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Investigation of the Effects of Physicochemical Properties of Dry Powder Inhalers on Batch-to-Batch Variability

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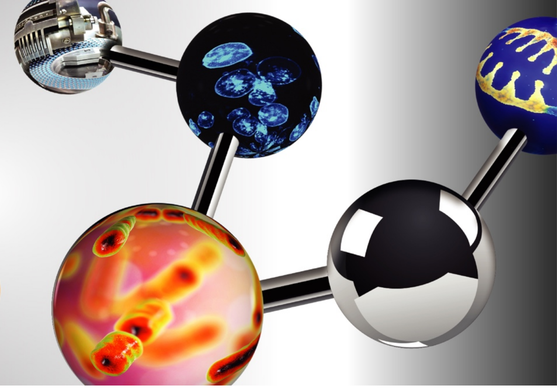

PURPOSE

- Variability of dry powder inhaler (DPI) products may originate from formulation, device, manufacturing and/or environmental factors.[1-3]
- So far, no systematic study has linked the physicochemical properties of DPI formulations as potential sources of batch-to-batch variability.
- In this study, we investigated the physicochemical properties of different batches of a commercially available DPI product and correlated these properties to variations in in vitro performance using statistical analysis methods.

OBJECTIVES

- Evaluate batch-to-batch variability of DPI products through a systematic performance screening of six different batches of high dose Advair® Diskus® [500 mcg Fluticasone Propionate (FP) and 50 mcg Salmeterol (Sal) – FP/Sal 500/50] in terms of aerodynamic particle size distribution (APSD) and FP dissolution rate.
- Determine correlations between the in vitro performance and physicochemical properties through a panel of physicochemical assays.
- Evaluate the effects of storage on the performance of the DPI products through thermal stress testing.

METHODS

- Six different batches of FP/Sal 500/50 were purchased (Table 1). Additionally, Batch X was thermally stressed following reported methods.[4] Temperature cycling was done by storing sample devices at -20°C for two days, followed by storage at 40°C and 75% RH for 2 days, repeated a total of 3 cycles. High temperature excursion is achieved by storing devices at -20°C for two days, followed by storage at 60°C and 75% RH for 2 days.

Table 1: Procured and thermally stressed batches with batch numbers and expiry dates

	Batch X	Batch Y	Batch Z	Batch A	Batch B	Batch C	Thermally Stressed Batch X40	Thermally Stressed Batch X60
Batch number	MR7J	K27G	RS4R	726A	HN9X	EK4X	MR7J	MR7J
Expiry date	4/2020	3/2020	4/2020	7/2020	9/2020	2/2021	4/2020	4/2020

Aerosol Performance

- 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 Dose <5 µm (FPD), and Geometric Standard Deviation (GSD).

METHODS

Dissolution Testing

- Powder from the FP/Sal 500/50 blisters were collected and added to the dissolution vessel containing 150 mL of 0.2% sodium dodecyl sulfate in pH 7.4 sodium phosphate buffer at 37ºC.
- 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 concentration was determined using an HPLC system with UV wavelength set to 228 nm.

Particle Size Measurement

- Particle size distribution of the dry powder was evaluated using Sympatec HELOS laser diffraction system (Sympatec GmbH, Clausthal-Zellerfel, Germany) with RODOS dispersing unit at dispersion pressures ranging from 0.5 to 4 bar. From this data set, the ease of deagglomeration of the powders was assessed using 50% de-agglomeration pressure (DA50), according to a previously reported method.[5]

Surface Energy Analysis

- The surface energy was evaluated using inverse gas chromatography (iGC) Surface Energy Analyzer (SMS, Alperton, UK). These experiments were conducted to determine the dispersive surface energy as well as the specific free energies of adsorption, respectively, while the dispersive energy component was calculated.[6]

Statistical Analysis

- Statistical analysis of differences in performance metrics between batches was performed using ANOVA with a post-hoc Tukey-Kramer HSD test using JMP 10.0 Software (SAS, Cary, NC). Bivariate statistical correlation analysis was performed to determine relations between the performance metrics and the physicochemical properties of the FP/Sal 500/50 DPI batches.

RESULTS

- Performance screening using the NGI showed significant differences in stage mass deposition between different batches as illustrated in Figure 1. Aerosol performance metrics such as FPD also showed statistically significant ($p<0.05$) differences for some batches (Table 2).
- Dissolution studies showed significant ($p<0.05$) differences between the batches at specific sampling time points although the dissolution profile comparisons using difference factor (f1) and similarity factor (f2) analysis did not show differences between the batches studied (Figure 2). Batches that showed different aerosol performance were not the same batches that showed variation in dissolution.
- Powder analysis using iGC provided several parameters that describe the potential for molecular interactions at the particle surface such as the specific surface area, wettability, dispersive surface energy and acid-base surface energy. Of these parameters, the dispersive surface energy showed the highest correlation with the aerosol performance (i.e., R^2: 0.7822 for FPD). Specifically, it was found that the thermally stressed batches (X40 and X60) had a greater surface energy than any of the other compared batches (Figure 3), and they were found to have the poorest overall aerodynamic performance. These results indicate that surface energy may serve as a potentially useful predictor of variability that exists inherently within the DPI samples.

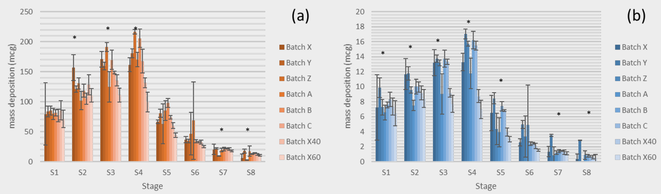

Figure 1: Impactor mass deposition of Fluticasone Propionate (a) and Salmeterol (b) using the NGI at flow rate of 80 L/min for 3 sec. Batch X40 and X60 are the thermally stressed batches. Data represented as mean ± standard deviation (n = 3). * denotes time points with significant differences (p<0.05) between dissolution of different batches

Table 2: APSD parameters (ED, FPD, EF, GSD) for FP and Sal. Data presented as mean ± standard deviation (n = 3).

Batches	ED (µg)	FPD (µg)	EF (%)	GSD
X_{sal}	224.86 ± 2.44	51.69 ± 5.42	89.94 ± 0.98	1.31 ± 0.03
X_{FP}	2450.16 ± 48.70	649.14 ± 38.90	98.01 ± 1.95	1.32 ± 0.05
Y_{sal}	250.15 ± 13.17	66.06 ± 1.87	100.06 ± 5.49	1.40 ± 0.02
Y_{FP}	2524.88 ± 132.55	648.61 ± 13.77	100.99 ± 5.30	1.34 ± 0.01
Z_{sal}	217.88 ± 31.70	49.79 ± 1.30	87.15 ± 12.68	1.31 ± 0.05
Z_{FP}	2483.57 ± 294.11	692.38 ± 8.61	99.34 ± 11.77	1.30 ± 0.04
A_{sal}	217.01 ± 01	41.65 ± 4.87	86.80 ± 4.43	1.39 ± 0.05
A_{FP}	2482.02 ± 97.87	617.58 ± 45.77	99.28 ± 3.92	1.38 ± 0.04
B_{sal}	205.76 ± 10.60	54.79 ± 3.97	82.30 ± 4.24	1.32 ± 0.01
B_{FP}	2264.44 ± 126.62	690.00 ± 50.03	90.58 ± 5.06	1.32 ± 0.01
C_{sal}	248.08 ± 10.41	53.35 ± 2.15	99.24 ± 4.16	1.33 ± 0.01
C_{FP}	2271.54 ± 159.64	593.17 ± 33.63	90.86 ± 6.38	1.34 ± 0.01
$X_{40\text{-}sal}$	212.40 ± 5.02	37.73 ± 1.95	84.95 ± 2.01	1.37 ± 0.04
$X_{40\text{-}FP}$	2374.98 ± 48.72	553.56 ± 21.72	95 ± 1.95	1.36 ± 0.01
$X_{60\text{-}sal}$	210.32 ± 4.84	31.60 ± 4.2	84.13 ± 1.94	1.37 ± 0.02
$X_{60\text{-}FP}$	2286.88 ± 26.03	445.41 ± 47.23	91.48 ± 1.04	1.37 ± 0.01

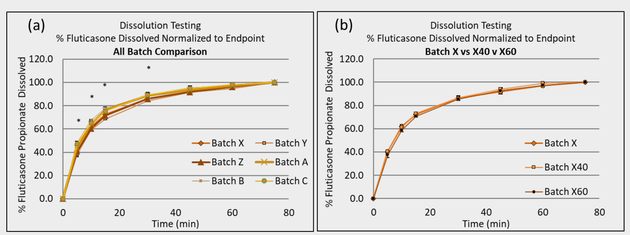

Figure 2: Dissolution time-curve of FP for all procured batches (a) and thermally stressed batches compared to batch X (b). Data is represented as mean ± standard deviation (n=3). * denotes time points with significant differences (p<0.05) between dissolution of different batches

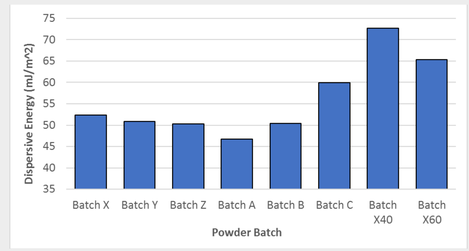

Figure 3: Dispersive surface energy of different batches calculated from several measurements on one aliquot of powder from each batch.

CONCLUSIONS

- The FP/Sal 500/50 DPI batches studied in this work showed significant differences regarding aerosol performance and dissolution profile. These differences may play a critical role in product performance and variability.
- Analysis of physicochemical properties of the batches highlighted methods that can be used to detect potential variability, especially iGC, which may be predictive of APSD differences.
- Understanding sources and parameters resulting in batch variation is essential to appropriate product development, manufacture and quality control of orally inhaled drug products.

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