure	HFA 134a Solubility (25 °C) (µg/g)	Dose (µg/actuation)	Density (g/mL)
HFA 134a		NA	NA	1.296, 1.226, 1.148 (0, 20, 40°C)
DSPC		0.025	NA	1.066
Mometasone Furoate		3.2	50-100	1.383
Glycopyrrolate		0.16	4-18	1.369
Formoterol Fumarate Dihydrate		0.015	4.5	1.303

Results

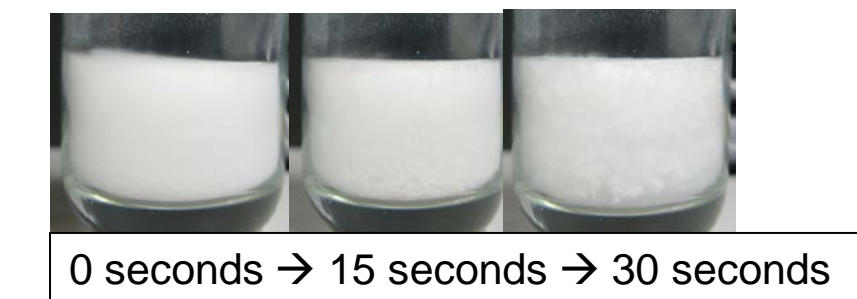
Phospholipid microparticles associate with API microcrystals to form a stable cosuspension



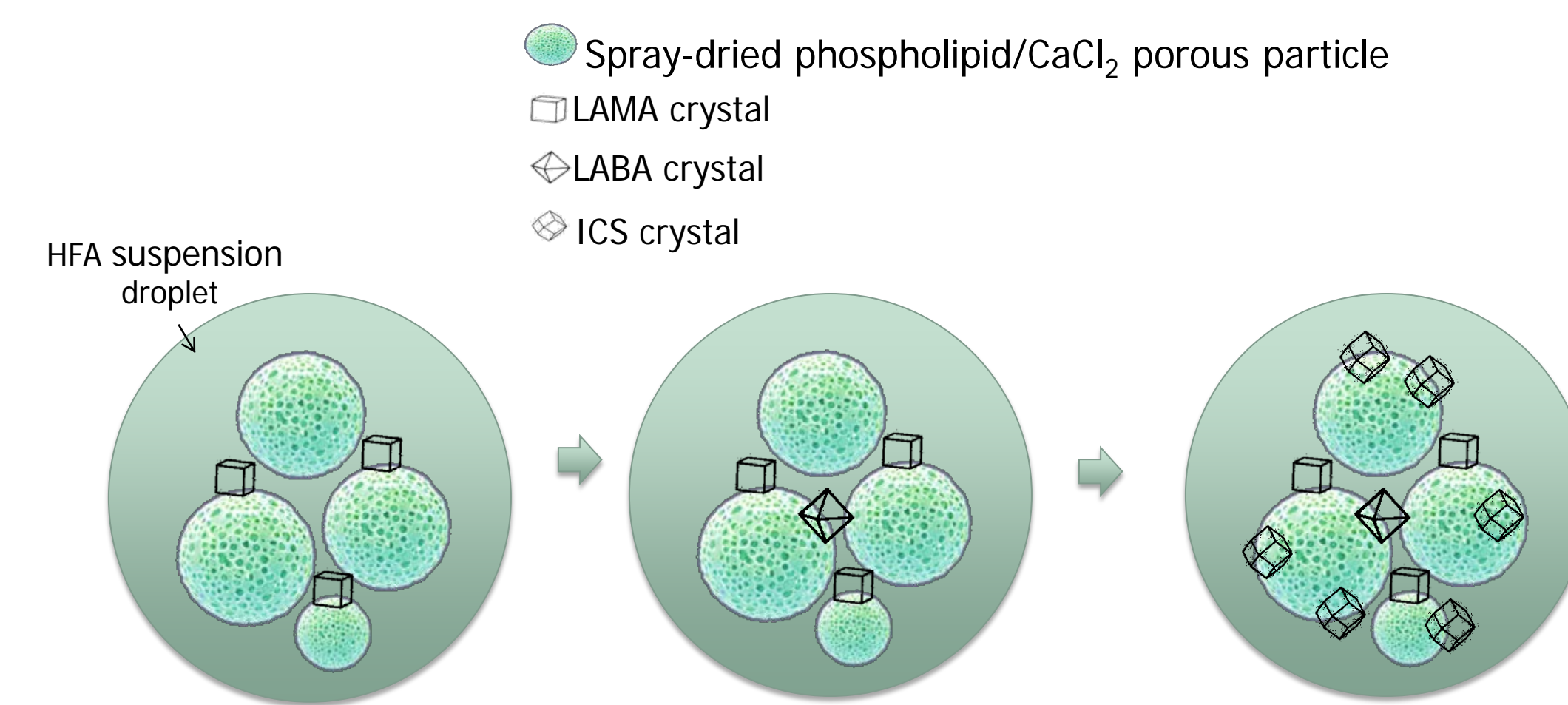
Suspension pMDI⁴



Cosuspension pMDI



Cosuspension enables seamless transition from mono to dual to triple combinations



Mono cosuspension = Dual cosuspension = Triple cosuspension

Equivalent performance for all actives in combination regardless of dose or physicochemical properties

Table 2. Fine particle fraction (FPF*) and median mass aerodynamic diameter (MMAD) of the individual components of an ICS/LAMA/LABA triple, corresponding double combinations and single component inhalers.

Actives in Combination	FPF (%)			MMAD (µm)		
	M	G	F	M	G	F
MGF	59	59	63	3.5	3.5	3.0
MG	56	56		3.7	3.8	
MF	57		60	3.5		3.1
GF		60	62		3.4	2.8
M	54			3.6		
G		57			3.7	
F			61			3.0
Average	57	58	62	3.6	3.6	3.0
SE (%)	3	3	2	2.3	4.5	3.7
Range	54-59	56-60	60-63	3.5-3.7	3.4-3.8	2.8-3.1

M: Mometasone Furoate (ICS); G: Glycopyrrolate (LAMA); F: Formoterol Fumarate (LABA)
 *FPF is sum of NGI stages 3 through filter divided by ex-actuator dose

Results

Cosuspension pMDI Eliminates Cosuspension Effects: Aerosol performance is independent of other components in combination

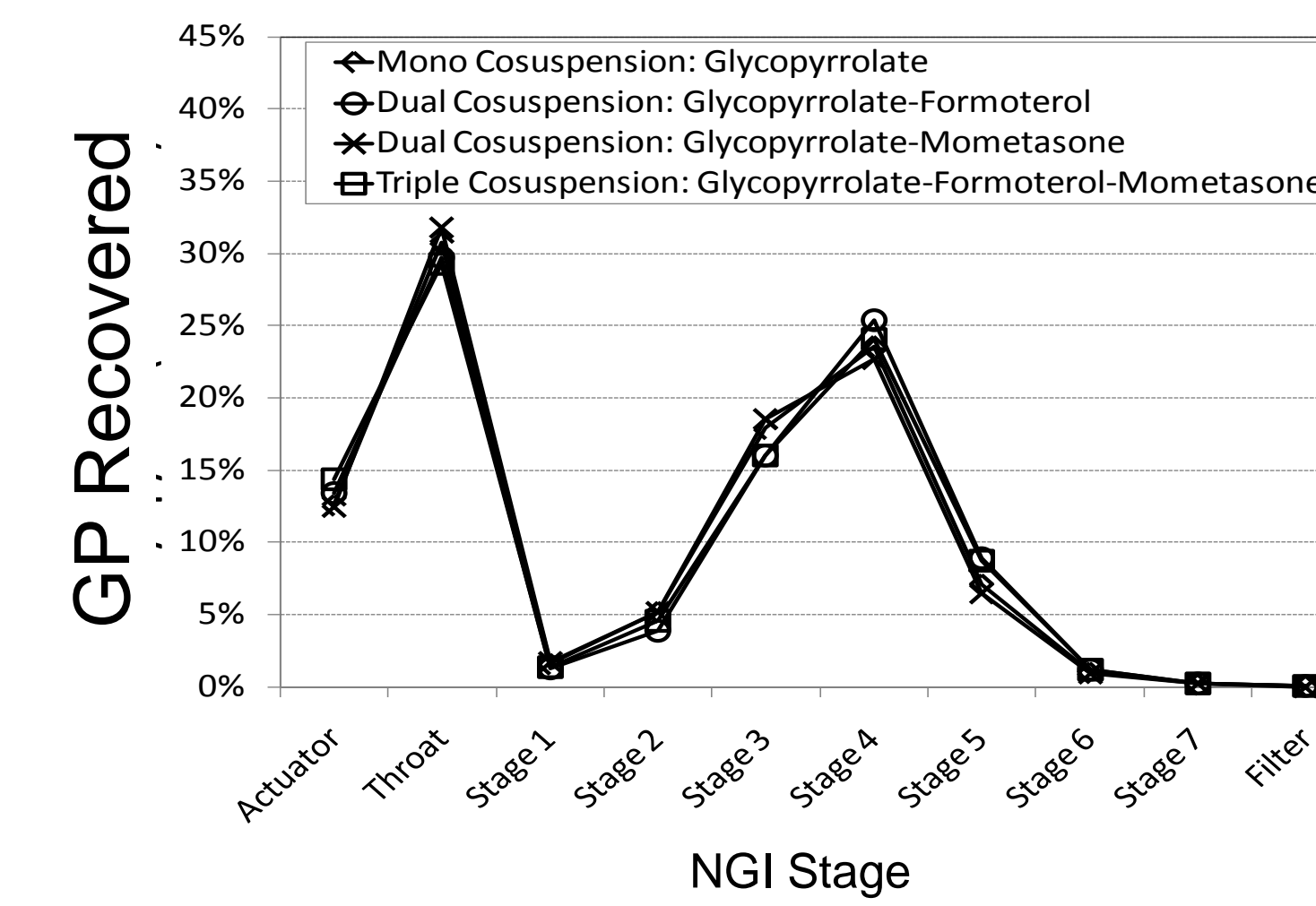


Figure 2. Aerodynamic size distributions of the glycopyrrolate component of (1) A monotherapy Cosuspension with a delivered dose of 36 µg glycopyrrolate (2) Dual cosuspension with a delivered dose of 36 µg glycopyrrolate and 5 µg formoterol fumarate (3) Dual cosuspension with a delivered dose of 36 µg glycopyrrolate and 50 µg mometasone furoate and (4) Triple cosuspension with a delivered dose of 36 µg glycopyrrolate, 5 µg formoterol fumarate and 50 µg mometasone furoate.

Table 3. Particle size distribution by laser diffraction of micronized drug

Micronized API/Size Distribution:	X ₁₀ (µm)	X ₅₀ (µm)	X ₉₀ (µm)	Span
Mometasone Furoate (MF)	0.4	1.1	2.8	2.2
Glycopyrrolate (GP)	0.5	1.3	3.0	1.8
Formoterol Fumarate Dihydrate (FF)	0.6	1.9	4.1	1.8

Cosuspension pMDI Eliminates Micronized API PSD Effects:

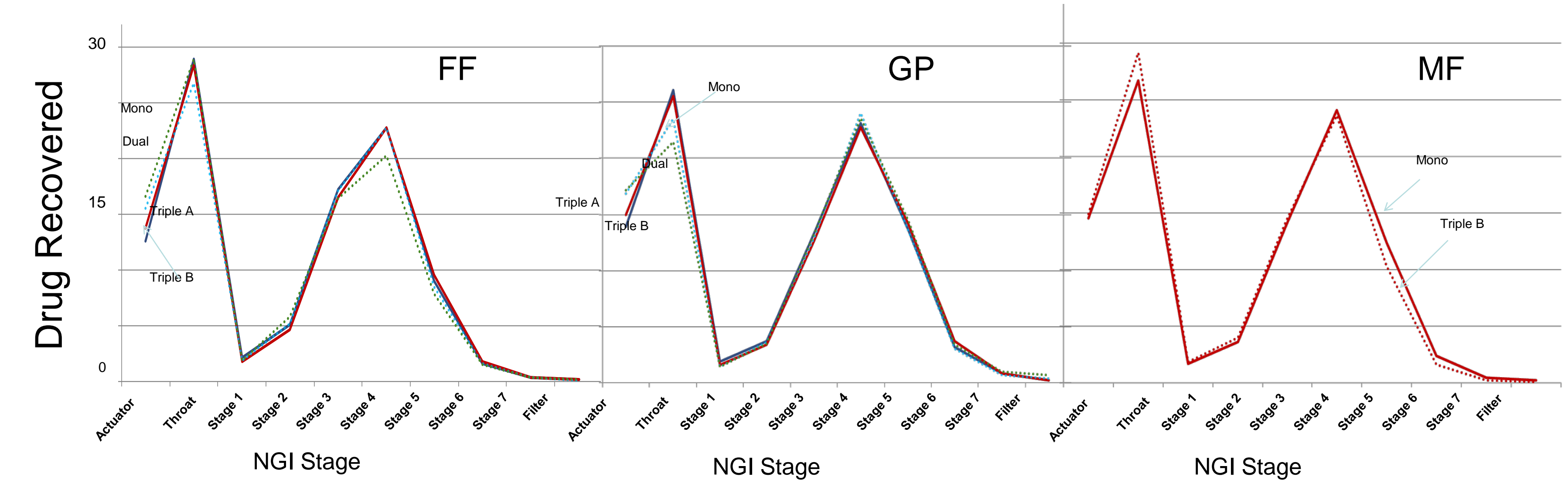


Figure 3. The PPF of any of the drugs in the cosuspension is equivalent regardless of the number of drugs in the formulation and tolerates variability in particle size distribution of the micronized drug shown in Table 3.

Cosuspension pMDI enables room temperature shelf life

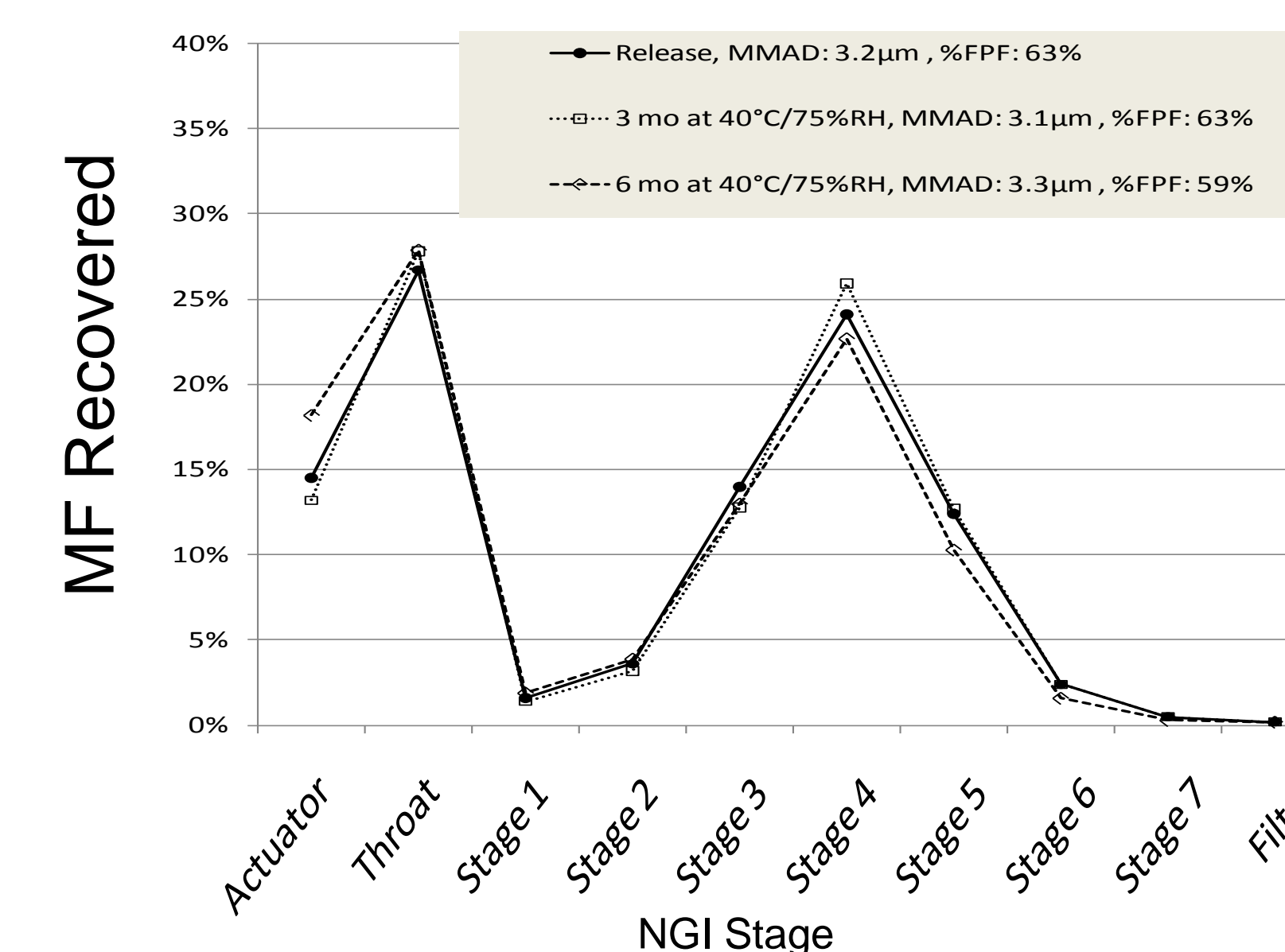


Figure 4: Cosuspension combination pMDI provides reproducible aerosol performance even after storage under stress conditions. Aerodynamic particle size distribution of mometasone furoate in a triple combination cosuspension pMDI after 0, 3, and 6 months storage at 40°C/75%RH.

Conclusions

The use of phospholipid microparticles allows the cosuspension pMDI to be readily customized for product performance and stability, without a need for further customizing the MDI device components.

- Physical stability for partially soluble API in HFA
- No coformulation effect (mono = dual = triple)
- Equivalent performance independent of dose and particle size of micronized drugs
- Room temperature shelf life

Cosuspension pMDI *in vitro* and clinical performance meet the requirements to become a versatile and universal platform for respiratory combination therapy.

References

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