

Patient-Centred Performance Testing of a Dry Powder Spacer: A Pilot Study Using Inhalation Profiles from Healthy Volunteers to Assess Drug Delivery Performance

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Summary

The use of inhalation profiles for testing the realistic aerosolization of the emitted dose from inhalers has been reported. High inter-patient and inter-device variability in the inhalation parameters of patients has been previously identified. The aim of this study was to employ a patient-centred pharmaceutical characterisation approach to assess the performance of a cyclone spacer for a Cyclohaler through collecting and ranking (as percentiles of the peak inspiratory flow (PIF) populations) the inhalation profiles of human volunteers through the spacer; and subsequently performing *in vitro* testing using an inhalation simulator. The aerosolization of cohesively- and adhesively-balanced blends was compared using full inhalation profiles and the peak inspiratory flow. However, the steady flow was an inadequate metric to assess inter-subject variability in fine particle delivery from a dry powder inhaler (e.g. for salmeterol xinafoate (SX) the throat deposition was $27.89 \pm 3.32\%$ at 25% and $25.45 \pm 3.08\%$ at 90%, respectively). A lower fine particle fraction (FPF) calculated as inhaler-emitted dose was measured for SX blends compared to salbutamol sulphate (SS) blends (e.g. at median PIF $19.23 \pm 3.93\%$ versus $14.61 \pm 2.38\%$), due to the higher throat deposition of SX. However, when using the inhalation profiles, higher doses of SX were emitted from the cyclone than SS. The current study showed the potential use of spirometer technology to collect inhalation profiles for patient-centred device testing. A full assessment of new (or generic) device functionality requires simulation of real-life inhalation conditions.

Introduction

For quality purpose [1] aerosol deposition from an inhaler needs to be tested at a constant flow. However, it does not represent the actual dose of drug that a patient would inhale, as patients do not inhale with a constant flow. It has been reported [2] that the inhalation manoeuvres of a patient consist of an initial acceleration, when the dose is usually delivered [3], a maximum peak inspiratory flow (PIF) that is the maximum flow that the patient achieves, and a deceleration of the flow, that indicates the manoeuvre is terminated. Studies showed that patients are able to maintain the PIF for longer when the resistance of the device is high [2, 4] rather than when the resistance is low. Also, the dose is released rapidly for devices such as Diskus and Turbuhaler, although the dose emitted from capsule-containing devices such as the Cyclohaler is released over a longer period of time [5]. It has been shown that the powder emptying rate from inhalers appears to increase when the acceleration slope increases [6]. The electronic lung device (ELD) has been used [2, 3, 7] in order to determine the aerosol deposition using both inhalation profiles and steady flow. The dose dispersion from the inhaler is driven by the patients' profiles that can be loaded into the ELD, whilst the steady flow allows the particle size determination into the impactor [7]. Some authors [8] have attempted to predict the slope of the inhalation pressure profiles using the PIFs through inhalers. Correlation was seen between PIF and pressure slopes for Turbuhaler and Diskus [4].

Previous work has shown tremendous inter-patient and inter-device variability in the inhalation parameters of human subjects through dry powder inhalers (DPIs) [2, 9] which dramatically affect the respirable mass delivered to patients. In our previous work [10] we demonstrated that the use of prototype of a reverse flow cyclone spacer for DPIs decreased the flow rate dependency of the respirable fraction and of the mass median aerodynamic diameter (MMAD) of the emitted dose [10]. The aim of the current work was to employ a patient-centred pharmaceutical characterisation approach to assess the performance of the spacer. Specifically inhalation profiles of human volunteers through the cyclone were collected. The profiles were then employed *in vitro* using an inhalation simulator to compare the aerosol deposition of representative DPI formulations, comparing both the impact of PIF and full inhalation profiling, to characterise the spacer performance.

Methods

An internal ethical approval from the University of Hertfordshire (number PHAEC/12-77) was obtained in order to assess inhalation profiles of 10 healthy subjects (screened for full demographic and health status information) through a cyclone-spacer prototype (Cheng 2) using the Vitalograph Pneumotrac spirometer. The cyclone-spacer was assessed alone as the resistance of the Cyclohaler was found not to affect the spacer. The effect of resistance of marketed DPIs was previously assessed on the spacer resulting in unchanged resistance of the spacer when inhalers were combined (data not shown). All patients completed a full lung function test as part of the protocol. The

participants then inhaled through the Cheng 2 (Engineering & Design Plastics, Cambridge, UK) attached to the spirometer in order to obtain inhalation profile, IV (inhaled volume) and PIF (peak inspiratory flow). Participants were permitted to practice an inhalation manoeuvre under training prior to the recorded inhalation.

The aerosolization of salbutamol sulphate: fine lactose: coarse lactose (SS:FL:CL) and salmeterol xinafoate: fine lactose: coarse lactose (SX:FL:CL) formulations through the cyclone spacer from a Cyclohaler® device was assessed using the Next Generation Impactor (NGI) with a model HCP5 vacuum pump and the Alberta idealized adult throat (all from Copley Scientific Ltd., Nottingham, UK). The performance was tested using the PIFs through the Cheng 2 of the healthy population at the 10%, 25%, 50%, 75% and 90% percentile values. The duration of the PIF was the time the volunteer feels comfortable during inhalation manoeuvre. The corresponding inhalation profiles from the healthy volunteers through the Cheng 2 from which the PIFs were identified were uploaded to the Breath Simulator 3000 (Copley, Nottingham, UK). The Cyclohaler®-cyclone combination was tested with SS:FL:CL and SX:FL:CL using eight gelatine capsules (Meadow Lab, UK) for each performed NGI analysis. Drug deposition within the impactor was determined using our previously validated and reported HPLC methods [10]. Statistical analysis was performed in Minitab using one-way ANOVA and post-hoc Tukey's test (multiple comparisons) or Student's two-tailed t-test for pairwise comparisons, both at 95 % confidence intervals.

Results and Discussion

All the volunteers who took part in the study were healthy as per the full lung function test result (Table 1). Moreover, a wide range of PIFs were achieved when the volunteers inhaled through Cheng 2. The PIFs derived from the cumulative distribution were as follows: 52.8 L min⁻¹ (10% percentile), 65.6 L min⁻¹ (25%), 72.7 L min⁻¹ (median), 79.9 L min⁻¹ (75%) and 89.1 L min⁻¹ (90%). In Figure 1 representative inhalation profiles through the Cheng 2 are shown.

Table 1. Table of Parameters Used to Define Healthy Volunteers (FEV₁= Forced Expiratory Volume in 1 sec; PEF = Peak Expiratory Flow, SVC = Slow Vital Capacity)

Females	5
Males	5
Smokers	0
FEV₁ % predicted	104.14 ± 8.51
PEF % predicted	103.87 ± 9.15
SVC	4.43 ± 0.865

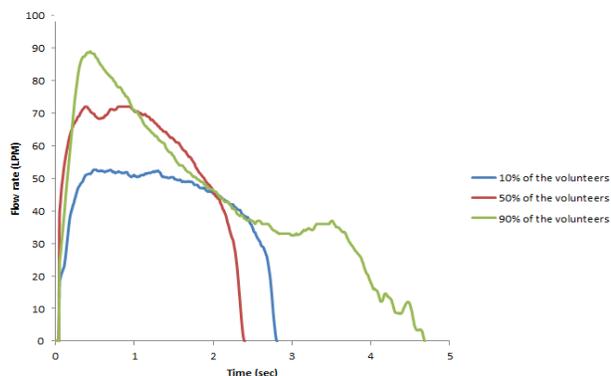


Figure 1. Representative Inhalation Profiles of Healthy Volunteers Through a Cheng 2 Spacer-Device.

Aerosolization studies of SX:FL:CL and SS:FL:CL were performed using the NGI with the idealized throat at the PIF of the 10-90% of the population. The Cyclohaler was used in series with the Cheng 2 and the recovery was within pharmacoepoel limits for both drugs at each flow rate (e.g. 75.16 ± 0.34% – 76.34 ± 2.04 for SS:FL:CL and 77.57 ± 2.44 % - 76.25 ± 1.29 % for SX:FL:CL% between 10-90% of the PIFs). The particle size distribution (PSD) in the current study, differed between the inhalation profiles and PIF (e.g. compare the ranking of the 90% (green) and 75% (pink) distributions in, Figures 2 and 3) for both SS:FL:CL and SX:FL:CL. It had been suggested [8] that the particle size of an aerosol is unchanged between a constant flow and an inhalation profile provided the constant flow rate approximates the PIF achieved in the profile. From this work it is evident that the PIF was not an adequate metric to assess inter-subject variability in fine particle delivery from a dry powder inhaler. For example the throat deposition for SX blends was similar for all the PIFs tested (e.g. 27.89 ± 3.32% at 25% and 25.45 ± 3.08% at 90%).

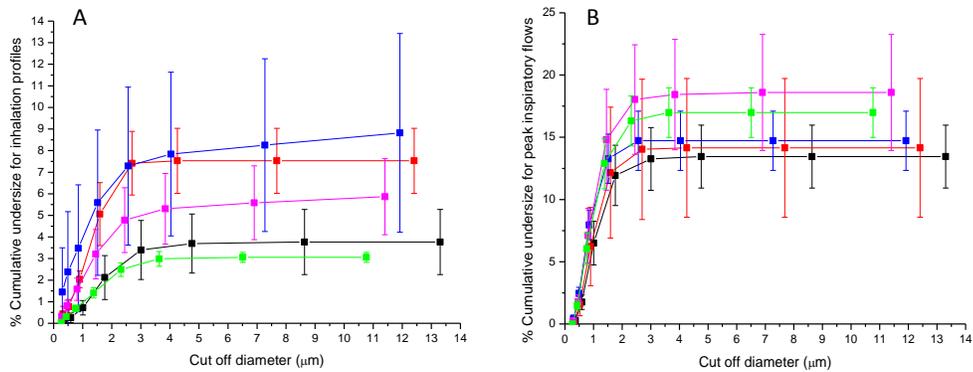


Figure 2. Cumulative Aerodynamic Undersize (%) of SS:FL:CL of Emitted Dose from the Cyclohaler with the Cheng 2 in Place at Inhalation Profiles (A, Black: 10%, Red: 25%, Blue: 50%, Pink: 75%, Green: 90%) and at Peak Inspiratory Flow (B, Black: 10%, Red: 25%, Blue: 50%, Pink: 75%, Green: 90%) (mean \pm SD, n=4)

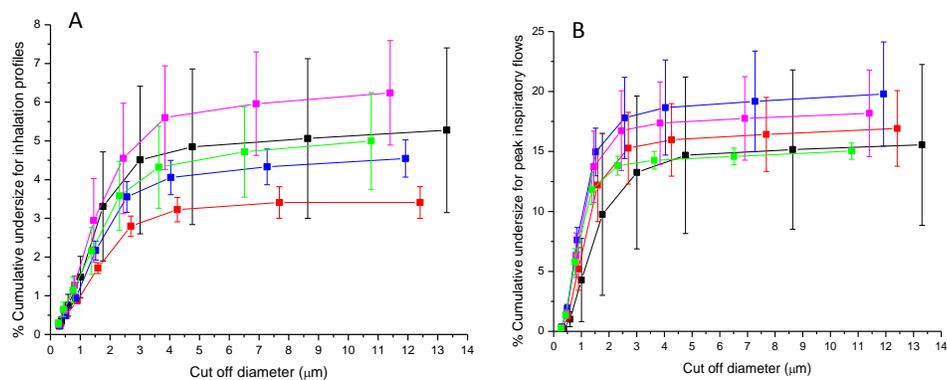


Figure 3. Cumulative Aerodynamic Undersize (%) of SX:FL:CL of Emitted D from Cyclohaler with the Cheng 2 in Place at Inhalation Profiles (A, Black: 10%, Red: 25%, Blue: 50%, Pink: 75%, Green: 90%) and at Peak Inspiratory Flow (B, Black: 10%, Red: 25%, Blue: 50%, Pink: 75%, Green: 90%) (mean \pm SD, n=4)

Interestingly, when employing PIFs a lower FPF (%sED) [10] was observed ($p < 0.05$) for SX:FL:CL (e.g. $72.39 \pm 3.92\%$ at 50% PIF) than SS:FL:CL (e.g. $99.97 \pm 0.08\%$ at 50% PIF). This is due to a higher Throat/PS (PS = pre-separator) deposition for SX formulation (e.g. $21.66 \pm 3.02\%$ at 10%) than SS where Throat/PS deposition was not detectable at any flow rate tested. The emission of SX from the spacer was higher than the SS formulation when inhalation profiles were used ($20.89 \pm 4.04\%$ vs. $10.66 \pm 1.52\%$ for the 50% PIF profile, respectively, $p < 0.05$). However, for both formulations, the % emission was dramatically reduced compared to when PIF were used instead. This could also explain the difference in the PSD in Figure 2 and 3. We have shown previously that aerosolization of SS from the adhesive blends is dominated by impaction events in the cyclone unlike cohesively-balanced blends of SX [12]. The contrasting behaviour for SS and SX when comparing PIF to inhalation profiles presumably occurs as, during the inhalation profiles, the steady flow is not present. Instead, due to the acceleration and deceleration it is hypothesized that lower force is applied to aerosolize the particles.

SX formulations showed a slightly higher FPD (the dose respirable by patients (Figure 4, A)) compared to SS:FL:CL when the inhalation profiles were used or at low values of PIF. Clearly, the physico-chemical properties of the APIs affect the deagglomeration mechanism inside the Cheng 2. Furthermore, using a constant flow (e.g. PIF) would lead to a constant energy involved in the aerosolization of the particles, whilst, when employing a flow rate loop (e.g. inhalation profiles) the flow is not constant, as acceleration and deceleration are present. This would lead to decreased values of FPD when inhalation profiles are used. The Cheng 2 showed relatively consistent MMADs but variable FPDs, especially at low flow rates (Figure 4, A and B). This could be due to poorer efficiency of emptying of the capsule.

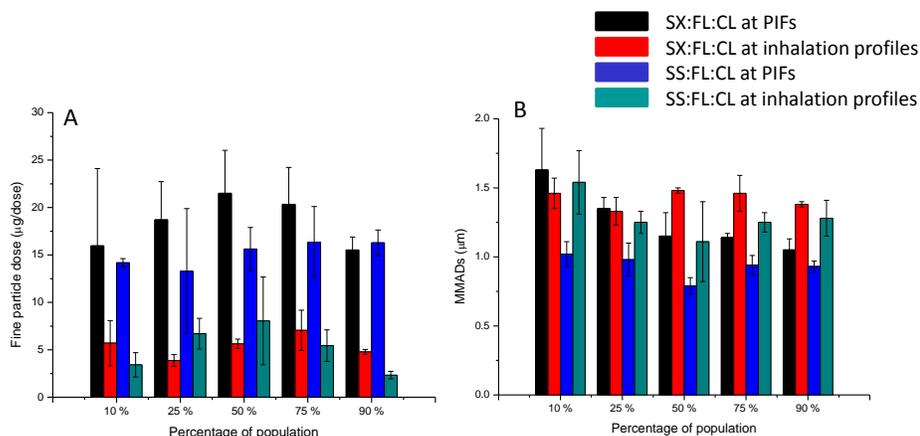


Figure 4. (A) Fine Particle Dose < 5 μm (FPD_{5μm}); and (B) Mass Median Aerodynamic Diameter (MMAD) of Salbutamol Sulphate (SS) and Salmeterol Xinafoate (SX) Formulation with Fine Lactose (FL) and Coarse Lactose (CL) Emitted From the Cyclohaler in Sequence with the Cheng 2 at the Peak Inspiratory Flow (PIF) and Inhalation Profiles (IP) of the % of the Population (mean ± SD, n = 4)

Conclusions

The pilot study showed a potential use of a spirometer technology to collect inhalation profiles to be employed in patient-centred device testing. The cyclone spacer was shown previously to mitigate the flow rate dependency of emitted dose and particle size for a number of formulations using square-wave flow profiles. In this work we have shown that full assessment of spacer functionality requires simulation of real-life inhalation conditions. The crucial dependence of drug delivery performance on physico-chemical properties of the formulation (e.g. cohesive vs. adhesive balance) was revealed by the mismatch between fine particle delivery when peak inspiratory flows were tested compared to the profiles of the real patient, as acceleration and inhaled volumes are parameters to consider. The observation that, by using the cyclone spacer, the variability in the aerodynamic diameter and fine particle delivery are consistently minimized alongside the reduction in throat deposition, represent highly positive finding of relevance to patient therapy.

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