In-silico assessment of airway deposition using functional respiratory imaging for mono, dual, and triple combination Co-Suspension™ metered dose inhaler formulations

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Introduction

- Co-Suspension™ Technology for metered dose inhalers (MDIs) is a promising new platform with the potential to deliver single or multiple active agent particles consistently and uniformly throughout the lung using phospholipid porous particles as suspension and aerosolizing agents.
- Adequate deposition of medicinal aerosols to the airways is important for achieving the intended therapeutic benefits in patients with chronic obstructive pulmonary disease (COPD).[1]
- Inconsistent drug delivery, either due to formulation issues or improper device use, may lead to inadequate drug delivery to the airways.
- Robust formulations containing single or multiple active agents, with similar *in-vitro* performance for each active agent within and across formulations, can be made using the Co-Suspension™ Technology.[2]
- In this computer simulation (*in-silico*) study, the deposition of different active agents from their Co-Suspension™ Technology formulations, and the impact of extrathoracic airway geometries, inhalation profiles, and actuation conditions on lung deposition, were assessed using functional respiratory imaging (FRI).

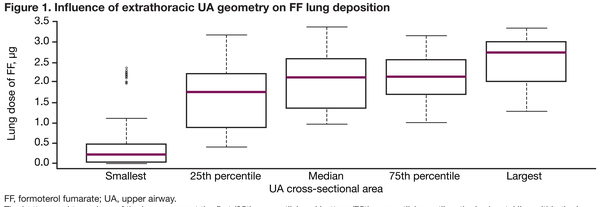
Methods

- Computerized tomography scans of 20 patients with COPD with a range of disease severity were selected.
  - COPD severity was based on the forced expiratory volume in 1 second (FEV_1), and included mild (n = 5, FEV_1 = 89.8±6.8% predicted), moderate (n = 5, FEV_1 = 59.9±11.6% predicted), severe (n = 5, FEV_1 = 33.3±6.7% predicted), and very severe (n = 5, FEV_1 = 27.5±9.5% predicted) COPD patients.
- Using the FRI workflow, three-dimensional (3D) computer models of the intrathoracic airways, lungs, and lobes were extracted. Five 3D models of extrathoracic upper airways were selected based on their minimal cross-sectional area (smallest, 25th percentile, median, 75th percentile, largest) and the geometry of the MDI was added to these models.
  - Every extrathoracic geometry was combined with one intrathoracic geometry of every disease severity.
- FRI was used to simulate the lung deposition of different formulations made by Co-Suspension™ Technology, using *in-silico* computational flow simulations, incorporating several drug- (measured by next-generation impactor) and device-specific parameters:
  - Delivered dose (µg)
  - Fine particle fraction (% of delivered dose)
  - Mass mean aerodynamic diameter (µm)
  - Geometric standard deviation
  - Plume velocity
  - Plume angle
- The above-mentioned drug delivery attributes of glycopyrrolate (GP) or formoterol fumarate (FF) monocomponents, GP and FF dual combination (GFF), and two strengths of budesonide/GP/FF triple combination (BGF) Co-Suspension™ Technology MDI formulations were used.
- The relative lobar expansion, as obtained from the subject-specific inspiratory and expiratory scans, were used as boundary conditions at the terminal airways. Sinusoidal inhalation maneuvers with flow rates of 15, 30, 60, 90, and 120 L/min were simulated. Aerosol injection was performed at two different timepoints: at the start of inhalation and when the flow rate was maximal.
- The influence of the different parameters on lung deposition was assessed using linear mixed-effect models.
- Equivalence of the various Co-Suspension™ Technology formulations was assessed using two one-sided tests.

Results

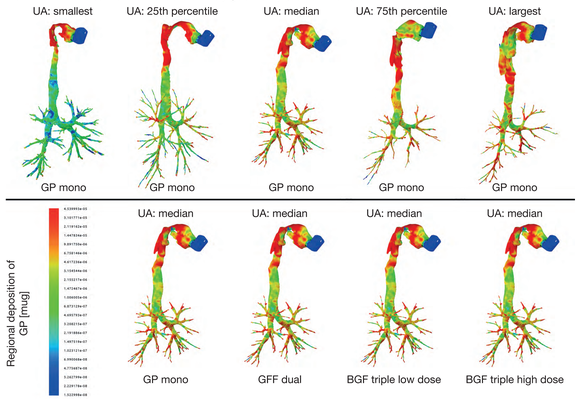
- Extrathoracic upper airway geometry has a large influence on deposition (Figures 1 and 2). Larger cross-sectional areas result in higher lung doses.
- For a given flow rate and disease severity, consistent lung deposition was obtained across mono, dual, and triple Co-Suspension™ Technology formulations (Table 1).
- The total lung deposition did not significantly change across the multiple formulation types (Figures 2 and 3).
- The total lung dose of both GP (Figure 2) and FF (Figure 3) was equivalent when delivered in mono, dual, and triple combinations.
- The influence of BGF MDI dose on the lung dose of budesonide is shown in Figure 4.

Figure 1. Influence of extrathoracic UA geometry on FF lung deposition



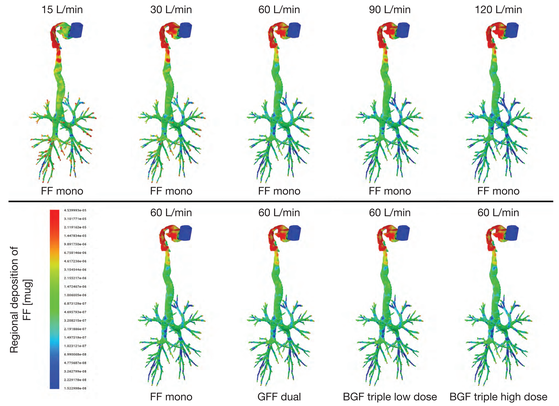
FF, formoterol fumarate; UA, upper airway.
The bottom and top edges of the box represent the first (25th percentile) and bottom (75th percentile) quartiles; the horizontal line within the box represents the median. The vertical lines show the minimum and maximum values, and circles represent extreme values 1.5 times above/below the interquartile range.

Figure 2. Influence of extrathoracic UA geometry on the regional deposition of GP in five patients with moderate COPD (top row); and the consistency when GP is co-administered with other active agents in the patient with the mean extrathoracic airway geometry (bottom row)



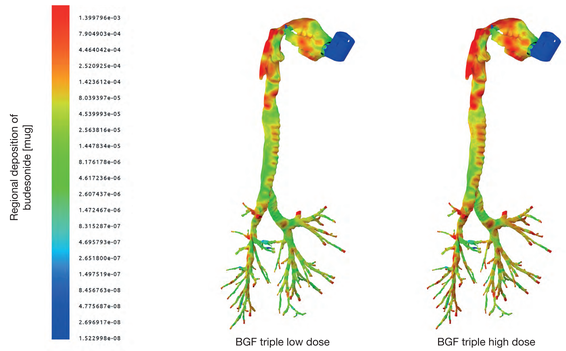
BGF, budesonide/glycopyrrolate/formoterol fumarate; COPD, chronic obstructive pulmonary disease; GFF, glycopyrrolate/formoterol fumarate; GP, glycopyrrolate; UA, upper airway.

Figure 3. Influence of inhalation flow rate on the regional deposition of FF for one patient with mild COPD (top row); and the consistency when FF is co-administered with other active agents at a fixed flow rate of 60 L/min for the same patient (bottom row)



BGF, budesonide/glycopyrrolate/formoterol fumarate; COPD, chronic obstructive pulmonary disease; FF, formoterol fumarate; GFF, glycopyrrolate/formoterol fumarate.

Figure 4. Influence of BGF MDI dose on the regional deposition of budesonide for one patient with very severe COPD



BGF, budesonide/glycopyrrolate/formoterol; COPD, chronic obstructive pulmonary disease.

Table 1. Total lung deposition of FF, GP, and budesonide as % of delivered dose for the different combinations and as a function of the inhalation flow rate

	Flow rate [L/min]				
	15	30	60	90	120
Total lung deposition of FF, % delivered dose					
FF mono	53±18	43±19	34±19	30±18	27±17
GFF dual	55±19	45±20	36±20	32±19	29±18
BGF triple low dose	54±19	45±20	36±19	31±19	28±18
BGF triple high dose	53±19	43±20	34±19	30±18	27±17
Total lung deposition of GP, % of delivered dose					
GP mono	54±18	44±20	35±19	31±19	28±18
GFF dual	55±18	45±20	37±19	32±19	29±18
BGF triple low dose	54±18	44±19	36±19	31±19	28±18
BGF triple high dose	53±19	43±20	35±19	30±18	27±17
Total lung deposition of budesonide, % of delivered dose					
BGF triple low dose	53±18	44±19	35±19	30±18	27±18
BGF triple high dose	52±18	42±19	33±19	28±18	25±17

BGF, budesonide/glycopyrrolate/formoterol fumarate; FF, formoterol fumarate; GP, glycopyrrolate; GFF, glycopyrrolate/formoterol fumarate.

Conclusions

- This computer simulation (*in-silico*) study supports the assertion that the Co-Suspension™ Technology MDI platform can deliver the aerosol consistently throughout the airways, regardless of the number of active agents included in the formulation.

References

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2. Vehring et al. Langmuir 2012;28:15015–15023.

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Author disclosures

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JS, MS, and SD are employees of Pearl Therapeutics Inc., a member of the AstraZeneca Group.

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