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ORIGINAL ARTICLES

Inspiratory Efforts Achieved in Use of the Technosphere® Insulin Inhalation System

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Abstract

Objective:

The Technosphere® Insulin (TI) inhalation system comprises TI powder premetered into unit dose cartridges and the patient-friendly, reusable, breath-powered MedTone® inhaler. This high-resistance system uses a patient's inspiratory effort to effect TI powder de-agglomeration and promote subsequent deep-lung delivery. This study reports on flow and pressure data achieved by patients with diabetes using the MedTone system.

Method:

MedTone inhalers containing empty cartridges were adapted with pneumotach measuring devices to capture inhalation profiles. The measuring apparatuses had negligible impact on the nominal MedTone system resistance level of 0.117 $kPa^{0.5}$/liters/min. Each of 56 subjects inhaled twice to mimic TI clinical study dosing instructions.

Achieved inhalation profiles were characterized by peak inspiratory flow (PIF), peak inspiratory pressure (PIP), and average pressure drop from the time of PIP to 4 s (P_{avg}).

Results:

The achieved mean PIF (± standard deviation [SD]) in all subjects was 26.74 (±6.06) liters/min after the first inhalation and was similar to the mean PIF of 26.25 (±6.23) liters/min achieved after the second inhalation. Mean PIP (±SD) achieved by subjects was 8.49 (±2.86) and 8.1 (±2.99) kPa, and mean P_{avg} drop (±SD) in all subjects was 6.53 (±2.24) and 6.09 (±2.08) kPa after the respective inhalations.

Conclusion:

Patients with diabetes demonstrated consistent inhalation efforts over two inhalations using the MedTone system. The achieved PIFs and PIPs demonstrate the capacity of this population to obtain sufficient inspiratory effort necessary for delivery of TI using the MedTone inhaler. Adequate postpeak pressures were also revealed, further supporting reliable and sustained inhalation efforts.

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Abbreviations: (NHANES III) National Health and Nutrition Examination Survey, (P_{avg}) average pressure, (PIF) peak inspiratory flow, (PIP) peak inspiratory pressure, (SD) standard deviation, (TI) Technosphere Insulin

Keywords: diabetes, inhalation effort, inhaled insulin, inhaler, Technosphere Insulin

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Introduction

Meeting guideline hemoglobin A1c levels remains a major challenge for patients with diabetes on insulin therapy, especially as subcutaneous injection remains the primary mode of insulin delivery. Published studies have demonstrated the safety and efficacy of insulin administered via the pulmonary route in subjects with type 2 diabetes,[1,2] paving the way for alternative delivery approaches aimed at replicating the physiological insulin secretion, improving glycemic control, and also potentially increasing patient compliance.

Inhalation of pharmaceutical agents into the conducting airways for local lung diseases like asthma and chronic obstructive pulmonary disease is well established. However, in systemic disease like diabetes, the drug is delivered into the lungs for its systemic activity and not the local effect. Therefore, the drug deposition needs to be targeted in the deep lung, where a thin alveolar-capillary membrane and large surface area allow rapid absorption into the pulmonary circulation and ultimately the systemic circulation.

Medical devices known as inhalers play a crucial role in the efficiency of pulmonary drug delivery. They interface with patients by acting as the conduit for drug delivery, performing numerous functions, including containment, protection, dispersion, and de-agglomeration, all necessary for directing the medicament to appropriate target tissues. When deep-lung absorption is desired, aerodynamic particle size and velocity of the drug entering the patient are of primary concern. Large aerodynamic size with excessive speed creates momentum that hinders particle navigation in the airways. Therefore, the air flow through the device or into the patient must be carefully considered to maximize the pharmaceutical agent's delivery.

Inhalers generally fall into one of three categories: metered dose inhalers, fine particle cloud inhalers, and breath-powered inhalers. Metered dose inhalers contain a liquid drug in a sealed canister and a propellant to expel the medicament upon actuation of a valve. Patients must simultaneously coordinate depression of the valve with execution of an inhalation maneuver. Fine particle cloud inhalers, such as nebulizers, generate a cloud or mist that a patient can inhale during normal respiration. These are employed generally with children, where the execution of multiple instruction sets cannot be relied on. Breath-powered inhalers rely on the patient's forced inspiration to entrain drug particles in an air stream. Advantages and disadvantages exist within each category, but all three methods have been successfully employed for the delivery of medicaments to patients worldwide.

Most types of breath-powered inhalers rely on a subject's inspiratory effort working in concert with the device resistance to generate a flow of air through the device. These two factors, patient-supplied inspiratory effort and inhaler-supplied flow resistance, together yield a flow rate of air as described by the Bernoulli principle.[3] **Equation (1)** is a reduction of this principle, relating flow, pressure, and resistance in a manner analogous to the way Ohm's law relates voltage, current, and resistance in an electrical circuit:

$$\sqrt{\Delta P} = \Phi * R \quad (1)$$

where ΔP is the supplied pressure drop in kPa, Φ is the flow rate in liters/min, and R is the system resistance in $kPa^{0.5}$/liter/min.

The MedTone® inhaler (Mannkind Corp., Valencia, CA) is a breath-powered inhaler system being developed for treatment of diabetes with Technosphere® Insulin (TI). Published study results support safe and efficacious administration of TI delivered to the pulmonary tract for treating patients with diabetes.[4–10] Food and Drug Administration approval is currently being sought. The system consists of two elements: a pocket-sized, breath-powered, high-resistance, reusable MedTone inhaler and a disposable cartridge containing premetered doses of TI inhalation powder. **Figure 1** displays the system elements and their use.

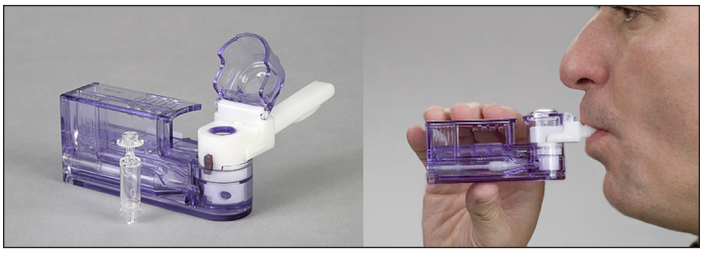

Figure 1. MedTone system.

Technosphere Insulin is a new inhalable insulin with a unique pharmacokinetic profile compared with all currently available insulins. Previous studies have

demonstrated that TI is rapidly absorbed (within 15 min), has a fast onset of action (approximately 25–30 min), and has a short duration of action (approximately 2–3 h).[11,12] Technosphere Insulin with an action profile that closely mimics physiologic meal-related endogenous insulin response has a potential to reduce postprandial blood glucose excursions with fewer occurrences of hypoglycemia while still effectively lowering hemoglobin A1c in subjects with diabetes mellitus.

Unlike other breath-powered inhalers, it exhibits high resistance to air flow as a means to control the balance between maximizing de-agglomeration of the inhalation powder into preferred aerodynamic sizes while minimizing overall particle velocity. It is hypothesized that a diverse population of patients can realize consistent peak inspiratory flows (PIFs, occurring in the first 2 s), peak inspiratory pressures (PIPs, occurring in the first 2 s), and average pressure (P_{avg}) from the time of PIP to 4 s—all key variables believed to be necessary for a successful administration of TI inhalation powder with the high-resistance MedTone inhaler.

Results of a clinical trial conducted on subjects in a TI treatment regimen using the MedTone inhaler and a flow-monitoring system are reported.

Materials and Methods

Eighteen to eighty-year-old male and female subjects with type 1 or type 2 diabetes randomized and receiving TI for at least 3 months or longer in an ongoing TI clinical trial were recruited for participation in the trial. Key inclusion criteria in the ongoing trials included males or females ≥18 and ≤80 years of age with the diagnosis of type 1 or type 2 diabetes, nonsmokers for prior 6 months (includes cigarettes, cigars, and pipes), urine cotinine test ≤100 ng/ml, and acceptable pulmonary function tests [forced expiratory volume in 1 s > 70% National Health and Nutrition Examination Survey (NHANES) III predicted, forced vital capacity > 70% NHANES III predicted, total lung capacity 80% predicted, and carbon monoxide diffusing capacity > 70% predicted[13]]. Written informed consent was obtained for all patients prior to participation in the study. Institutional review board and independent ethics committees for all participating centers provided study approval.

Method

MedTone inhalers containing empty cartridges (i.e., no TI dose) were adapted with pneumotach measuring systems (4700 series pneumotachs with series 1110 amplifier, Hans Rudolph, Inc., Kansas City, MO) to capture inhalation profiles. **Figures 2** and **3** provide images of the equipment. A breathing filter was installed in line between the pneumotach and the MedTone system to ensure turbulent flow effects on measurement accuracy were minimized. Assessment of these measuring apparatuses demonstrated a negligible impact on the nominal MedTone system resistance of 0.117 $kPa^{0.5}$/liter/min.

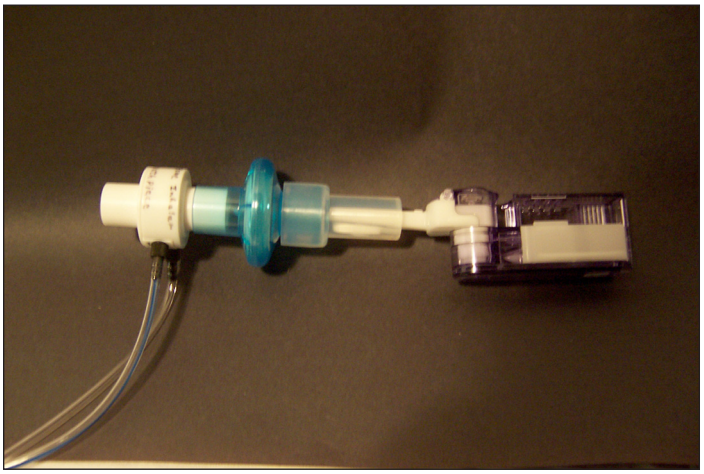

Figure 2. Inhaler setup. Disposable mouthpiece not shown.

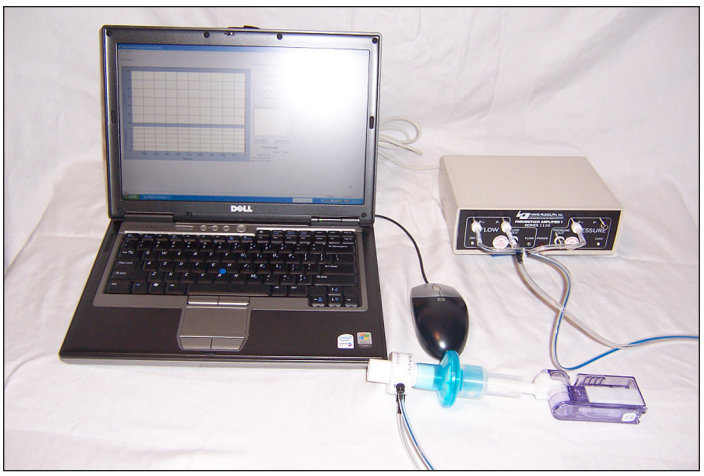

Figure 3. Study system hardware.

Both pressure and flow data were captured every 0.002 s for the duration of the inhalation maneuvers. All data were recorded using a customized Visual Basic (Microsoft, Inc., Redmond, WA) data acquisition program and a laptop (see **Figure 3**).

Prior to data collection, the subjects were given a verbal refresher on the instructions to "breathe in fast and hard for 5–8 s" included as part of the TI therapy initiation and provided in the user's manual for enrolled patients.

Each of the 56 subjects was instructed to inhale two times to mimic TI clinical study protocol dosing instructions. To compare subjects, all profiles were characterized for PIF within the first 2 s of the inhalation, PIP within the first 2 s, and P_{avg} from point of PIP to 4 s.

Results

As shown in **Table 1**, 56 subjects (42 male and 14 female) with type 1 or type 2 diabetes with the mean age of 52.07 years (standard deviation [SD] ±12 years) participated.

A sample inhalation profile (pressure versus time) collected with the study equipment, identifying the preferred pressure characteristics, is shown in **Figure 4**. A similar profile of flow rate versus time is generated by the system but is not shown here.

During use, TI discharge from the delivery system generally occurs within the first second of the inhalation maneuver followed by a wash period free of the TI inhalation powder. **Figure 5** displays the delivery system action overlaid onto a set of sequential inhalation efforts.

The results are summarized in **Table 2**. The first two columns show the average results for the first two inhalations and their SDs. The third column shows the average difference between the two inhalations and the SD of the differences. The average difference between inhalations is small compared to the magnitude for each inhalation. This shows there is little difference between inhalations on average. The SD of those differences is small when compared to the magnitude for each inhalation (fourth column), as is the intrasubject coefficient of variation (fifth column), showing there is little difference between inhalations for each patient.

Figures 6, **7**, and **8** show box plots and Bland-Altman plots[14] for the three measurands. The red line and shaded bands on the Bland-Altman plots represent the 95% confidence limits on the mean difference between the second and first inspiration parameter across all patients. For each parameter, the band's proximity to zero difference indicates that the mean difference between inhalations was small. Moreover, the vertical range of the data is near zero and much narrower than the horizontal range, clearly demonstrating the intrasubject repeatability of the two maneuvers.

Table 1.
Subject Demographics

Demographic Characteristic	
Gender, *n* (%)	
Male	42 (75.0)
Female	14 (25.0)
Age (years)	
N	56
Mean (SD)	52.07 (12.31)
Median	52.5
Range	(23–77)
Age groups (years)	
18–30	3 (5.4)
31–49	19 (33.9)
50–64	25 (44.6)
65+	9 (16.1)
Diabetes Type, *n* (%)	
Type 1	17 (30.4)
Type 2	39 (69.6)

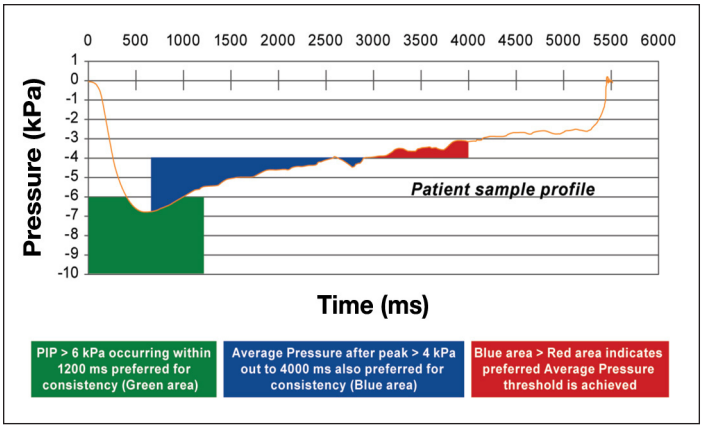

Figure 4. Pressure versus time in a single inhalation profile.

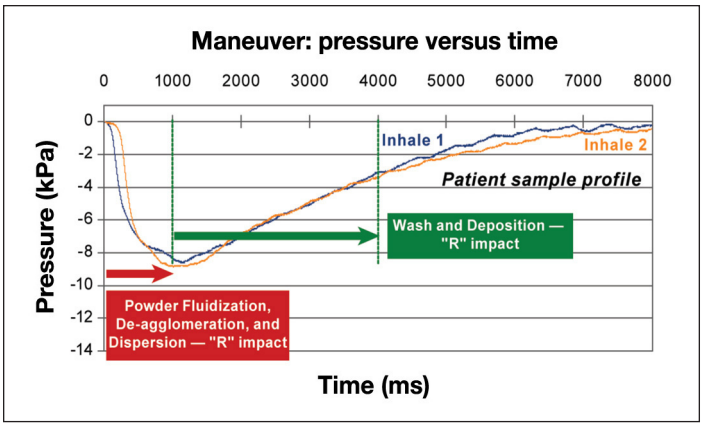

Figure 5. Two inhalation pressure profiles overlaid with powder action. *R*, flow resistance.

None of the Bland-Altman plots had statistically significant slopes ($p > .26$); therefore, 95% confidence intervals for the mean differences between inhalation 1 and inhalation 2 were calculated. The differences between the first and second inhalation averaged -0.50 ± 0.66 liters/min for PIF, -0.39 ± 0.27 kPa for PIP, and -0.41 ± 0.21 kPa for P_{avg}

Table 2.
Results for the First and Second Inhalation Efforts[a]

	First inhalation	Second inhalation	Difference (second–first inhalation)	SD of differences / average over both inhalations	Intrasubject coefficient of variation
Mean PIF (±SD) liters/min	26.74 (6.06)	26.25 (6.23)	-0.50 (2.46)	0.09	0.07
Mean PIP (±SD) kPa	8.49 (2.86)	8.10 (2.99)	-0.39 (1.00)	0.12	0.09
Mean P_{avg} (±SD) kPa	6.53 (2.24)	6.09 (2.08)	-0.41 (0.78)	0.12	0.10

[a] The intrasubject SD was computed by averaging the variances of the two inhalations of each subject and then taking the square root. The coefficient of variation was computed as the ratio of the SD to the overall mean.

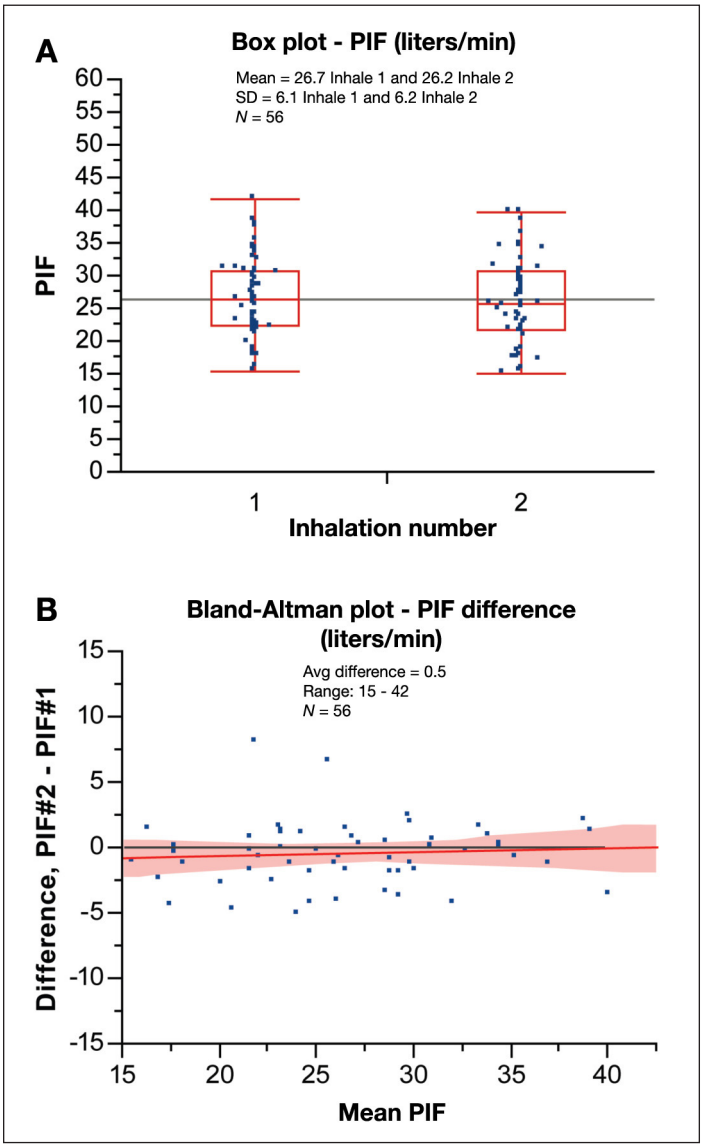

Figure 6. (A) Box plot for PIF. **(B)** Bland-Altman plot for PIF.

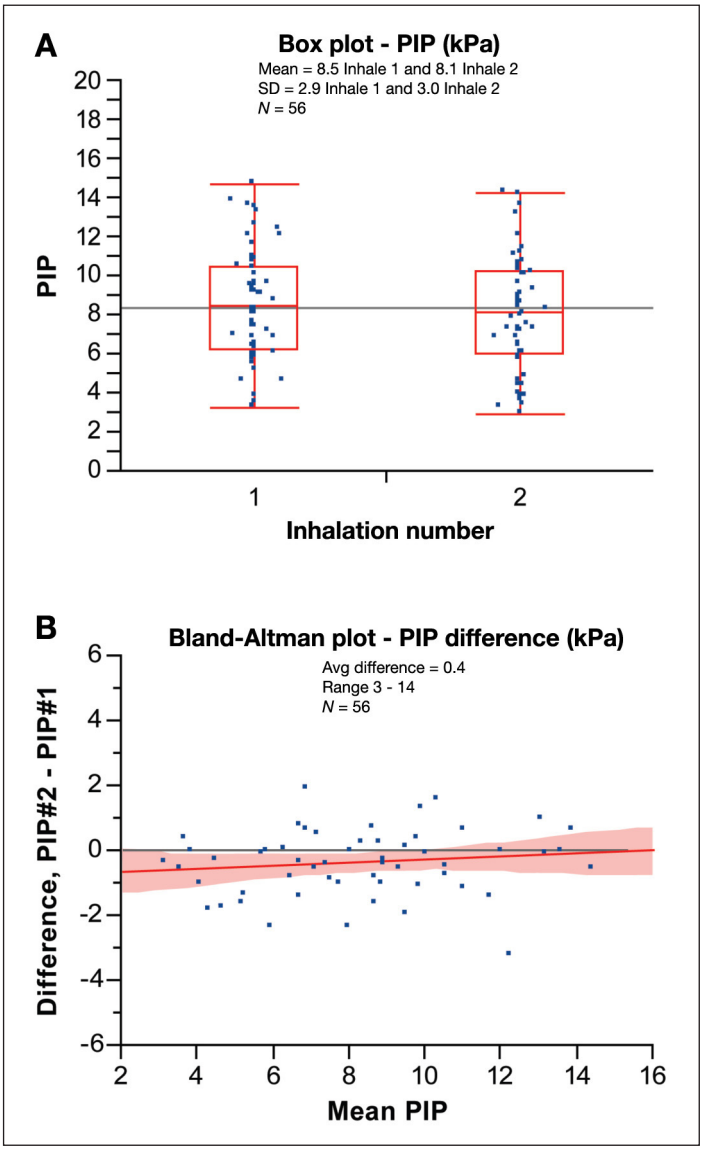

Figure 7. (A) Box plot for PIP. **(B)** Bland-Altman plot for PIP.

(95% confidence intervals). The confidence intervals of the latter two differences do not include zero, so they are *statistically* significant, but the small magnitude of those differences make it clear that their statistical significance is merely the result of very reproducible data. More importantly, the small magnitude of the mean differences and the small magnitude of the observed differences on the Bland-Altman plots clearly demonstrate the intrasubject repeatability of the sequential inhalation maneuvers.

Discussion

The principal function of the MedTone inhaler during TI delivery is to harness and direct a patient's inhalation effort by employing a level of resistance to throttle air flow. This level is characteristic of the internal flow path, orifices, and geometries of the system necessary for dispersion and de-agglomeration of the cartridge contents. The interaction of the inhaler and cartridge elements is simplified graphically in **Figure 9**, showing how air flow moves around the outside of the cartridge while a portion travels through. The cartridge contents are lifted and entrained with air entering the lower inlet port and then de-agglomerated at the upper exit port. Here, the escaping content is recombined with the air moving around the outside of the cartridge before traveling into the subject's airways.

As pressure is supplied during the inhalation maneuver, the magnitudes of flow streamlines shown in **Figure 9** are a result of the system resistance. With increasing energy or pressure applied across the system, a resulting increase in flow lifts and de-agglomerates the TI inhalation powder into particles of appropriate aerodynamic sizes necessary for pulmonary deposition. **Figure 10** is a plot of pressure and resulting flow data points collected experimentally with the MedTone system (inhaler and empty cartridge). The slope of the experimental line is the system resistance value and is best predicted by **Equation (1)** in the region highlighted.

From *in vitro* predictive deposition testing using industry standard cascade impaction and geometric particle sizing methodologies, the threshold PIP for optimal MedTone inhaler performance is approximately 4–6 kPa (or approximately 22 liters/min), achieved within 1200 ms. Below this pressure, resulting air flows that de-agglomerate the TI inhalation powder become less efficient and the particle sizes of the discharged powder increases. Conversely, pressures in excess of this threshold result in diminishing reductions of the

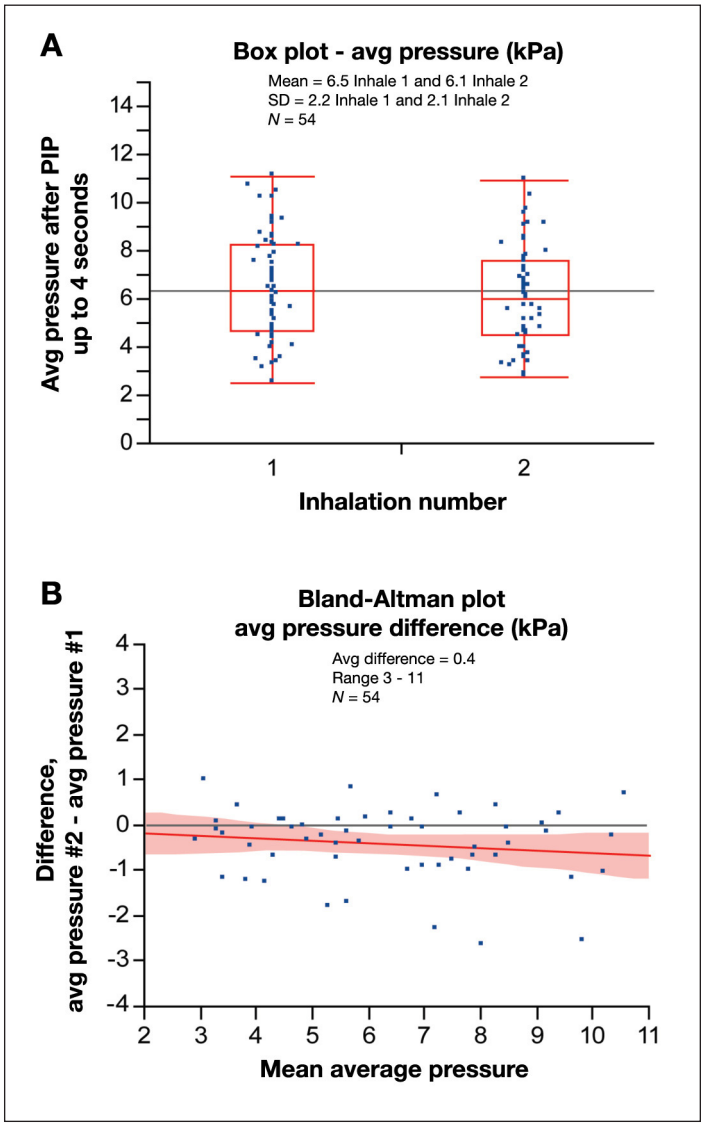

Figure 8. (A) Box plot for P_{avg}. **(B)** Bland-Altman Plot for P_{avg}.

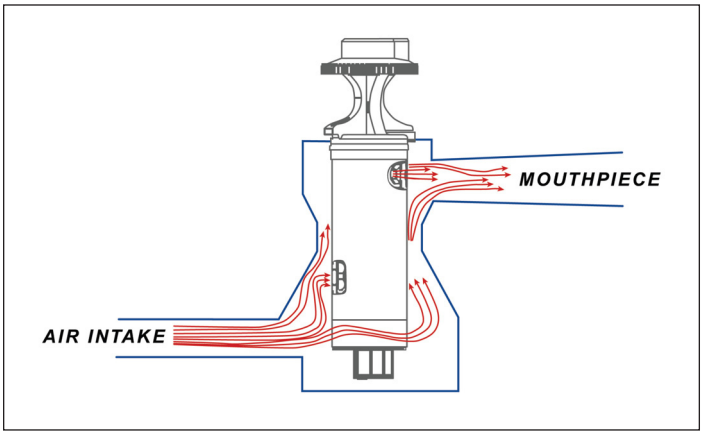

Figure 9. Resulting air flow through the MedTone system.

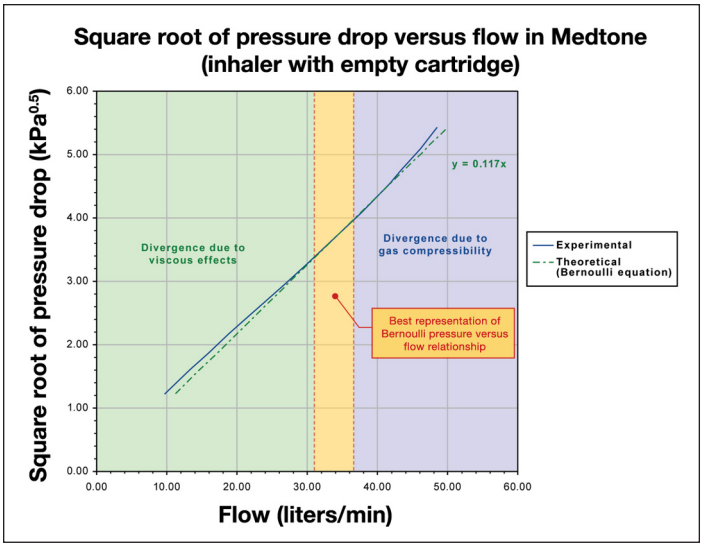

Figure 10. Pressure and Flow relationship existing in the MedTone system.

aerodynamic particle sizes. To demonstrate this pressure/flow dependence, data from geometric particle size analysis are presented in **Table 3**. These data include the measured particle sizes from the emitted plumes at the 16th, 50th, and 84th size percentiles using a Sympatec HELOS laser diffraction instrument.

Last, the presence of a P_{avg} greater than 4 kPa, held out to 4000 ms after achieving PIP, is desired to presumably support flow rates necessary to drive deep-lung depositions.

Delivery of TI inhalation powder for the treatment of diabetes utilizing the breath-powered MedTone inhaler is largely dependent on patient inhalation efforts. As discussed, achieved effort expressed in patient-supplied pressure drop is the driving mechanism for TI delivery. The high resistance exhibited by the MedTone delivery system reflects unique geometries and features utilized to focus and direct energy onto TI inhalation powder de-agglomeration. Therefore, pressure and flow profiling with the device as conducted in this study provides valuable insights to system use and patient capability. Importantly, "experienced subjects" were chosen in this study to minimize possible "learning-curve effects" on the inhalation efforts from the subjects and to reflect "steady state" usage post-TI initiation.

When considering the PIF, PIP, and P_{avg} parameters, two key points are noteworthy. First, the population in whole demonstrated sequential efforts possessing similar average values and similar ranges. Second, individuals

Table 3.
Flow/Pressure Effect on Geometric Particle Sizes of TI Inhalation Powder Emitted from a MedTone Delivery System

Flow rate	*N* (discharge cycles per 1 inhaler)	Average 16th percentile size (µm)	Average 50th percentile size (µm)	Average 84th percentile size (µm)
15.0 liters/min	10	2.47	10.65	27.28
28.3 liters/min	10	1.35	4.20	13.14
40.0 liters/min	10	1.19	3.29	9.59

exerting large efforts and individuals exerting small efforts demonstrated similar differences between their respective sequential inhales. Combined, these results support the notion that device resistance and system use did not impact the inhalation effort.

Based on predictive deposition testing performed *in vitro* (discussed earlier), the data obtained for PIF and PIP imply that the *in vivo* use of the delivery system is conducive for effective TI administration. Additionally, evident from the data, 3 months into a TI therapy regimen, users can properly and reliably use the system as intended. The P_{avg} data demonstrated that the inhalation efforts were reliably sustained for at least 4 s (all but two patients on first inhale effort only). All of this suggests the use of the system is not beyond the capabilities of patients with diabetes.

The present study offers encouragement that TI administration can be consistent and reproducible in the breath-powered MedTone delivery system.

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