

The 3M™ Taper Dry Powder Inhaler Device

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Introduction

The 3M™ Taper Dry Powder Inhaler (DPI) uses a microstructured carrier tape (MCT) to enable delivery of pure API without the need for lactose carrier particles or complex formulation development (Figure 1). The API is stored in small dimples in the MCT prior to delivery and is released from the MCT by a breath-triggered impactor that strikes the MCT to release the drug making it available to the patient. This approach allows for 120 pre-metered doses to be delivered from a pocket-sized DPI device. A significant amount of patient research was conducted in order to optimize the user interface of the device (1, 2). This led to a device with a simple 3-step operation (open-inhale-close), feedback of dose delivery from a visual color indicator and an audible click, and a dose-by-dose counter with large (3 mm) font size.



Figure 1: Taper DPI with Microstructured Carrier Tape (MCT)

Taper Design Overview

DESCRIPTION OF THE MICROSTRUCTURED CARRIER TAPE (MCT)

At the heart of the 3M Taper DPI is the MCT in which the API is stored. The MCT contains the API in small micro-depressions ("dimples"). Within the device, a fixed length of the MCT is presented into the dosing zone prior to delivery of a dose. The amount of API delivered with each dose is determined by the number of dimples, the volume of each dimple, and the density of API powder packed into the dimples. Individual doses in the range from 100 µg to 1 mg are possible. Lower doses can also be delivered but may require blending the API with lactose. Figure 2 shows pictures of a single dimple as well as regions of the MCT before and after filling the dimples with albuterol sulfate.

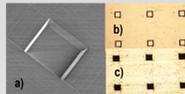


Figure 2: a) Image of a Single Dimple; b) Empty MCT; c) Albuterol Sulfate Filled MCT

The dimple geometry for the Taper MCT has been designed to provide a balance between API retention in the dimples throughout dimple filling and device storage, while promoting release of API from dimples during dosing. The high van der Waals forces and mechanical interlocking forces associated with cohesive micronized API helps retain the API in the MCT dimples prior to delivery. In excess of 90 percent of the API is released from the web during dosing.

FILLING OF THE DIMPLES ON THE MCT

An asynchronous roller coating method is used to fill the MCT dimples with API (Figure 3). The coating roller and the MCT move in the same direction, but at different linear speeds, with the coating roller speed typically about three times faster than the MCT speed for most consistent dimple filling. Once the coating process has stabilized, a layer of powder will have formed on the roller. The process is then run close to steady state conditions where the powder feed rate matches the dimple filling rate. We control several critical coating parameters to minimize variability of loaded API to 2-3% relative standard deviation.

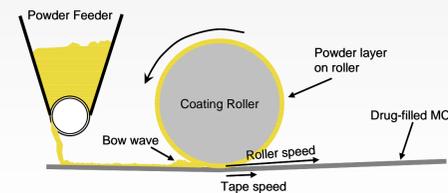


Figure 3: Asynchronous Roller Coating Method for MCT Filling

Patient and Healthcare Provider Research

3M has conducted patient use studies (Figure 4) and interviewed healthcare providers in several global markets to gain valuable patient input for device design purposes (1, 2). 3M also surveyed pharmaceutical companies to understand what they value in a DPI design. The Taper DPI is designed to be intuitive and easy to use for patients while meeting the needs of healthcare providers, pharmaceutical companies, and regulatory agencies.

•Patients and Respiratory Nurses are seeking:

- Easily transportable device, small enough to be concealed in the hand
- Audible or visual indication that the dose has been taken
- Intuitive to use design with a comfortably shaped mouthpiece
- Non-medical appearance
- Affordable cost

•Pharmaceutical companies' expectations included:

- Pharmaceutical performance; efficiency and dose consistency
- "Manufacturable" cost



Figure 4: 3M Patient Use Studies Included all Main FDA Patient Groups

The 3M Taper device incorporates these features into a single compact device which includes an intuitive three step process to use (open – inhale – close), and has a ready-indicator feature in addition to a dose counter. These features are further described in the 'Taper Design Features' section below.

Taper Design Features

MOISTURE PROTECTION

Moisture protection is provided for two purposes: protection of the API-loaded device over its intended shelf life using a low moisture vapor transmission rate (MVTR) overwrap and conventional desiccant, and protection of the API-loaded device over the duration of use by incorporating an engineered desiccant into the device. These protective measures can be tailored to maintain the relative humidity over a range that is appropriate for the selected API. Figure 5 demonstrates that the Taper device provides control of moisture within 30 – 60%RH for a minimum of 90 days after removal of the secondary packaging. The device was stored at 25°C/75%RH after removal of the secondary packaging, and was actuated 120 times over the duration of testing.

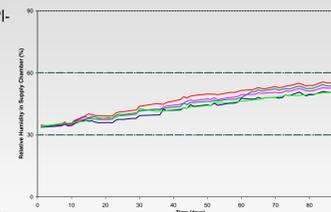


Figure 5: Taper DPI Provides Moisture Control Within 30 – 60% RH for a Minimum of 90 Days

The optimal relative humidity range provided by the engineered desiccant can be customized for individual APIs, with the minimum acceptable %RH defined to prevent static effects and the maximum acceptable %RH defined to prevent API agglomeration.

DEVICE FEATURES FOR IMPROVED PATIENT COMPLIANCE

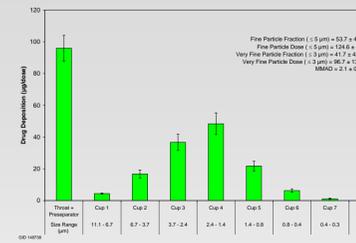
Several features have been provided in the Taper design to enhance patient ease of use, and ultimately, compliance. These features include a ready indicator which lets the patient and/or caregiver know the dose has been delivered by changing from green to red, as well as by providing an audible click. A dose counter with a large font size is used to track each dose, so that the patient is aware of when to obtain a new device.

The device size is small enough to be easily carried in a pocket and discreetly held in the hand, providing up to 120 pre-metered doses. The small device size for the large number of doses is enabled by the unique capability to deliver neat API, without the need to use large amounts of a lactose carrier. Fine particle fractions between 40 – 70 % are typically achieved.

The Taper DPI is a breath-actuated device, where the patient's inhalation releases a mechanical spring which provides energy to aerosolize the API. This spring is compressed as the patient opens the mouthpiece cover prior to dosing. This active delivery mechanism triggers dose delivery once the target flowrate is achieved.

Taper Pharmaceutical Performance

Figure 6: Albuterol Sulfate NGI With Nominal Dose of 250 µg



The Taper DPI achieves a fine particle fraction of 54% for albuterol sulfate (Figure 6) and a fine particle fraction of 41% and 52%, respectively, for a fluticasone propionate/salmeterol xinafoate blend (Figure 7) when measured by Next Generation Pharmaceutical Impactor (NGI) at a flowrate of 85 LPM/4 kPa pressure drop.

Figure 7: Fluticasone Propionate/Salmeterol Xinafoate NGI With Nominal Dose of 76.6 µg FP/34.5 µg SX

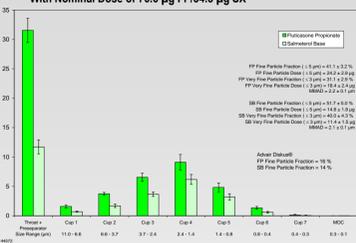


Figure 8: Albuterol Sulfate Dose Content Uniformity Testing With Nominal Dose of 284 µg

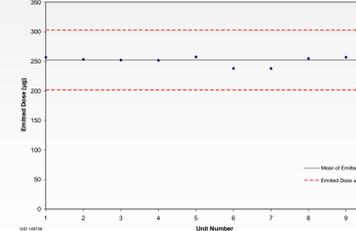
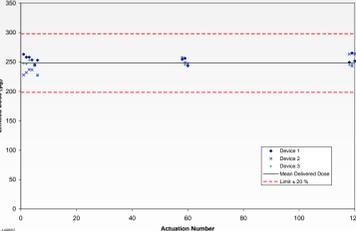


Figure 8 demonstrates the dose content uniformity over 10 devices. In all cases, the emitted dose is well within the ± 20% limits. Figure 9 shows through life medication delivery results over 120 doses for three devices containing albuterol sulfate, demonstrating the excellent through life delivery consistency of Taper. Dose content uniformity and throughlife delivery tests were performed at 85 LPM/4 kPa pressure drop.

Figure 9: Albuterol Sulfate Throughlife Delivery With Nominal Dose of 284 µg



Taper Mechanical Performance and Robustness

API-FILLED MCT IS ROBUST TO VIBRATION STRESS

The Taper device was subjected to vibration testing to assess the loss of API from the dimples in the MCT under realistic vibration stresses expected to occur during product distribution. Ten devices were tested following ASTM D4169, which specifies motion in all three axes at a frequency varied from 10-200 Hz, resulting in an accelerated spectral density of 1 m²/s² (1.5G) for 30 minutes on each axis. The albuterol sulfate emitted dose was measured both before (control) and after device exposure to this high intensity vibration stress (Figure 10).

Results show no statistical difference in emitted dose as a result of vibration stress when compared to the control (green bar); p-values were calculated using paired t-test. The blue bars represent the emitted doses from the next four dosing units along the MCT, which were exposed to vibration prior to actuation.

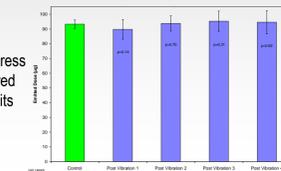


Figure 10: Emitted dose pre-vibration (green) and post-vibration (blue)

DEVICE IS MECHANICALLY ROBUST WHEN DROPPED

Four devices were evaluated for overall ruggedness by dropping each device twelve times onto concrete (twice from six different orientations), starting from a 1 meter height. After completion of drop testing, the devices were evaluated for proper mechanical function and inspected for broken parts. All devices were observed to be intact, with no broken parts, and were fully mechanically functional after completion of dropping. Devices were confirmed to trigger upon exposure to inspiratory flow, proper web advancement was demonstrated, and the dose counters and ready indicators were fully functional, demonstrating the mechanical ruggedness of the device.

Conclusions

3M has designed the Taper DPI to offer a pocket-sized, patient friendly device capable of delivering up to 120 pre-metered doses of pure API, where the selected dosage can range from 100 µg up to 1 mg. The breadth of this dosage range allows flexibility for product development with a broad range of APIs, and the ability to deliver neat API avoids the need for complex formulation development. Delivery of lower doses is also possible (requires blending with lactose to bulk up the formulation). The design is based on market research, which resulted in an operationally intuitive design; a ready indicator; audible feedback of dose delivery; and an easy to read dose-by-dose counter. The Taper DPI is a breath-actuated, medium to low airflow resistance device providing consistent dose delivery.

An engineered desiccant has been incorporated into Taper, providing moisture protection of the API loaded device for 90 or more days after removal from the secondary packaging. The desiccant can be optimized to control relative humidity for different APIs. Mechanical stress tests have demonstrated excellent device ruggedness, with no failures in device function even after dropping or exposing to vibration stresses.

3M offers a full range of feasibility, development, and manufacturing capabilities combined with regulatory guidance to help bring products to market. Broader 3M corporate technologies further offer the ability to leverage expertise in materials and particle engineering as well as process development. For more information, visit our website at 3M.com/dds

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