3M Drug Delivery Systems

Comparative Performance of the 3M™ Taper Dry Powder Inhaler Device
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Overview of 3M™ Taper DPI

The 3M™ Taper dry powder inhaler delivers high fine particle fractions (typically ~ 50% of emitted dose < 5 μm) and does not require a lactose carrier. Key to the Taper design is the microstructured carrier tape (MCT). The MCT contains numerous microstructure cavities or “dimples” (50-200 μm diameters and 25-100 μm depth) that are filled with micronized drug. Dimple density predominantly defines the dose with drug loading demonstrated from 0.005 to 2 mg/actuation. Winding drug filled MCT onto a spool allows for up to 120 doses to be stored in a compact pocket-sized device with integrated moisture protection (humidity maintained typically 30-60% RH, tailored to product requirements). Cohesive forces (primarily van der Waals) maintain the drug inside the dimples until breath-actuated delivery imparts sufficient energy for drug release from the MCT. The Taper device shown in Figure 1 also contains a dose counter, a dose ready-indicator and patient feedback (visual and audible) confirming that a dose was delivered.

Figure 1. 3M™ Taper DPI

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For all DPI devices, non-respirable drug particles (generally aerodynamic diameters > 5 μm) impact on the throat and are swallowed. Reducing non-respirable drug has the potential to reduce undesired side effects. Improving DPI delivery efficiency also has economic benefits since the same respirable mass can be delivered while loading less drug into the device. Aerodynamic particle size distribution measurements were performed for Taper devices loaded with either albuterol sulfate, a long-acting beta agonist (LABA), or a corticosteroid. The Next Generation Pharmaceutical Impactor (“NGI”, MSP Corporation, Shoreview, MN) was used at 85 LPM, which resulted in a pressure drop of 4 kPa for both Taper and Advair DISKUS®. Similar assessments for DISKUS®, Turbohaler®, and Easyhaler® using multi-stage impactors/impingers (at least 4 kPa pressure drop) were reported elsewhere1,2. Taper generally demonstrated a two-fold improvement in fine particle fractions (FPF, % of emitted dose < 5 μm) over the other DPI devices (see Figure 2).

Figure 2. Fine Particle Fractions for 3M Taper Relative to Advair DISKUS, Ventolin DISKUS2, Turbohaler2,3, and Easyhaler2
Variation in patient inhalation flow profile can impact the amount of drug delivered to the lung from a DPI device. Flow rate sensitivity was evaluated for the 3M Taper device and compared with Advair DISKUS® using individual inhalation profiles recorded by a mini Pulmonary Wave Generator (mPWG). Device specific inhalation profiles were selected from four subjects (two female and two male) based on physiologically differentiable parameters of peak inspirational flow rate and total inspirational volume (see Figure 3). In-vitro drug delivery testing was conducted using the mPWG, an idealized Alberta throat and the dose sampling apparatus (sample collection tube) from USP <601>. The amount of drug captured by the sample collection tube provided an estimate of lung dose. Taper demonstrated superior efficiency with, on average, 46.2% of the Taper emitted dose targeted for lung delivery versus only 21.7% for DISKUS®. Both Taper and DISKUS® were relatively insensitive to variation in biologically relevant inhalation flow profiles. Maximum differences in predicted lung dose were 23% for Taper and 29% for DISKUS® (refer to Figure 4).

Figure 3. Taper specific flow profiles recorded from four subjects (two female and two male)

Figure 4. Impact of In-Vitro Simulated Breath Profile on Predicted Lung Dose for Taper and DISKUS® (N=3). Predicted lung doses were normalized by dividing by the average lung dose. ED=emitted dose
**Taper Drug Dosing Range**

The number and dimension of the dimples in the dosing zone of the MCT (approximately 2 cm²) predominately determines the dose delivered from Taper. MCTs with varying dimple patterns were filled with albuterol sulfate to assess Taper dose range capabilities. Emitted doses were collected per USP <601> using Apparatus B at 85 lpm, which is equivalent to a pressure drop of 4 kPa across the device. Devices were constructed with approximately 0.005-2 mg albuterol sulfate per actuation. The corresponding delivered doses from these devices are shown in Figure 5, demonstrating Taper’s broad dose range capability. The high correlation between loaded and emitted dose indicates effective drug release from the MCT and low device hold-up (~11% on average) across the dose range. Fine particle fractions were measured using the NGI apparatus (85 LPM/4 kPa). Figure 6 demonstrates high fine particle fractions for drug loaded at ~0.005-2 mg/actuation with an overall average of 58%.

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**Figure 5. Taper dose range demonstrated with albuterol sulfate (N=5-20)**

![Taper Dose Range Graph](image1)

**Figure 6. Taper fine particle fractions for albuterol sulfate (N=2-3)**

![Fine Particle Fraction Graph](image2)

R² = 0.9996

FPF(avg) = 58%
Stability of Taper Drug Products

An informal stability study was performed with albuterol sulfate to evaluate device performance over 6 month long-term storage. The MCT dose content was about 200 µg which provided a target emitted dose of 194 µg. Devices sealed in foil pouches were stored at 25°C/65%RH and tested periodically over a 26-week period. Taper demonstrated excellent dose content uniformity with essentially no change in mean emitted dose (refer to Figure 7). Additionally, all 49 emitted doses measurements throughout the stability study were within ±15% of the target emitted dose. Similarly, through-life testing at 26 weeks showed minimal trending over 120 actuations with all results well within ±15% of target (see Figure 8). Particle size of the emitted dose also remained stable with the mean fine particle mass < 5 µm within 10% of initial for each timepoint through 26 weeks (refer to Figure 9).

Figure 7. Emitted dose content uniformity for Taper albuterol sulfate DPI over 26 weeks storage at long term conditions (25°C/60% RH). N=9-10 per pull point.

Figure 8. Through-life dose content uniformity for Taper albuterol sulfate after 26 weeks storage at 25°C/60% RH. N=3 at beginning, middle (60 actuations) and end of life (120 actuations).

Figure 9. Fine particle mass for Taper albuterol sulfate DPI measured over 26 weeks storage at long term conditions (25°C/60% RH), N=5.
Conclusions

The 3M™ Taper DPI has demonstrated high efficiency with typical FPF of ~50%, a two-fold improvement over DISKUS®, Turbohaler®, and Easyhaler®. Predicted Taper lung dose is relatively insensitive to inhalation flow profile, similar to DISKUS®. Doses from 0.005 to 2 mg/actuation have been loaded and consistently delivered from Taper. Excellent stability was observed in the Taper device through 6 months storage (25°C/60% RH).

References
