Development of a low-volume *in-vitro* dissolution method for assessing variability in fine particle doses of dry powder inhalers

W1030-03-14

Varsha V. Nair [a], Amr Hefnawy [a], Matthew J. Herpin [a], Kairui Feng [b], Nathan Reed [c], Tian Ma [d], Elizabeth Bielski [b], Sneha Dhapare [b], Bryan Newman [b], Susan Boc [b], Hugh D.C. Smyth [a]

a The University of Texas at Austin, College of Pharmacy, Division of Molecular Pharmaceutics and Drug Delivery, Austin, TX
b Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD
c Office of Testing and Research, Office of Pharmaceutical Quality, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Saint Louis, MO
d Office of Bioequivalence, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD

CONTACT INFORMATION: Varsha V. Nair (varshanair@utexas.edu), Hugh D.C. Smyth (hugh.smyth@austin.utexas.edu)

PURPOSE

- Over the last 2 decades, several methods for assessing the dissolution of orally inhaled drug products have been evaluated that require multiple doses to attain a quantifiable mass.
- For inhaled drug products, like a dry powder inhaler (DPI), where the labeled dose is typically a single actuation, these multi-actuation approaches may mask inter-dose variability and are not representative of a single dose or the amount of drug product that reaches the lung.
- A DPI's lung deposition is dependent on the particle size and aerodynamic performance. The particles depositing in the lungs are referred to as the fine fraction, generally ranging from 0.5 to 5 µm aerodynamic diameter.[1]

OBJECTIVES

- The purpose of this study was to develop a low-volume *in vitro* dissolution method for testing the fine particle dose (< 5 µm) of orally inhaled dry powders using a single dose from a commercial DPI.
- This method was used for systematic screening of dissolution differences across five different batches of low dose Advair® Diskus® [100 mcg fluticasone propionate (FP) and 50 mcg salmeterol xinafoate (Sal) – FP/Sal 100/50].

METHODS

- A fast-screening impactor (FSI) with a USP induction port and pre-separator containing a specialized insert used at a **90 L/min flow rate with a 4 L** actuation volume was coupled to a Fine Fraction Collector (FFC) that collected the powders with aerodynamic particle size smaller than 5 µm, the Fine Particle Fraction (FPF), on a filter housed within the FFC (method 3 in Figure 1).

Table 1 : Study parameters

Parameter	Value
Number of actuations	1
Dissolution media (volume)	0.2% sodium dodecyl sulphate in phosphate buffered saline, pH 7.4 (15 mL)
Temperature	37°C
RPM	50 rpm up to 60 minutes 75 rpm from 60-75 minutes
Time points	5, 10, 15, 30, 45, 60, 75 min
Detection	HPLC at 228 nm

METHODS

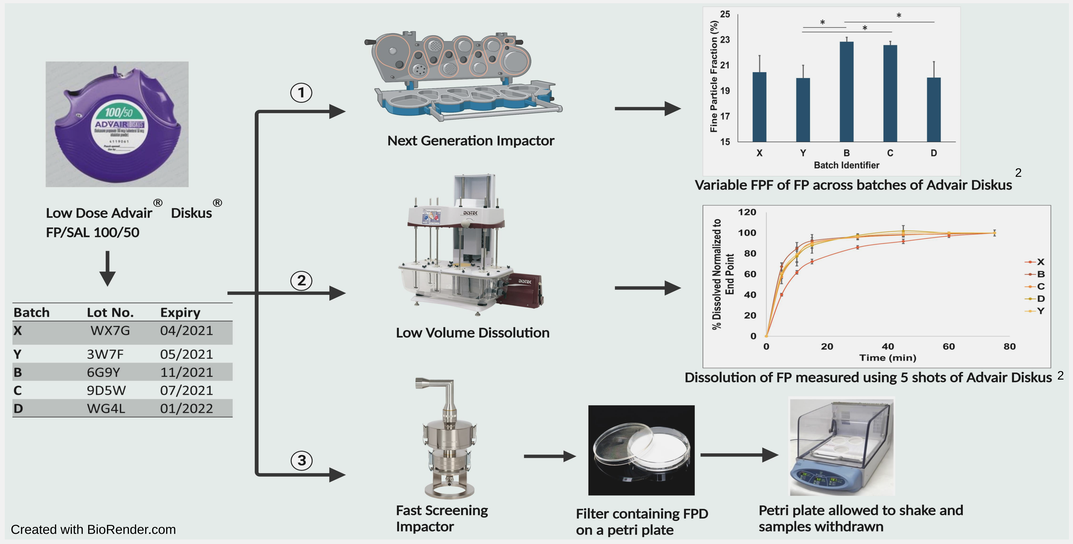

Figure 1: Graphical representation of the various methods used for measuring the aerosol performance and dissolution behavior of DPIs. 1) NGI was previously used to quantify the FPF (< 5 µm) for 5 batches of FP/Sal 100/50 which revealed significant differences among batches. 2) Five shots of FP/Sal 100/50 were used to assess the dissolution behavior using a small volume (150 mL) dissolution apparatus. 3) Third method utilizes 1 shot of FP/Sal 100/50 to be passed through the FSI and the FPF is collected in a filter. The dissolution for the FPF collected on the filter is assessed using a benchtop shaker with 15 mL media. The method was able to detect differences across batches at a biologically relevant dose.

RESULTS

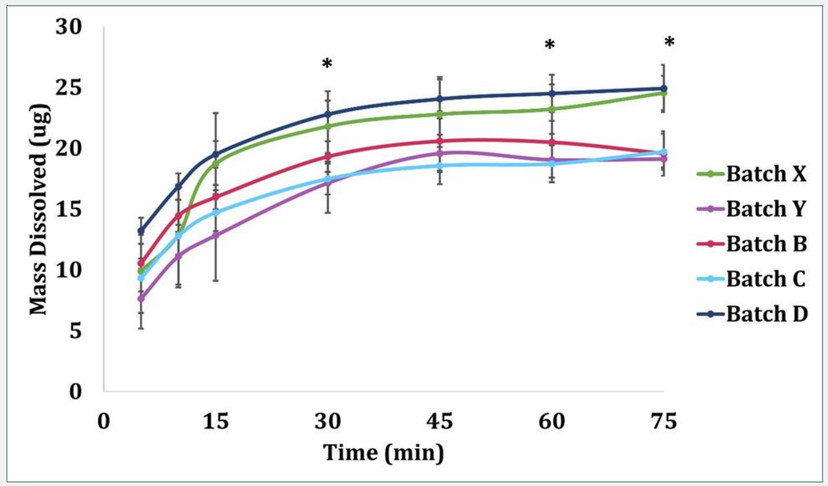

Figure 2: Dissolution time-curve of FP for all batches. Statistically significant ($p<0.05$) differences were observed between batches C-D and D-Y at 30 minutes, batches C-D and D-Y at 60 minutes and batches B-D, B-X, C-D, C-X, D-Y and X-Y at 75 minutes. Data are represented as mean ± standard deviation (n=3). Asterisks indicate significant differences at that particular time point.

- Dissolution testing of the five batches of FP/Sal 100/50 revealed that the powders exhibited an initial burst release of FP followed by plateau after 45 minutes, as shown in Figure 2.
- The dissolution profiles showed significant differences between batches at 30-, 60-, and 75-minutes time points.
- At 30 minutes, Batch D showed significantly higher mass dissolved ($p<0.05$) as compared to Batch C and Y.
- Batch C and Batch Y also exhibited significantly lower mass dissolved from Batch D at 60 minutes and 75 minutes.
- Additionally, at 75 minutes, the mass of dissolved FP in Batch B was lower than Batch D and Batch X, while Batch X exhibited higher dissolved mass as compared to Batch C and Batch Y.
- The calculated difference (f1) and similarity (f2) factors have been summarized in Table 2.

RESULTS

Table 2: Difference factor (f1) and similarity factor (f2) comparisons. Values that fall within the standard range (f1: 0-15 and f2: 50-100) generally ensure sameness of the compared curves.[3] Bold numbers indicate values outside the similarity range.

Batch	f1	f2
Y vs. X	7	61
B vs. X	**19**	**43**
C vs. X	8	57
D vs. X	13	50
Y vs. B	**21**	**43**
Y vs. C	9	59
Y vs. D	15	**49**
B vs. C	10	54
B vs. D	5	65
C vs. D	6	68

CONCLUSIONS

- A low-volume, *in-vitro* method to study the dissolution of a single respirable dose from commercial DPIs was successfully developed.
- Through the systematic screening of five batches of Advair® Diskus® 100/50, it was determined that the method is capable of detecting differences in the dissolution profile using this low-volume system.
- This method may provide complementary advantages of low volume unstirred models, like the RespiCell™, and common paddle/stirred methods used for testing bulk powders.

FUNDING

Funding for this work was made possible, in part, by the U.S. Food and Drug Administration through Contract HHSF223201810169C. Views expressed in this poster are from the authors and do not necessarily reflect the official policies of the Department of Health and Human Services and FDA, nor does any mention of trade names, commercial practices, or organization imply endorsement by the U.S. Government.

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