# Evaluating the Dissolution of Commercially Available Metered Dose Inhaler (MDI) Drug Products from Realistic In Vitro Experiments

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## INTRODUCTION

**Currently, regulatory guidelines for quality testing of orally inhaled drug formulations do not include dissolution testing.**

However, multiple studies have demonstrated a strong relationship between release rate and pharmacokinetic and pharmacodynamic properties [1].

Therefore, to better understand the critical dissolution study parameters that may provide an improved correlation with in vivo performance metrics, this work examined the effects of different surfactants in the dissolution media, and the use of a realistic anatomical mouth-throat (MT) model during sample collection, using commercial MDI products.

## OBJECTIVES

1. Whether orally inhaled and nasal drug products (OINDP) dissolution profiles are solely dependent on the active pharmaceutical ingredient (API) solubility or if it is also dependent on the choice of the surfactant when selecting the dissolution media for dissolution experiment
2. During sample preparation, whether passage through an anatomical MT may influence dissolution performance.

## METHODS

Two FDA-approved and commercially available suspension MDI products (Flovent® HFA and Advair® HFA) containing fluticasone propionate (FP) were utilized for this study.

### Aim 1

An abbreviated Anderson Cascade Impactor (ACI) at 28.3 L/min was used to collect the fine particle dose < 3.3 µm (USP throat) or the lung dose (OPC Medium MT model in combination with stage 2) on a filter membrane. Three dissolution media (**0.5% w/v Tween-80, 0.14% w/v sodium dodecyl sulfate (SDS), and 10 g/mL bovine serum albumin (BSA)** in phosphate buffered saline) at 100 mL were used to achieve a **solubility of 5 µg/mL for FP** at 37°C. The **dissolution** was evaluated at different time points using an **adapted USP V Apparatus** (paddle over disk), with the filter side down in a sandwich orientation [2]. f1 difference and f2 sameness evaluation between the dissolution profiles was performed in Python 3.10. As per the FDA Guidance for Industry, an f1 close to 15 and f2 less than 50 indicate the dissolution profiles differ from each other.

### Aim 2

The lung dose was collected for a **range of MT models (AIT, OPC, VCU)** utilizing the medium inhalation profile followed by dissolution assessment described in Aim 1.

## RESULTS AND DISCUSSION

Solubility of FP increased with increasing concentrations of Tween-80 and SDS, however no relationship was observed between FP solubility and concentration of BSA (Figure 1).

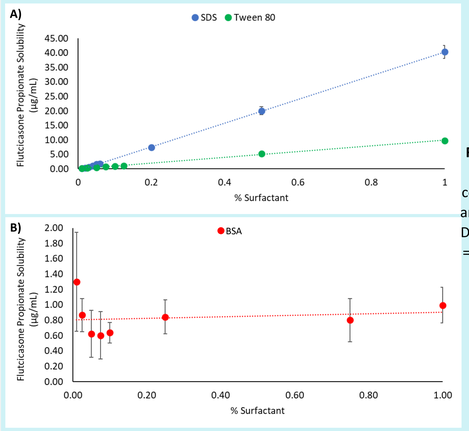


**Figure 1:** Solubilities of fluticasone propionate API in varying concentrations of **A)** SDS, Tween-80 and **B)** BSA. % surfactant is in % w/v. Data and error bars: mean ± SD of N = 3 per concentration of surfactant.

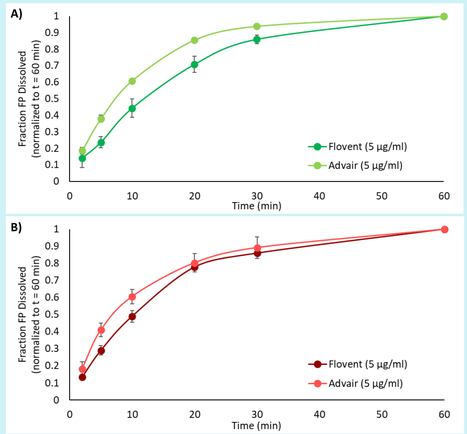


**Figure 2:** Dissolution of Fluticasone Propionate from Flovent® HFA and Advair® HFA at a solubility of 5 µg/mL in **A)** Tween-80 and **B)** SDS. Data and error bars: mean ± SD of N = 3 – 5 per datapoint.

The % SDS and Tween-80 needed to achieve the same FP solubilities are presented in Figure 1. Using Tween-80 as the surfactant, it was found that fluticasone propionate from Advair® HFA dissolved faster (Figure 2A). Comparison of the profiles suggested that the best balance between observed variability and differences between the two formulations was observed for 0.5% Tween-80 (f1 = 12.90; f2 = 96.46) providing a FP solubility of 5 µg/mL as compared to 0.14% SDS at the same FP solubility (f1 = 8.60; f2 = 98.00). Results agree with literature findings [3], and with the original hypothesis that dissolution rate is primarily affected by solubility and not the nature of the surfactant (f1 = 8.42; f2 = 97.95; Figure 3).

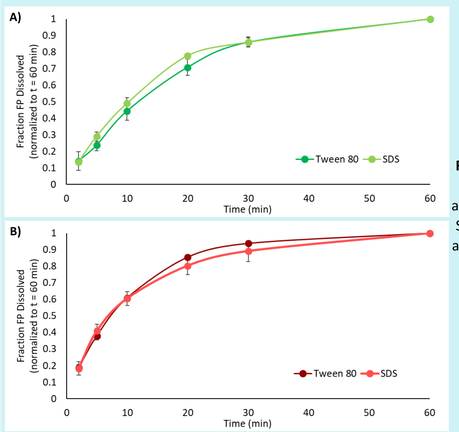


**Figure 3:** Dissolution of Fluticasone Propionate from **A)** Flovent® HFA and **B)** Advair® HFA in Tween-80 and SDS at a solubility of 5 µg/mL. Data and error bars: mean ± SD of N = 3 – 5 per datapoint.

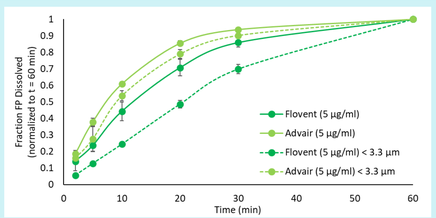


**Figure 4:** Effect of differences in particle size on dissolution profiles of Fluticasone Propionate from Flovent® HFA and Advair® HFA in Tween-80 at a solubility of 5 µg/mL. Data and error bars: mean ± SD of N = 3 per datapoint.

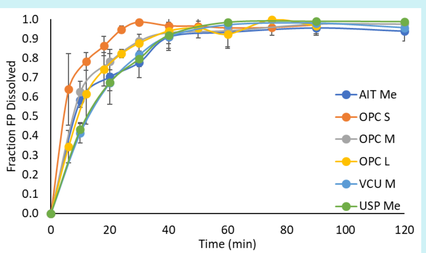


**Figure 5:** In vitro dissolution profiles for different MT models and medium inhalation profile for Flovent® HFA. AIT = Alberta Idealized Throat; OPC = Oropharyngeal Consortium; VCU = Virginia Commonwealth University; USP = United States Pharmacopeia. Me = metal; S = small; M = medium; L = large. Data and error bars: mean ± SD of N = 3 per datapoint.

## RESULTS AND DISCUSSION (CONT.)

When comparing the dissolution of the lung fraction of Advair® HFA and Flovent® HFA to the fine particle fraction < 3.3 µm, the Advair® HFA showed a higher rate of dissolution for both the lung fraction and fine particle fraction < 3.3 µm. However, for both drug products, the material collected as lung dose (using the OPC M MT model to collect material passing stage 1) appeared to dissolve faster than the fine particle fraction < 3.3 µm (USP throat, material passing stage 2 of the aACI; f1 = 38.08, f2 = 89.08; Figure 4). Whether this is related to the OPC M throat needs further investigation.

Finally, the choice of the MT model appeared to influence dissolution of FP from Flovent® HFA at earlier time points (f1 = 13.87, f2 = 42.57; Figure 5). The OPC S MT appeared to facilitate a faster dissolution, passage through which may have occurred quicker as compared to the other MT models which showed comparable dissolution profiles.

## CONCLUSION

The use of synthetic surfactants in this research indicated that solubility may be more critical for impacting dissolution performance as compared to the choice of surfactant used in the study design. However, in the case of BSA, a concentration dependent change in solubility was not observed. Thus, further studies are warranted regarding surfactant selection with bio-relevant surfactants and drug substance solubility to better understand their impact on dissolution performance. Furthermore, it appeared that the choice of the MT model affected the dissolution of FP, as observed from the Flovent® HFA study, indicating the dissolution study outcomes may be sensitive to the choice of the MT model at earlier time points.

## REFERENCES

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## ACKNOWLEDGEMENTS

Funding for this work was made possible, in part, by the U.S. Food and Drug Administration through Contract 75F40119C10154 and Grant U01FD004943. Abhinav Mohan was supported by a fellowship program administered by the Oak Ridge Institute for Science and Education (ORISE) through an interagency agreement between the U.S. Department of Energy and the U.S. FDA. The views expressed in this abstract are from the authors only and do not necessarily reflect the official policies of the Department of Health and Human Services, nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.

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