

Background and Objectives

Epinephrine is the first-line therapy for severe allergy and anaphylaxis, and there are reasons why inhaling epinephrine would be superior to current delivery methods:

1. Fast absorption [1] to quickly treat symptoms.
2. PK would be more consistent than the well-known variability from EAs.[2]
3. Direct delivery to the airways to treat upper [3] and lower airway symptoms [4]
4. No metabisulfite preservative for sensitive patients [5]

Epinephrine metered dose inhalers (MDIs) have been around since the 1950s, indeed, one of the first MDIs approved contained epinephrine. [6] Epinephrine MDIs have been studied for the treatment of anaphylaxis. Early studies showed promising PK, but often with 20 or more inhalations, limiting practicality. [7] In a more recent study, the authors concluded that while there may be benefits in treating the respiratory symptoms, they were doubtful that a sufficient dose could be effectively delivered to treat systemic symptoms and stop mast cell degranulation. [8]

Since 1991, patients experiencing allergic reactions to in-clinic skin testing and who are sensitive to metabisulfite have been treated with inhaled epinephrine via epinephrine metered dose inhalers (MDIs).

- CFC MDI Formulation (pre-2012): Systemic components of reaction (e.g., hypotension, pruritis) had incomplete reversal of symptoms often requiring supplementation with antihistamines and H2 blockers. Upper airway symptoms (laryngeal/pharyngeal edema) showed improved resolution.

- HFA MDI Formulation (2018-onwards): Systemic components resolved, while upper airway symptoms responded poorly and less completely relative to treatment with the CFC MDI.

Clinical observations prompted efforts to improve the aerosol delivery of epinephrine. Ideal product would provide rapid and reliable resolution of upper airway laryngeal/pharyngeal edema while also obtaining rapid resolution of systemic symptoms.

Advanced experimental methods like those developed at the Aerosol Research Lab of Alberta (University of Alberta) can predict drug deposition from MDIs. [9] Such methods provide a means for understanding and optimizing inhaler performance.

The present work describes the development a novel inhaler that optimizes epinephrine delivery for treatment of anaphylaxis

Methods

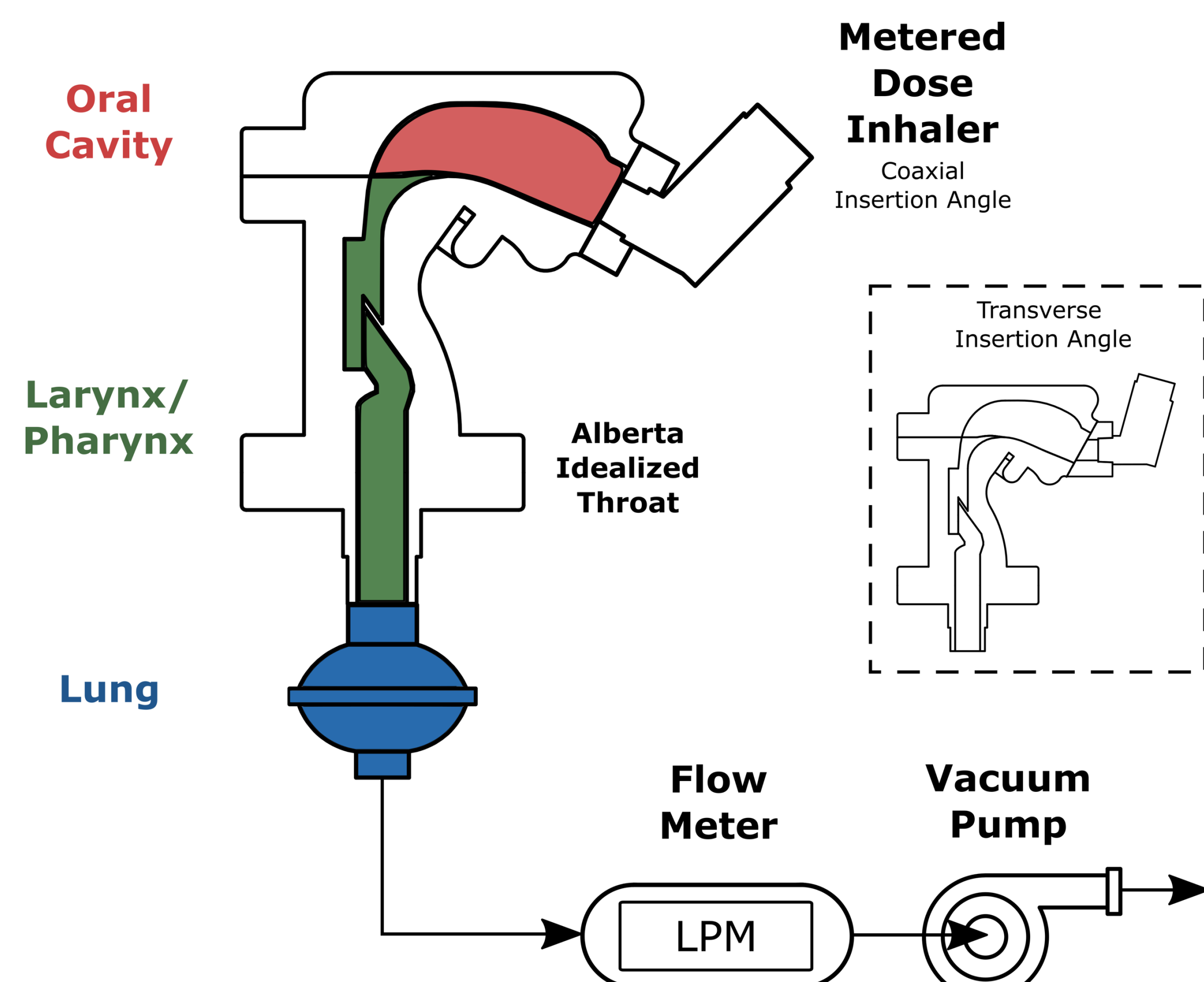


Figure 1. Experimental setup used to evaluate epinephrine MDI performance in a sectioned polymer Alberta Idealized Throat

A sectioned version of the Alberta Idealized Throat, constructed via polymer rapid prototyping, was first used to evaluate regional deposition from two epinephrine MDIs (CFC MDI and HFA MDI).

Inhalers were actuated into the sectioned Alberta Idealized Throat following established methods⁹, via the setup shown in Figure 1.

- A range of flowrates and insertion angles captures some elements of real-world MDI use.
- Epinephrine recovered from the oral cavity, larynx/pharynx (the throat), and a downstream filter representing the lung was assayed via UV spectroscopy, reported here as % emitted dose.

Results were interpreted in the context of clinical observations to identify targets for MDI optimization.

A Novel MDI was then developed to optimize the delivery of epinephrine for resolving the symptoms of allergic reactions and anaphylaxis.

Results and Discussion

Figure 2 shows regional deposition for various flowrates and insertion angles. MDIs show differences in regional dose delivery and consistency of delivery across flowrates and angles.

CFC MDI:

- Very high deposition in the oral cavity (i.e., >80% at 30 L/min),
- marginal deposition in the throat (~11% at 30 L/min), and
- consistently low (<10%) dosing to the lungs.

HFA MDI (relative to CFC MDI):

- Reduced deposition in oral cavity,
- Similar (marginal) deposition in throat, and
- Large increases in lung dosing (up to ~20% to ~60%, depending on flowrate, angle).

Novel MDI

- Improved deposition in larynx pharynx to address local edema,
- improved lung dosing to resolve systemic symptoms,
- less sensitivity to orientation of inhaler in mouth for improved ease of use,
- more consistent performance across various flowrates to decrease intersubject variability.

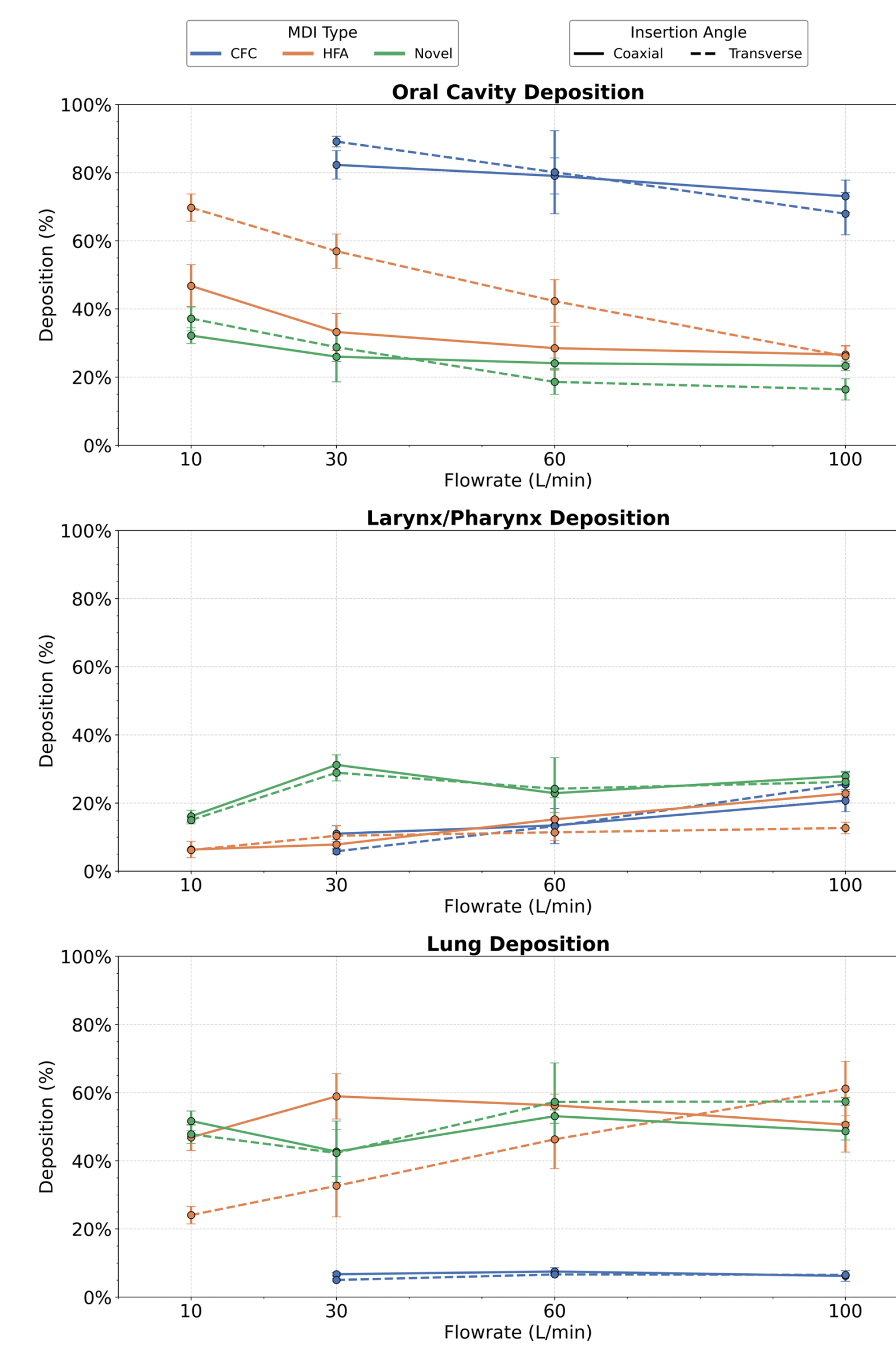


Figure 2. Regional deposition for each MDI

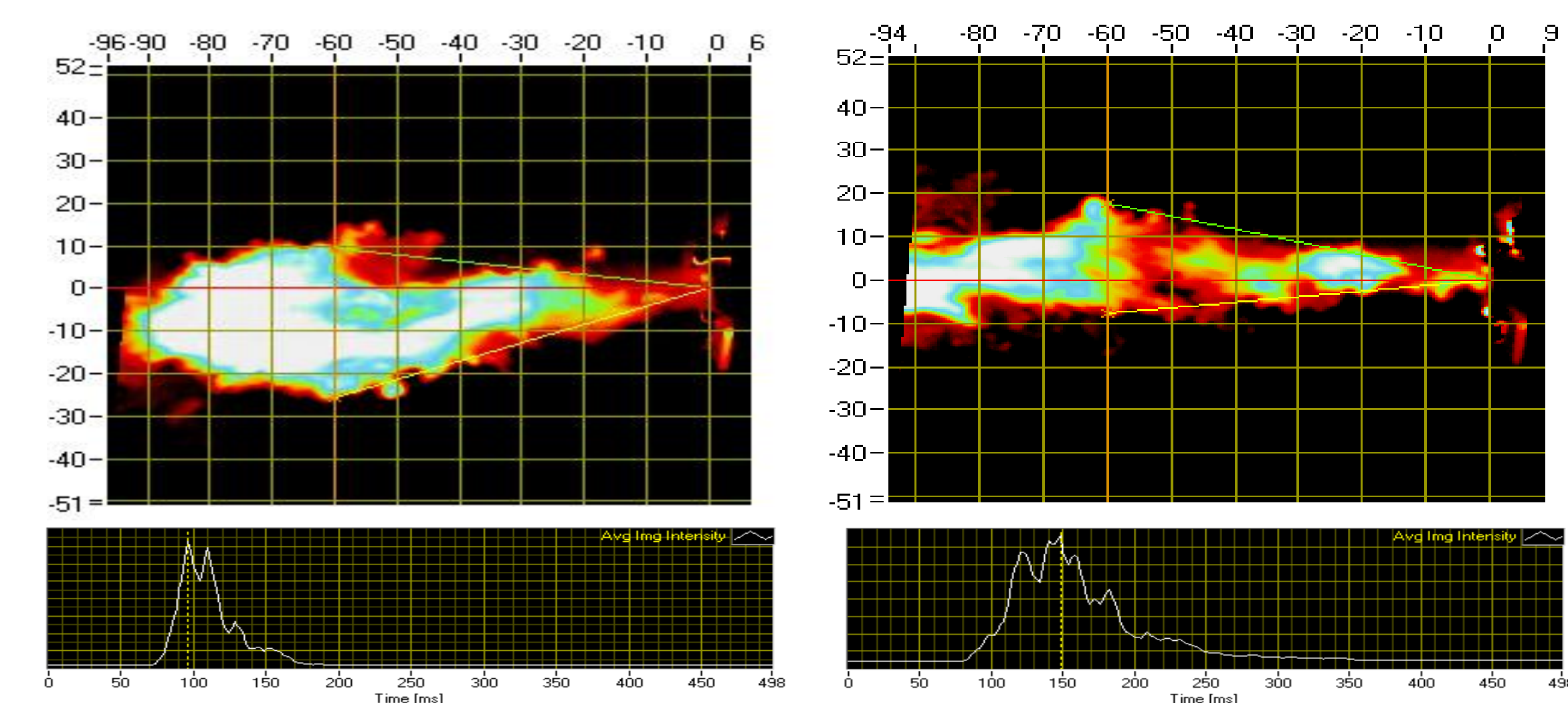


Figure 3. Plume Measurements of (left) HFA MDI and (right) Novel MDI

Conclusions

Optimal characteristics for an aerosolized epinephrine MDI were identified. A Novel MDI was developed that shows optimized targeting to both the throat and lungs. This Novel inhaler has the ability to provide targeted, personalized, orientation independent delivery of epinephrine allowing potential fast and more complete resolution of acute allergic reactions and anaphylaxis. Future work will investigate the efficacy of the novel MDI to treat symptoms of an allergic reaction.

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