In Vitro Batch-to-Batch Variability of Fluticasone Propionate and Salmeterol Dry Powder Inhalers

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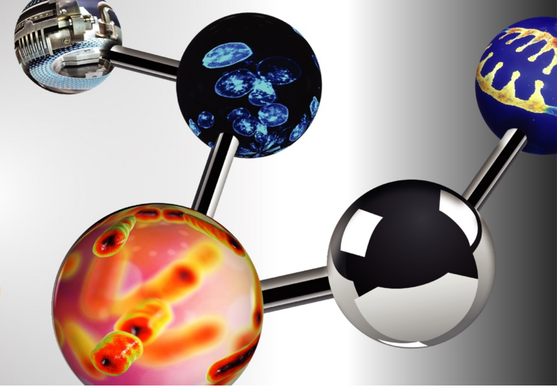
Varsha V. Nair[a], Amr Hefnawy[a], Hugh D.C. Smyth[a], Jieon Lee[b], Kairui Feng[b], Elizabeth Bielski[b], Sneha Dhapare[b], Bryan Newman[b], Denise S. Conti[b,c], Susan Boc[b], and Matthew J. Herpin[a]

[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] *Present:* Office of Safety and Clinical Evaluation, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD.

CONTACT INFORMATION: varshanair@utexas.edu, matt.herpin@utexas.edu, hugh.smyth@austin.utexas.edu



PURPOSE

Batch-to-batch variability has been reported in dry powder inhaler (DPI) products.[1,2,3] Batch variability of five different batches of low dose Advair® Diskus® [100 mcg Fluticasone Propionate (FP) and 50 mcg Salmeterol (Sal) – FP/Sal 100/50] was assessed in terms of aerodynamic particle size distribution (APSD) and FP dissolution rate.

OBJECTIVE

The objective of this study was to assess the in vitro deposition performance and dissolution of five batches of FP/Sal 100/50.

METHODS

Aerodynamic Particle Size Distribution Testing

- Five different batches of FP/Sal 100/50 were sourced from a local pharmacy and were labelled as shown in Figure 1.
- In vitro aerosol performance was tested using a Next Generation Impactor (NGI) with a USP induction port and pre-separator at 80 L/min for a time equivalent to 4 L of air flow being allowed to pass through the device. The pressure drop across the device was maintained at 4 kPa.
- Five shots were actuated into the apparatus and the drug mass of FP and Sal deposited on each component and NGI stage was quantified via RP-HPLC using 0.6% ammonium acetate /methanol (30/70) as mobile phase and a UV detector set at 228 nm to assay both active ingredients.
- APSD performance metrics calculated were as follows: Emitted Dose (ED), Emitted Fraction (EF), Fine Particle Fraction (FPF), Fine Particle Dose <5 µm (FPD), Respirable Fraction (RF), Mass Median Aerodynamic Diameter (MMAD) and Geometric Standard Deviation (GSD).

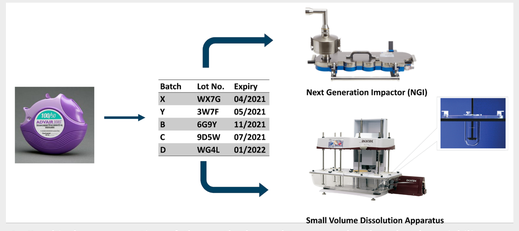


Figure 1: Graphical representation of the methods used to screen batch-to-batch variability amongst 5 batches of FP/Sal 100/50.

METHODS

Dissolution Testing

- Powder from the FP/Sal 100/50 blisters were collected and added to the small volume dissolution vessel containing 150 mL of 0.2% sodium dodecyl sulfate in pH 7.4 sodium phosphate buffer at 37°C.
- Paddle speed was set at 50 rpm and 1 mL samples were drawn at 5, 10, 15, 30, 45, 60, and 75 minutes (with the paddle speed increased to 75 rpm for last interval from 60 to 75 minutes to establish an endpoint for dissolution).
- The collected samples were filtered, and the concentrations were determined using an HPLC system with the UV wavelength set to 228 nm.
- Statistical analysis was performed by comparing the means using ANOVA with a post-hoc Tukey-Kramer HSD test using JMP 10.0 Software (SAS, Cary, NC).
- The difference factor (f1) and similarity factor (f2) were calculated as per the U.S. FDA guidance.[4]

RESULTS

- The NGI stage-by-stage deposition of the 5 batches showed significant differences in the amount of drug mass deposited in each stage for both FP and Sal.
- Figure 2A reveals the significant differences in the FPF of FP. Similarly, significant differences were observed in the FPF of Sal, shown in Figure 2B.
- Figure 3A reveals the significant differences in the MMAD of FP. Similarly, significant differences were observed in the MMAD of Sal, shown in Figure 3B.
- The additional aerodynamic performance metrics (ED, EF, FPD, RF, and GSD) also showed significant differences across batches X, Y, B, C, and D (not depicted).
- Dissolution testing revealed significant differences between batches exists at 5, 10, 15, 30, and 45-minute time points (Figure 4, Table 1). However, the difference factor (f1) and similarity factor (f2) were unable to detect the statistically significant differences in the dissolution profiles.
- In most cases, batches with different dissolution metrics displayed differences in APSD parameters. For example, Batch X differed from all other batches in most of the APSD metrics and showed significant differences from all batches across the dissolution time curve.
- Batch X showed only 61% dissolution at 10 minutes while Batches C, D, and Y exhibited approximately 78% dissolution at the 10 minutes time point, while Batch B presented approximately 85% dissolution at the same time.
- Batch X was also significantly different from batches B, C and D at 5, 10, 15, 30, and 45 min.

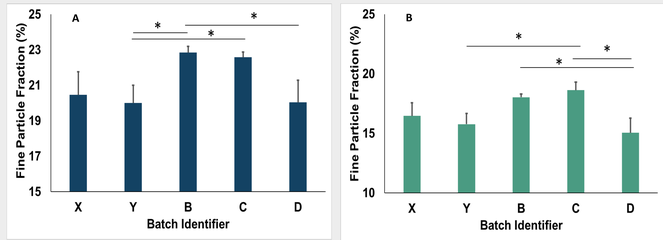


Figure 2: A) FPF of FP across the five batches (significant differences (p<0.05) were observed between batches B-D, B-Y, C-Y). Data are presented as mean ± standard deviation (n=3). B) FPF of Sal across the five batches (significant differences were observed between batches B-D, C-D, C-Y). Asterisks (*) indicate statistically significant (p<0.05) differences. Data are presented as mean ± standard deviation (n=3).

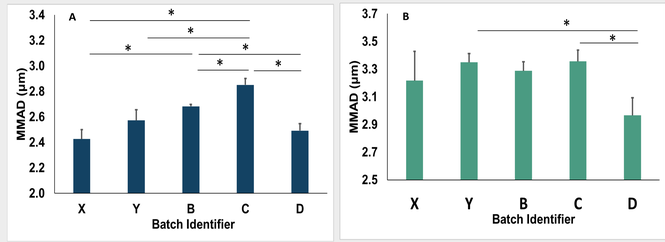


Figure 3: A) MMAD of FP across the five batches (significant differences (p<0.05) were observed between batches C-B, C-D, C-Y, C-X, B-D, B-X). Data are presented as mean ± standard deviation (n=3). B) MMAD of Sal across the five batches (significant differences (were observed between batches Y-D, C-D). Asterisks (*) indicate statistically significant (p<0.05) differences. Data are presented as mean ± standard deviation (n=3).

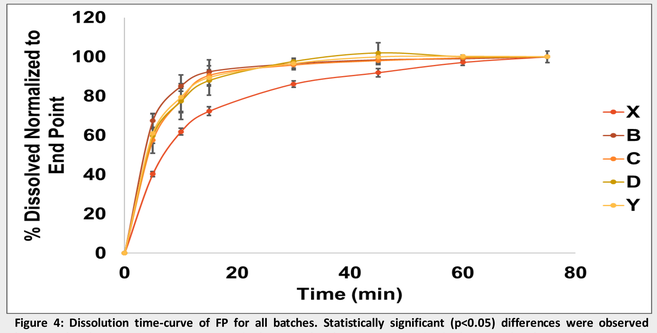


Figure 4: Dissolution time-curve of FP for all batches. Statistically significant (p<0.05) differences were observed between batches B-X, C-X, D-X, Y-X at 5 min; between batches B-X, Y-X at 10 min; between batches B-X, C-X, D-X, Y-X at 15 min; between batches B-X, C-X, D-X, Y-X at 30 min; and between batches D-X, Y-X at 45 min. No statistically significant (p<0.05) differences were observed between batches at 60 min. Data are represented as mean ± standard deviation (n=3).

Table 1: Difference factor (f1) and similarity factor (f2) of batches B, C, D, and Y with respect to Batch X. Values that fall within the standard range generally ensure sameness of the compared curves.

	Standard Ranges	B	C	D	Y
f1	0-15	12	7	8	7
f2	50-100	49	60	54	61

CONCLUSIONS

- This study revealed that the different batches of FP/Sal 100/50 DPI had significant differences in APSD performance and dissolution rates.
- These differences amongst batches may be indicative of varying physicochemical properties, which may play a role in product performance and variability between batches.
- In follow-up studies, to investigate the sources of variability, the physicochemical properties of DPI formulations that influence APSD performance, dissolution rate (of both bulk and fine particle fraction), and batch-to-batch variability will be conducted using a comprehensive panel testing of analytical techniques along with statistical approaches.

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