# Development of Mono, Dual, and Triple Combination pMDIs without Coformulation Effect

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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 may not be equivalent to that of the individual components or from combinations in which the dose of one or more of the components is varied.

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

Extensive *in vitro* characterization of Pearl's triple combination MDIs, containing a LAMA, a LABA and an ICS, and their corresponding double and mono MDIs, demonstrate remarkable chemical stability, physical stability and aerosol performance as good as or better than the most efficient combination pMDIs currently available.

Clinical experience with a LAMA and LABA combination demonstrates that Pearl's cosuspension technology has the potential of becoming the next generation combination pMDI product platform (1-3).

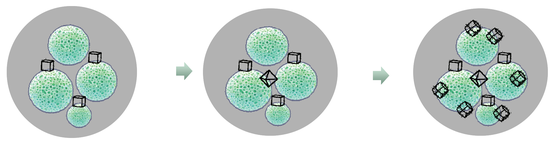
## Materials and Methods

Pearl formulations are suspension pMDIs formulated with micronized actives such as FF (at ~5 µg/actuation), GP (at ~36 µg / actuation), and MF (at ~50 µg/actuation) cosuspended with spray-dried low density microparticles in a hydrofluoroalkane (HFA) propellant.

These microparticles contain phospholipid and calcium chloride in the ratio of 2:1 and are present in the product at a concentration of ~300 µg/actuation.

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 SEM and aPSD using NGI) and chemical attributes (drug content and degradation).

**Mono cosuspension = Double cosuspension = Triple cosuspension**

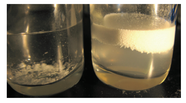


Spray-dried phospholipid/$CaCl_2$ porous particle
LAMA crystal LABA crystal ICS crystal

Presented on May 8th, at RDD 2011, Berlin, Germany

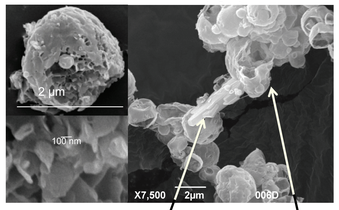
## Results

### Phospholipid microparticles associate with API microcrystals to form a stable cosuspension



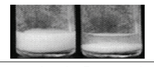
Micronized GP alone (left vial) and micronized GP cosuspension with phospholipid microparticles (right vial) demonstrating formation of drug-microparticle ensembles that remain associated even upon actuation (as shown on picture on the right)

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




Glycopyrrolate crystals
Phospholipid Microparticles

pMDI with Micronized Active[4]



0 seconds → 5 seconds

Cosuspension pMDI

0 seconds → 15 seconds → 30 seconds

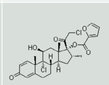
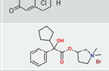
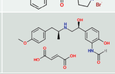
### Equivalent performance for all actives in combination regardless of dose or physicochemical properties

**Table 1. Fine particle fraction (FPF) and MMADs of the individual components of an ICS/LAMA/LABA triple combination, corresponding double combinations and single component pMDIs**

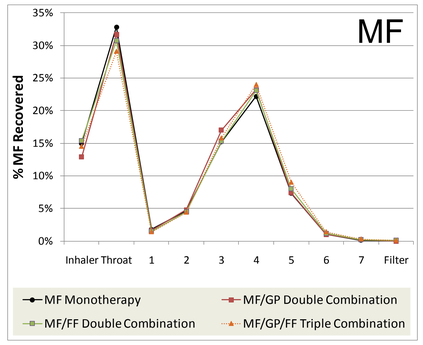
| Actives in Combination | FPF (%) | | | MMAD (µm) | | |
|---|---|---|---|---|---|---|
| | MF | GP | FF | MF | GP | FF |
| MF/GP/FF | 59 | 59 | 63 | 3.5 | 3.5 | 3.0 |
| MF/GP | 56 | 56 | | 3.7 | 3.8 | |
| MF/FF | 57 | | 60 | 3.5 | | 3.1 |
| GP/FF | | 60 | 62 | | 3.4 | 2.8 |
| MF | 54 | | | 3.6 | | |
| GP | | 57 | | | 3.7 | |
| FF | | | 61 | | | 3.0 |
| Average | 57 | 58 | 62 | 3.6 | 3.6 | 3.0 |
| RSD (%) | 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 |

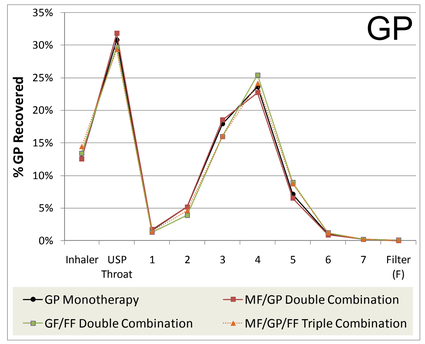
Mometasone Furoate (ICS); Glycopyrrolate (LAMA); Formoterol Fumarate (LABA):
FPF: Fine particle mass from stages 3 to filter of NGI divided by NGI delivered dose; MMAD = Mass Median Aerodynamic Diameter

**Table 2. 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 Eliminates Coformulation Effect: Aerosol performance is independent of other components in combination



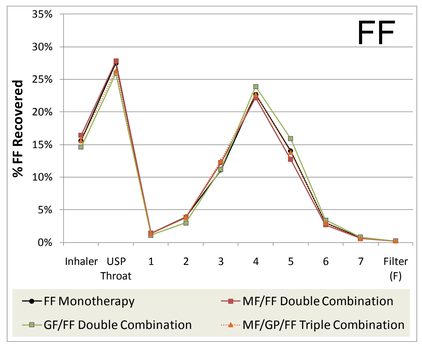




Figure 1. Aerodynamic PSD of MF, GP, and FF in Pearl Cosuspension pMDIs is equivalent regardless of the number and type of drugs in the formulation and tolerates variability in particle size distribution of the micronized drug (shown in Table 3.)

### Cosuspension pMDI enables long term physical stability of partially soluble actives

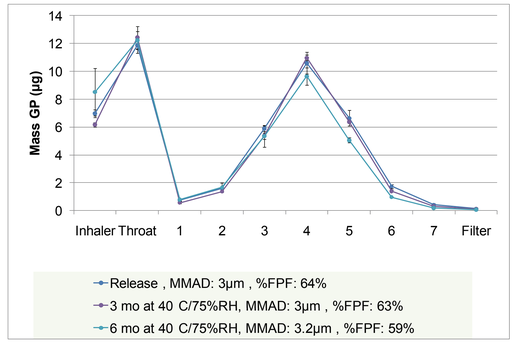



Figure 2:. Aerodynamic PSD of GP in a triple combination cosuspension pMDI shows stable aerosol performance after 0, 3, and 6 months storage at 40°C/75%RH.

### Cosuspension pMDI Eliminates Micronized API PSD Effects

**Table 3. Micronized drug PSD by laser diffraction**

| Micronized Drug | $x_{10}$ (µm) | $x_{50}$ (µm) | $x_{90}$ (µm) | Span |
|---|---|---|---|---|
| MF | 0.4 | 1.1 | 2.8 | 2.2 |
| GP | 0.5 | 1.3 | 3.0 | 1.8 |
| FF | 0.6 | 1.9 | 4.1 | 1.8 |

## Conclusions

The Pearl cosuspension pMDI platform enables :

- Seamless transition from mono to dual to triple combinations
- Delivery of microcrystalline API with the following features not previously available :
  - -No coformulation effect (mono = double = triple)
  - -Physical stability for partially soluble APIs in HFA
  - -Dose, size, solubility, density independent performance

*In vitro* and clinical performance of Pearl cosuspension pMDIs meet the requirements to become the next generation platform for drug delivery to the lungs in major disease areas.

## References

1. Orevillo CJ, St Rose E, Fischer T, Alameda P, Reisner C. A novel glycopyrrolate metered dose inhaler formulation demonstrates superior bronchodilator efficacy relative to placebo and comparable efficacy and safety to Spiriva® Handihaler® in patient with COPD *Am. J. Respir. Crit. Care Med*., 2010; 181: A4450.
2. Marjason J, Orevillo CJ, St Rose E, Ferguson GT, Vehring R, Joshi V, Dwivedi S, Reisner C. Assessment of safety and pharmacokinetic profile of a novel fixed combination of glycopyrrolate and formoterol HFA pMDI in healthy volnteers *Am. J. Respir. Crit. Care Med*., 2010; 181: A4455.
3. Quinn D, Ferguson GT., Orevillo CJ, Luckey A, St Rose A, Fischer T, Granko H, Reisner C. A novel formoterol fumarate metered dose inhaler formulation demonstrates comparable bronchodilator efficacy relative to Foradil® Aerolizer® and favorable safety outcomes in patients with COPD. *Am. J. Respir. Crit. Care Med*., 2010; 181: A4458.
4. . Dellamary, LA, Tarara, TE, Smith, DJ, Woelk, CH, Adractas, A, Costello, ML, Gill, H, Weers, J G. Hollow porous particles in metered dose inhalers, *Pharm. Res*., 2000; 17: 168-174.