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In vitro aerosol characterization of Staccato® Loxapine

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ABSTRACT

Medicinal aerosol products (metered dose and dry powder inhalers) require characterization testing over a wide range of use and pre-operating stress scenarios in order to ensure robust product performance and support submissions for regulatory approval. Aerosol characterization experiments on Staccato® Loxapine for inhalation (*Staccato* Loxapine) product (emitted dose, particle size, and purity) were assessed at different operating settings (flow rates, ambient temperature and humidity, altitude, and orientation) and at nominal test conditions following exposure to various stresses on the device (mechanical shock, vibration, drop, thermal cycling, and light exposure). Emitted dose values were approximately 90% of the coated dose at every condition, meeting target specifications in each case. Aerosol purity was consistently >99.5% for every test setting, with no reportable impurities according to ICH standards (>0.1%). Particle size averaged 2 μm (MMAD) and was independent of the different test conditions with the exception of different airflow rates. Particle size decreased slightly with airflow, which may assist in maintaining constant deep lung deposition. The combination of high emitted dose efficiency and a particle size range ideally suited for lung deposition, along with the consistency of these key aerosol attributes, suggests that the *Staccato* system has distinct advantages over more traditional aerosol systems.

1. Introduction

Medicinal inhalers may be deployed in a wide variety of patient use settings, spanning a large range of operating conditions (ambient temperature and humidity, inhalation rates, device orientations, etc.). Additionally, inhaler devices may be exposed to mechanical or thermal stresses prior to actual use, which have the potential to affect their overall performance and/or reliability. As part of its draft guidance on metered dose and dry powder inhalers (FDA, 1998), the Food & Drug Administration (FDA) requires product characterization testing of an inhaler in order to establish an acceptable window of use and pre-operating stress conditions. This type of testing occurs during the drug product's development cycle and is a necessary part of the filing for product approval by the FDA.

The literature describes the negative impact of certain use conditions on aerosol properties from traditional technologies such as metered dose inhalers (MDI) and dry powder inhalers (DPI). Emitted dose can be significantly affected by airflow rate (Boer et al., 1996; Malton et al., 1996; Meakin et al., 1995a,b; Palander et al., 2000; Ross and Schultz, 1996; Tarsin et al., 2004; Zanen et al., 1992), operating humidity and temperature (Jashnani et al., 1995; Jashnani and Byron, 1996; Meakin et al., 1995a,b; Zhu et al., 2008; Harper et al., 2007), and may also be affected by orientation (Meakin et al., 1995b). Relative humidity of the operating environment can also have an effect on aerosol particle size in DPIs and MDIs (Jashnani et al., 1995; Martin and Finlay, 2005). The inconsistency in emitted dose content and particle size can potentially affect total lung deposition and dosing reliability which in turn can affect drug disposition and therapeutic potential. Dosing consistency and reliability can be especially critical for drugs of systemic action, especially if the therapeutic window is narrow. Additionally, many inhalers require a specific user technique for efficient drug delivery. For example, timing actuation with inspiration can be critical for metered dose inhalers (Lenney et al., 2000; Newman, 2009). Therefore, it is essential to develop inhalers that provide consistent and reliable dosage and particle size over a wide range of settings and user techniques.

The *Staccato* system is a novel condensation aerosol technology. The basic concept is rapid and efficient vaporization of a thin film of pure drug coated on a metallic substrate inside of an airway (Rabinowitz et al., 2004). This concept has been incorporated into a relatively small handheld oral inhalation device. Each *Staccato* system consists of three core components: a heating substrate, a thin film of pure drug, in this case loxapine (5 or 10 mg) on the substrate and an airway where aerosol forms and is entrained in the inhaled airstream as shown in Fig. 1. The substrate's surface transiently reaches temperatures of ~400 °C within approximately two hundred milliseconds after being triggered by a patient's inhalation,

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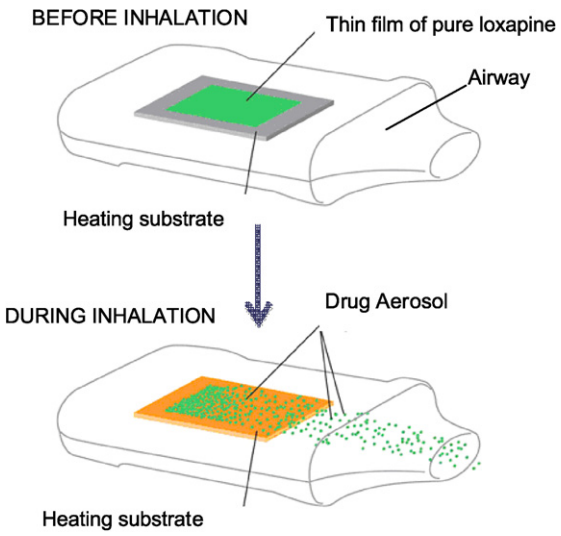

Fig. 1. *Staccato* Loxapine single dose system.

before cooling quickly back to room temperatures. This thermal pulse causes the drug film to quickly vaporize and then condense in the airstream to produce aerosol particles. The thinness of the drug film precludes excessive thermal degradation of the drug by limiting the duration of exposure to the high temperatures needed for vaporization (Rabinowitz et al., 2004; Myers et al., 2007). Mass median aerodynamic diameter (MMAD) values achieved with the technology are generally in the ~2 μm range, ideally suited for alveolar delivery (Hinds, 2nd ed. 1999). The *Staccato* system has been developed for a variety of pharmaceutical agents in the treatment of a number of acute and intermittent medical conditions, such as agitation, breakthrough pain, and migraine headaches. A New Drug Application (NDA) for *Staccato* Loxapine was recently submitted for the rapid treatment of agitation in patients with schizophrenia and bipolar disorder. Current treatment options for these patients are either oral antipsychotics, which are slow to provide relief, or intramuscular injections, which are invasive. Clinical efficacy studies (Lesem et al., in press) show that *Staccato* Loxapine can decrease agitation within 10 min of administration, in a non-invasive fashion.

This paper describes the *in vitro* aerosol data that were collected as a part of the product characterization program for *Staccato* Loxapine. In general for traditional inhalation drug products, the critical aerosol parameters of interest are emitted dose and particle size. Given the nature of aerosol formation in the *Staccato* Loxapine product (thermal generation), aerosol purity is also a critical attribute. Another unique aspect of the *Staccato* system is the temperature of the aerosol leaving the device. While the airstream becomes warm, it remains well within safe and tolerable levels for patients (Noymer et al., in press).

2. Materials and methods

2.1. Materials and supplies

Several lots of *Staccato* Loxapine in 5 and 10 mg dose strengths were manufactured at Alexza Pharmaceuticals (Mountain View, CA).

2.2. Emitted dose and aerosol purity characterization

Emitted dose was determined based on the methods described in United States Pharmacopeia (USP) chapter ⟨601⟩ for dose content uniformity of drug aerosols. Aerosolized loxapine was collected on glass fiber filters, extracted with methanol from the dose unit sampling apparatus (DUSA) assembly and device components, and analyzed by ultra performance liquid chromatography (UPLC) as described below. The cumulative drug recovery (total deposition in the device and filters) averaged over all experiments was 98 ± 4% of the average coated dose (the dose loaded onto the heating substrate). Generally $N = 3$ experiments were run for emitted dose unless otherwise noted.

The method to collect extracts for aerosol purity was performed in the same manner as described for emitted dose, with the exception that the filter extracts were analyzed by a reverse phase high performance liquid chromatography (HPLC) method described in Table 1. Three replicate aerosol purity experiments were performed at each condition of interest. Aerosol purities were analyzed for all conditions except following mechanical shock and vibration. Shock and vibration may affect the emitted aerosol dose (through detachment of the coated drug on the substrate), but there is no apparent mechanism in which shock or vibration would detrimentally affect aerosol purity.

2.3. Particle size characterization

Particle size distribution (PSD) was characterized according to USP ⟨601⟩ using the Next Generation Cascade Impactor (NGI) (MSP, St. Paul, MN) along with a USP induction port but no pre-separator. A preliminary study determined that particle re-entrainment did not occur on the plain collection cups. Following device actuation and aerosol generation, the induction port, collection cups, and fil-

Table 1
Methods for Loxapine concentration and purity determination.

Method type	Quantitation	Purity determination
Method	UPLC	HPLC
Column	Waters Acquity UPLC BEH C18, 1.7 μm, 2.1 mm × 50 mm	Waters YMC Pro C18, 150 × 4.6 mm, 3 μm
Mobile phase	0.2% TFA in 30/70 acetonitrile/water	A: Water with 0.1% TFA B: Acetonitrile with 0.1% TFA Gradient (Time – A:B) 0 – 85:15 15 – 65:35 23 – 20:80 24.5 – 20:80 25 – 85:15 30 – 85:15
Injection volume	1 μl	10 μl
Flow rate	0.6 ml/min isocratic	0.8 ml/min
Detection	296 nm, PDA detector	254 nm, PDA detector
Temperature	35 °C	30 °C

ter were extracted separately with methanol and quantified via UPLC. The mass of drug on each NGI stage, the mass median aerodynamic diameter (MMAD), geometric standard deviation of the distribution (GSD), and fine particle fraction (FPF, the percentage of emitted drug mass contained in particles <6 μm) were determined for each run. Three PSD measurements were taken for each sample condition.

2.4. Chromatographic methods for aerosol analysis

UPLC was used for analysis of loxapine quantity while HPLC was used for loxapine purity analysis. Detailed information for chromatographic methods is summarized in Table 1. For purity, loxapine content and the impurities/degradation product content were reported as a percentage of total area under the curve. The limit of detection of impurities is 0.02%. For loxapine quantitation, reference standards were used to calculate sample concentrations.

2.5. Experimental conditions

In this present work, study of *in vitro* aerosol performance for *Staccato* Loxapine is divided into two parts. In the first part of the work, aerosol performance was measured following exposures to various stresses to simulate the conditions that may occur before actual device use. Aerosol performance following each stress test was conducted at the nominal operating conditions: 25 ± 2 °C for temperature; 40 ± 5% for relative humidity; ~760 mm Hg for atmospheric pressure; and 28.3 ± 0.5 L/min for airflow through the device when testing emitted dose and emitted purity and 30 ± 0.5 L/min for testing particle size. In the second part of the work, aerosol performance was measured under several different experimental use conditions involving different airflows, ambient temperatures, ambient relative humidity conditions, and device orientations. Test conditions were selected based on the FDA Draft Guidance for MDIs and DPIs (FDA, 1998). Details for each of these tests are described subsequently. Aerosol performance was characterized for two dose strengths (5 mg and 10 mg). For the sake of brevity, only the data for the 10 mg dose strength will be presented here; the results and trends for the 5 mg dose strength were equivalent.

2.5.1. Pre-operating stress condition tests

2.5.1.1. Photostability. Staccato Loxapine products are stored in a multi-laminate foil pouch, their primary package, until immediately prior to use. The purpose of the photostability test is to confirm that short-term exposure to light after removal from the pouch has no impact on aerosol performance of the drug products. This photostability test was performed according to ICH Q1B guidance "Photostability Testing of New Drug Substances and Products," meeting the requirements of overall illumination ≥1.2 million lux hours and integrated near-UV energy ≥200 W-h/m^2. Three different exposure durations were studied—12, 24, and 74 h.

2.5.1.2. Thermal cycling. Staccato Loxapine products were exposed for either one or three temperature cycles between −20 °C for 48 h and 40 °C/75%RH for 48 h. This thermal cycling test was performed per 1998 FDA draft guidance "Stability Testing of New Drug Substances and Products".

2.5.1.3. Mechanical robustness. During handling and transport of the drug product, it is possible that the product will experience some forms of mechanical stress. Mechanical robustness testing verified the aerosol performance (emitted dose and particle size) following standard shock, vibration, and drop exposures. The shock, random vibration, and sinusoidal vibration exposures were conducted per International Electrotechnical Commission (IEC) standards. The procedure for mechanical shock was derived from IEC/EN 60068-2-27 (peak acceleration = 50 g, duration = 11 ms, pulse shape = half sine), random vibration from IEC/EN 60068-2-64 (frequency range = 20–500 Hz (flat spectrum), acceleration spectral density = 0.02 g^2/Hz, duration of conditioning = 9 min), and sinusoidal vibration from IEC/EN 60068-2-6 (frequency range = 10–500–10 Hz (one cycle), vibration intensity = 1 g (zero to peak), sweep rate = 1 octave/minute, duration = 10 sweep cycles in each axis). For drop exposures, in pouch or without pouch, devices were subjected to drop testing according to IEC/EN 60601-1. Devices were dropped three times onto a hardwood board (50 ± 5 mm in thickness) from a height of 1 m, from different starting orientations (Fig. 2). Separate sets of devices were used for each of the five mechanical robustness tests.

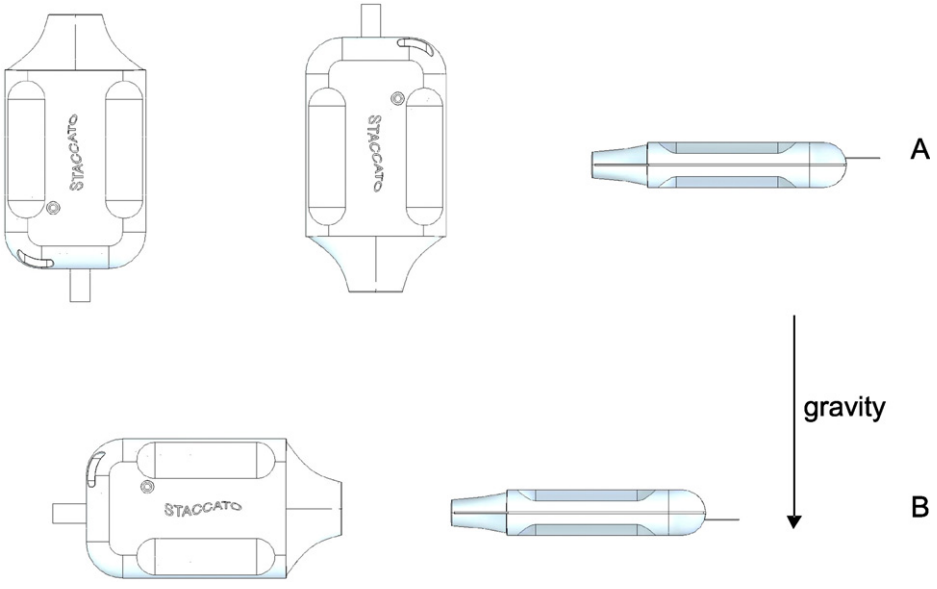

Fig. 2. Device orientation studies. The three orientations in A were used for drop testing pre-use. In addition to the positions in A, the two additional orientations in B were used for aerosol characterization under various operating conditions.

2.5.2. Different operating conditions

Here, aerosol performance was collected for the *Staccato* Loxapine product at operating conditions that are different from the standard test condition, where the airflow is set at 28.3 L/min (or 30 L/min for particle size testing) and the device is held flat with the long axis perpendicular to the direction of gravity. The parameters of interest were flow rate (inhalation rate), altitude, ambient temperature and relative humidity, and device orientation. In order to study the effect of each use factor, only one parameter was varied while the others were kept at the nominal testing conditions described above. Flow rates of 15 L/min and 45 L/min were chosen as the low and high airflow cases, respectively because these flow rates represented ±50% from the nominal of 30 L/min and also a wide range of inhalation efforts (approximately 1.3–11 cm H_2O given the device resistance of 0.075 (cm $H_2O)^{1/2}$ min/L = 48 $Pa^{1/2}$ s L^{-1}). Flow rates higher than 45 L/min are achievable by a user but would require a very substantial inhalation effort. An altitude of 8000 ft is equivalent to the pressure (∼564 mm Hg) in cabins of commercial aircraft (Federal Aviation Regulation 25). The humidity interval spans a broad range (15–90% RH) which encompasses the full capacity of the environmental test chamber, and the 15 and 30 °C settings were chosen because the product is intended to be used at room temperature. The different orientations (Fig. 2) span the range of possible holding positions during use.

3. Results and discussions

3.1. Emitted dose

Average emitted dose and device residual values for the pre-operating stress and different operating conditions are shown in Table 2. For all conditions, average emitted dose values were 96–112% of the historical mean emitted dose (9.1 mg). All results including pre-operating stress and different operating conditions are plotted in Fig. 3. The mean emitted dose is relatively consistent across the entire range of tested conditions. Moreover, individual emitted dose values are highly reproducible, with a relative standard deviation less than 4% for each condition tested. The consistency in the emitted dose performance of the *Staccato* Loxapine product indicates the reliability of the delivery system and that the effect of stresses such as exposures to light, thermal cycling, and mechanical shock/vibration/drop had minimal impact on the aerosol performance of the *Staccato* Loxapine product. In addition, emitted dose data for different operating conditions indicate that the device is robust over a large range of use scenarios. This consistency stems from the mechanism of aerosol formation and control over the loaded (coated) dose in the *Staccato* Loxapine product. The manufacturing spray coating process results in very tight control over the coated dose on each part. The mean coated dose values for each of the 10 mg *Staccato* Loxapine lots was within 0.1 mg of the target coated dose (10.0 mg) with relative standard deviations of <2%. In addition, the energy for producing and dispersing the aerosol particles comes from the heat source inside the device, and that amount of energy is independent of the user.

A comparison of emitted dose performance between the *Staccato* Loxapine product and other commercially available inhaler devices, over a range of inhalation flow rates, is depicted in Fig. 4 (individual aerosol samples). For comparison purposes, the emitted dose for *Staccato* Loxapine was calculated based on the historical mean emitted dose (9.1 mg). *Staccato* Loxapine product delivered 100–112% when tested over a 3-fold range of flow rates (15–45 L/min). The emitted dose of the *Staccato* Loxapine product increased very slightly with flow rate due to a small decrease in residual drug within the device itself. However, emitted dose would plateau at flow rates beyond 45 L/min since there is very little drug

Table 2
Emitted dose and device residual summary for pre-operating stress and different operating conditions.

Condition	Testing parameter	Average amount of drug (mg) ± 1 standard deviation		*N*
		Emitted dose	Device residual	
Pre-operating stress condition				
Photostability	12 h	9.2 ± 0.2	0.5 ± 0.2	3
	24 h	9.2 ± 0.1	0.5 ± 0.1	3
	74 h	9.2 ± 0.2	0.6 ± 0.1	3
Thermal cycling	1-cycle	9.4 ± 0.2	0.5 ± 0.0	3
	3-cycle	9.4 ± 0.0	0.5 ± 0.0	3
Mechanical robustness	Mech. shock	9.4 ± 0.4	0.5 ± 0.1	30
	Sinusoidal vib	9.5 ± 0.2	0.5 ± 0.1	30
	Random vib	9.4 ± 0.4	0.5 ± 0.1	30
	Drop in pouch	9.0 ± 0.4	0.6 ± 0.2	30
	Drop without pouch	8.9 ± 0.4	0.5 ± 0.1	30
Operating condition				
Flow rate	15 L/min	9.5 ± 0.2	0.8 ± 0.1	9
	28.3 L/min	9.7 ± 0.3	0.4 ± 0.2	9
	45 L/min	10.2 ± 0.1	0.3 ± 0.1	9
Temperature	15 °C	9.6 ± 0.3	0.5 ± 0.0	9
	25 °C	9.7 ± 0.3	0.4 ± 0.2	9
	30 °C	9.8 ± 0.1	0.5 ± 0.1	9
Relative humidity	15%RH	9.6 ± 0.1	0.5 ± 0.1	3
	50%RH	9.4 ± 0.1	0.6 ± 0.1	3
	90%RH	9.4 ± 0.2	0.6 ± 0.1	3
Altitude	8000 ft	9.2 ± 0.2	0.7 ± 0.0	6
Orientation use	Logo up	9.4 ± 0.1	0.6 ± 0.1	3
	Logo down	9.6 ± 0.3	0.5 ± 0.2	3
	Sideways	9.5 ± 0.2	0.6 ± 0.1	3
	Mouthpiece up	9.4 ± 0.3	0.4 ± 0.1	3
	Mouthpiece down	9.0 ± 0.4	0.7 ± 0.1	3

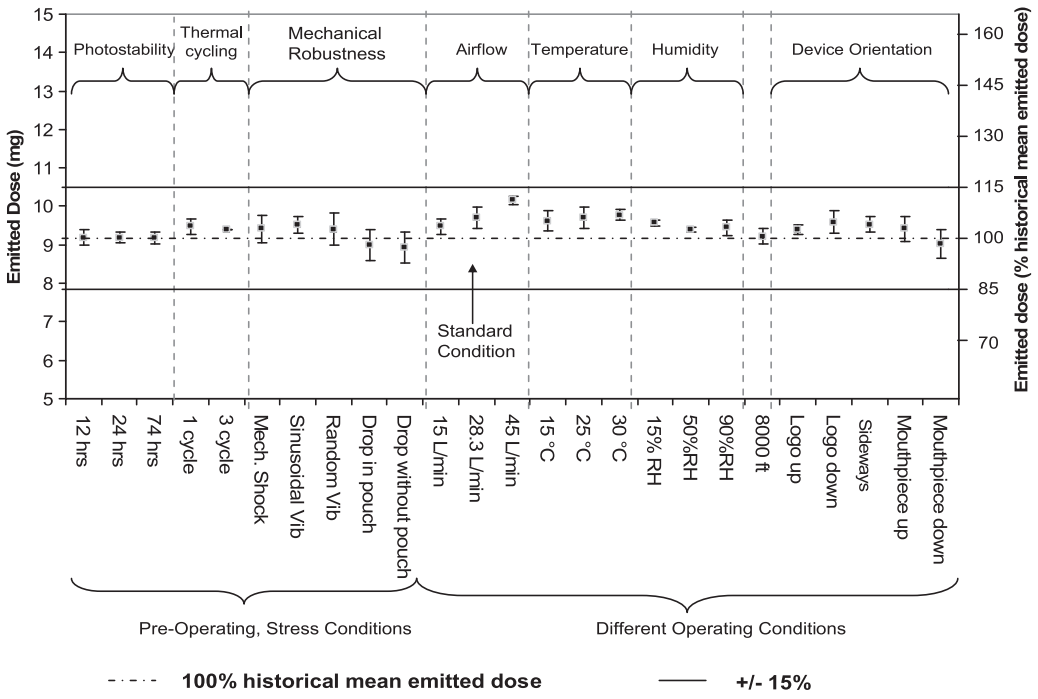

Fig. 3. Emitted dose summary for 10 mg *Staccato* Loxapine—pre-operating stress conditions and different operating conditions. Each data point is the average value of three or more tests and error bars represent ±1 standard deviation.

residual in the device at this condition, and the emitted dose cannot exceed the dose loaded onto the substrate (the coated dose). Compared to other inhaler technologies, the variability in emitted dose as a function of air flow rate from the *Staccato* Loxapine product is small.

Fig. 5 shows a comparison of emitted dose collected at different operating humidities for *Staccato* Loxapine and Exubera® (data taken from Harper et al., 2007). Over a wide range of humidities, the emitted dose delivered from *Staccato* Loxapine was more consistent than those from the Exubera DPI. In fact, Exubera's emitted dose is <90% of the label claim at 25 °C/75%RH or beyond. The Staccato aerosol stays within 5% of the historical mean up to the highest humidity tested at 25 °C, 90%RH, and does not show ambient temperature effects up to at least 40 °C (Fig. 3). Loxapine is not hygroscopic and no excipients are present, meaning there is nothing (such as lactose) which is likely to absorb water from the environment.

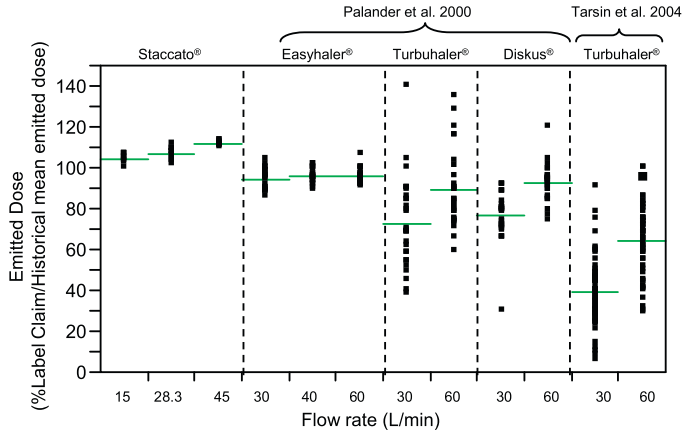

Fig. 4. Individual emitted dose data at various flow rates: a comparison between *Staccato* Loxapine and other inhaler devices (Palander et al., 2000; Tarsin et al., 2004). Literature data were interpolated from published figures. Horizontal lines indicate sample averages.

3.2. Particle size

The particle size results for the pre-operating stress conditions and different operating conditions are summarized in Table 3. The FPF (<6 μm) values ranged from 83 to 93% for all conditions and individual GSD values were between 2.0 and 2.3. The average MMAD values for the *Staccato* Loxapine product ranged from 1.9 to 2.2 μm for the pre-operating stress conditions, and from 2.0 to 2.4 μm for the different operating conditions with the exception of the flow rate which will be discussed subsequently.

The MMAD values are plotted in Fig. 6 in which the standard test condition is 30 L/min. MMAD values for all conditions are in the 2 μm range, which is in the middle of the ideal range for deep lung delivery (Hinds, 2nd ed. 1999). Furthermore, MMAD values for the pre-operating stress and non-standard use conditions are comparable to the standard test condition. These results suggest that exposures to light, temperature, or mechanical stresses prior to use have no effect on particle size diameter for the *Staccato* Loxapine product. Similarly, most use conditions (temperature, humidity,

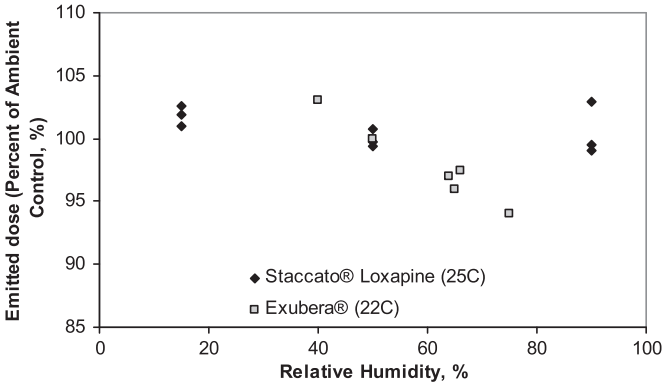

Fig. 5. Emitted dose versus ambient relative humidity near room temperature: a comparison between the present work and earlier published results for the Exubera® inhaler (Harper et al., 2007).

Table 3
Mass median aerodynamic diameter (MMAD) summary for pre-operating stress and different operating conditions.

Condition	Testing parameter	Average MMAD ± 1 standard deviation	*N*
Pre-operating stress condition			
Photostability	12 h	1.9 ± 0.0	3
	24 h	2.0 ± 0.1	3
	74 h	2.0 ± 0.1	3
Thermal cycling	1-cycle	2.2 ± 0.2	3
	3-cycle	1.9 ± 0.1	3
Mechanical robustness	Mech. shock	1.9 ± 0.1	9
	Sinusoidal vib	1.9 ± 0.1	9
	Random vib	1.9 ± 0.1	9
	Drop in pouch	2.0 ± 0.1	9
	Drop without pouch	2.1 ± 0.1	9
Operating condition			
Flow rate	15 L/min	2.8 ± 0.1	9
	30 L/min	2.1 ± 0.1	9
	45 L/min	1.7 ± 0.0	9
Temperature	15 °C	2.0 ± 0.1	9
	25 °C	2.1 ± 0.1	9
	30 °C	2.1 ± 0.0	9
Relative humidity	15% RH	2.2 ± 0.0	3
	50%RH	2.2 ± 0.1	3
	90%RH	2.2 ± 0.2	3
Altitude	8000 ft	2.4 ± 0.1	6
Orientation use	Logo up	2.1 ± 0.1	3
	Logo down	2.1 ± 0.1	3
	Sideways	2.0 ± 0.1	3
	Mouthpiece up	2.1 ± 0.1	3
	Mouthpiece down	2.1 ± 0.1	3

altitude, or device orientation) have negligible effect on particle size.

The one condition where there is a noticeable effect on particle size is airflow rate. Over the range of 15–45 L/min, the particle size decreases approximately as the square root of the flow rate. This decrease with increasing airflow is expected given the determinants of particle size in the thermal vaporization process (Rabinowitz et al., 2004). Once the drug molecules vaporize from the surface, they instantaneously condense and begin to aggregate into particles. The rate of aggregation depends on the particle number concentration, which is the number of particles per unit volume (of air). Thus increasing flow rate increases the volume of air diluting the vaporizing molecules, which in turn leads to less aggregation. Particle size theoretically varies inversely with the cubic root of flow rate (Rabinowitz et al., 2004), fairly close to the experimental values observed here.

In practice, the fact that particle size decreases with increasing airflow rate may very well be advantageous for the *Staccato* system. Recent *in vitro* experiments showed that this variation in particle size with flow rate resulted in low, constant oropharyngeal deposition of aerosol in a physical model representative of the upper

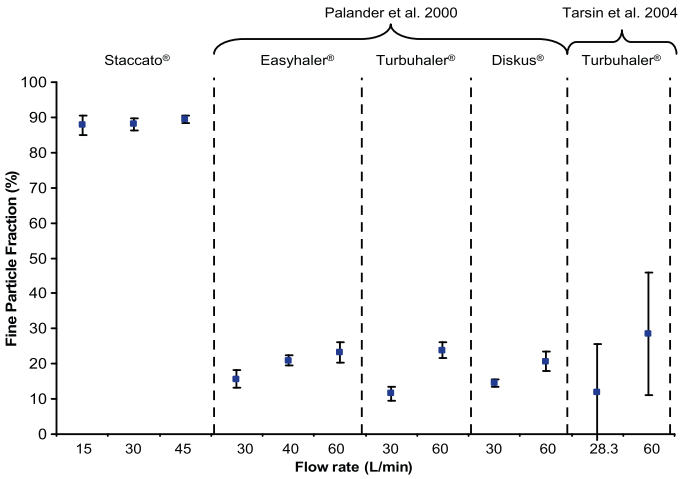

Fig. 7. Fine particle fraction results at various flow rates: a comparison between the present work and earlier published results (Palander et al., 2000, FPF/FPD (fine particle dose): 0–5 μm and Tarsin et al., 2004, FPD: 0–5.8 μm). Each data point represents the average value of three or more tests and error bars represent ±1 standard deviation.

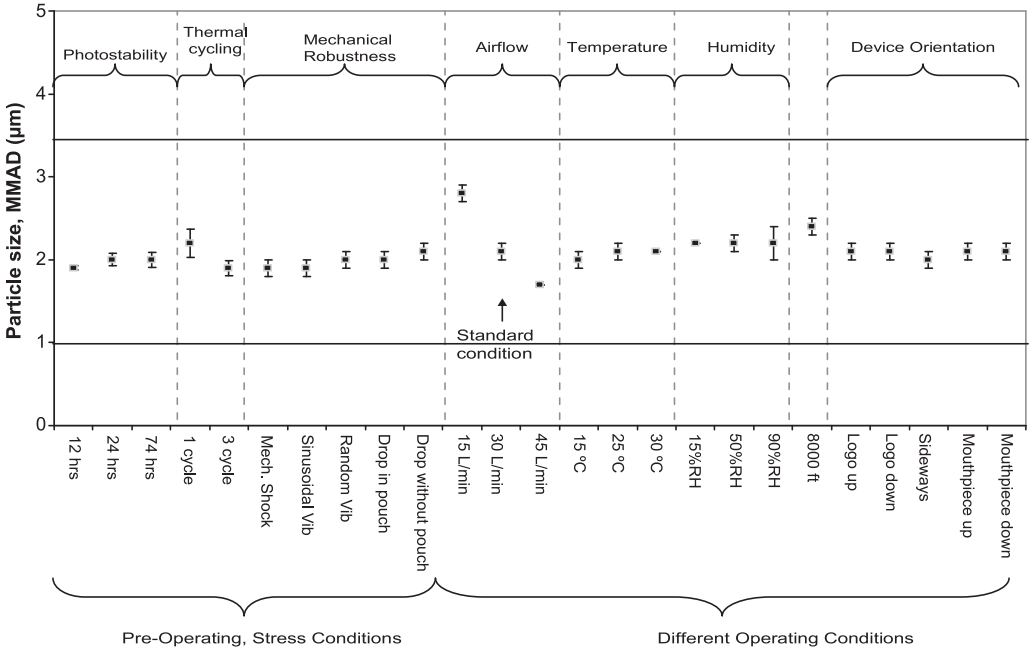

Fig. 6. MMAD results for 10 mg *Staccato* Loxapine. Each data point is the average value of three tests and error bars represent the standard deviation of the tests.

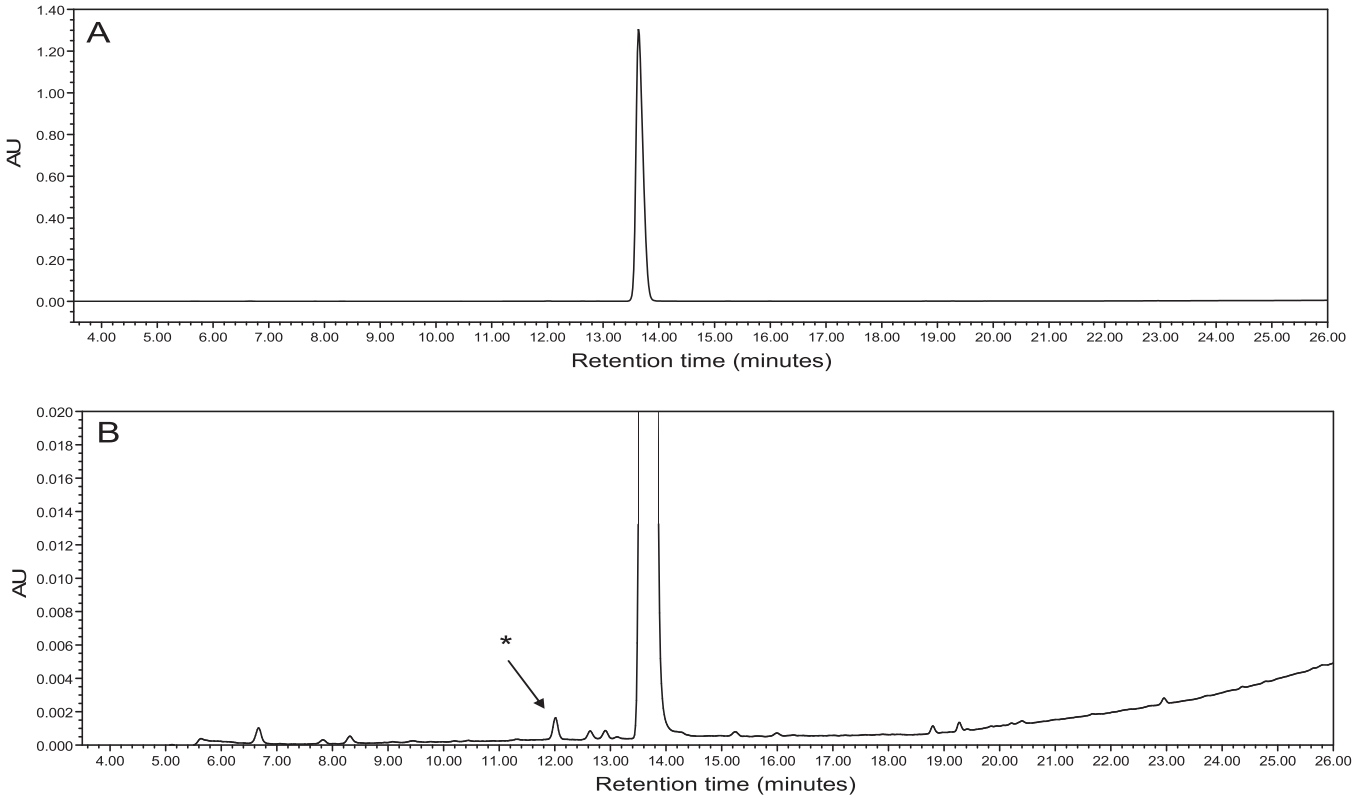

Fig. 8. HPLC chromatograms for aerosol purity. A: Full scale. B: Expanded scale. The peak marked with an asterisk is representative of a 0.05% impurity.

airway (Dinh et al., 2010). Other inhaler systems that produce a constant particle size versus flow rate would tend to exhibit increasing oropharyngeal deposition with increasing inhalation rate.

Fine particle fraction (FPF) is a standard measure used to estimate the portion of the emitted dose that would most likely reach the lungs. Fig. 7 depicts the fine particle fraction as a function of flow rate for *Staccato* Loxapine along with earlier published results for other inhaler devices. Across the tested flow rates ranging from 15 to 45 L/min, the FPF of the *Staccato* Loxapine product was consistently higher than other inhaler devices, by about 3-8X. The reliability in FPF of *Staccato* Loxapine from this study suggested that the portion of the emitted dose reaching the lungs would also be consistent. The findings here are in good agreement with those from previous *in vitro* results (Dinh et al., 2010).

3.3. Aerosol purity

Aerosol purity was characterized for pre-operating stress as well as various operating conditions. Loxapine aerosol was >99.5% pure for all test conditions. No significant trends were observed for the various use and pre-operating stress conditions. Per ICH guidance Q3B(R2), no impurities above the reportable level (0.1%) were detected for any test conditions. Fig. 8 shows a chromatogram from a typical aerosol sample.

4. Conclusions

Product characterization experiments on the *Staccato* Loxapine drug product show consistent performance for emitted dose, aerosol purity, and particle size distribution over a wide range of scenarios. Exposures of the device to various stresses (mechanical shock, drop, and vibration, thermal cycling, and light exposure) prior to actuation did not alter performance. Likewise, use of the product at different settings (flow rates, ambient temperature and humidity, altitude, and orientation) showed excellent consistency. The only parameter showing a significant effect was particle size as a function of flow rate, in line with theoretical considerations of particle aggregation in condensation aerosols. Experiments simulating extrathoracic deposition show this result is actually beneficial for ensuring consistent drug delivery to the lungs (Dinh et al., 2010). In comparison to a number of commercially available inhaler systems, the *Staccato* Loxapine system performed better and more consistently over a broad range of operating settings and pre-use stress conditioning. The results highlight the robust aerosol properties of the new *Staccato* system technology with respect to different use scenarios.

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