

Developing an **Efficient**
Dry Powder Inhaler
3M Conix™ DPI

White Paper / Spring 2011

Introduction

introduction

Inhalation drug delivery has fundamental advantages for therapy of diseases of the respiratory tract, thanks to its target-specific nature. This method of administration minimizes systemic absorption and adverse effects compared with drugs that must travel through the gastrointestinal tract. Consequently, inhalation has long been used for treatment of lung diseases such as asthma and chronic obstructive pulmonary disease (COPD). The growing prevalence of these conditions is now placing increasing demands on the healthcare industry to develop new methods of treatment that are both cost effective and that encourage maximum patient compliance. The World Health Organization estimates that there are 300 million asthma sufferers worldwide, as well as 230 million people with COPD, making the development and refinement of inhalation treatments a key concern for the health care community.

Recent breakthroughs in inhalation therapy have raised the additional possibility of its use in delivering larger molecules, such as proteins and peptides. This growing market continues to evolve, and the clear benefits of inhalation now make it poised to become the delivery route of choice for a wide variety of inhaled therapies, for both local and systemic drug delivery.

Within the inhalation category, drugs can be delivered via a nebulizer, metered dose inhaler (MDI) or a dry powder inhaler (DPI). This paper will examine the unique advantages offered by a dry powder inhaler, as well as outline the development of a new DPI device.

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The Role of Dry Powder Inhalers

The pressurized metered dose inhaler (pMDI) is now more than 50 years old, and while this method of drug delivery has become second only to the tablet as the most common form of medication, certain limitations and drawbacks of the technology have led to greater exploration and development of alternatives.

One prominent alternative inhalation therapy is the dry powder inhaler. The development of DPI technology accelerated in the late 1990's, with the impending phaseout of the chlorofluorocarbon (CFC) propellants used in pMDIs. Unlike pMDIs, DPIs require no propellant; the energy used to deliver the active pharmaceutical ingredient (API) typically comes from either the patient's inspiration or an active (powered) feature of the device. The devices are designed to draw air through a dose of powdered medication, which consists of either micronized drug particles with larger carrier particles (typically lactose) or simply micronized drug particles held together in loose aggregates. An additional advantage of the breath-actuated nature of DPIs is that patients do not have the same issue of coordinating inspiration with actuation that can sometimes occur with pMDIs.

DPI devices can be categorized into four distinct types. Devices are either active or passive, and utilize either a reservoir of formulation which is sampled by the device to meter a dose, or pre-metered doses. Each of these four types are potential options to the product developer, each having its own strengths and challenges. Historically, devices reaching the market have typically been passive systems due to the unit cost and regulatory challenges associated with active devices. However, this is now starting to change and active devices are beginning to reach the market. Both reservoir (e.g., Turbuhaler®)* and pre-metered (e.g., Handihaler®)* devices are well represented in the market place.

*Turbuhaler is a registered trademark of the AstraZeneca group of companies. Handihaler is a registered trademark of Boehringer Ingelheim Pharmaceuticals, Inc.

The Voice of the Industry

New DPI devices are being widely tested in the pharmaceutical industry, highlighting the market's interest in this technology. 3M has recently developed two DPI devices, and in the process has gathered significant data on the needs of patients, health care providers and the pharmaceutical industry. This variety of stakeholders makes the development of a drug delivery technology a serious undertaking, but the insights gleaned from research with these groups, combined with 3M's existing inhalation development experience and expertise, can contribute significantly to the ultimate success of a device.

In 3M's recent survey of the pharmaceutical industry, executives from segments including generic manufacturers, medium/specialty manufacturers, and "big pharma" were questioned as to their interest in evaluating DPI devices, as well as the qualities they look for in a device and in a supplier.

The following DPI attributes were identified as most important to the survey group:

- A high respirable fraction (fine particle dose, FPD)
- Breath triggered, with dose release at a consistent flow rate
- Compatible with a range of formulations
- Protection against low/high dosing in the hands of patients

The overall design of an inhalation product did not rank as an area of top concern with the pharmaceutical industry; however, developers stated that robustness and ease of use would be desirable provided that their top needs were satisfied.

Ideal Device

Dose size: 500 mcg- 2 mg

No. of doses: One month's supply (30-120)

Respirable fraction: 55%



Meeting the Needs of Patients

Patient compliance is vital to the success of an inhalation product. Data shows that compliance has been a frequent hurdle for inhalation device users, with improper technique common among patients. Devices must be designed with simplicity in mind, with consideration given to the varying levels of patient education, literacy and attention spans. Simplicity is helpful not only to the patient, but also to the nurses, physicians and respiratory therapists who are charged with training patients to properly use their devices.

To determine the qualities of a DPI device most important to patients, research was conducted via interviews and observation of patients' use of inhalers. The top patient needs identified via this research underscore the need for a product with a simple, easy to use design. In terms of a device's size, patients expressed a wish for a device that was easy to conceal in the hand and easily transportable. Patients also identified a need for feedback that a dose had been delivered, either through an audible or visual indication. The intuitiveness of using the device was identified as a priority, as well as design that did not appear "medical." Finally, patients expressed a need for a device with an ergonomically shaped mouthpiece.

Asthma nurses were also surveyed in order to gain the perspective of health care providers. This group identified an affordable cost as a top need. They also echoed the list of patient needs, especially in their wishes for a device that is easily concealable, that doesn't look "medical," and that delivers feedback that a dose has been taken. Asthma nurses also stated that it was important that an inhaler device was intuitive to use.

Patients' Top DPI Needs

- Easy to conceal
- Delivers feedback that dose has been delivered
- Intuitive design
- Doesn't look "medical"

3M applied the insights gained from its research with the pharmaceutical industry, patients and health care providers to its recent development of the 3M Conix™ Dry Powder Inhaler. The device uses an innovative reverse-flow cyclone design to offer effective drug delivery and simple operation.

The 3M Conix™ Dry Powder Inhaler

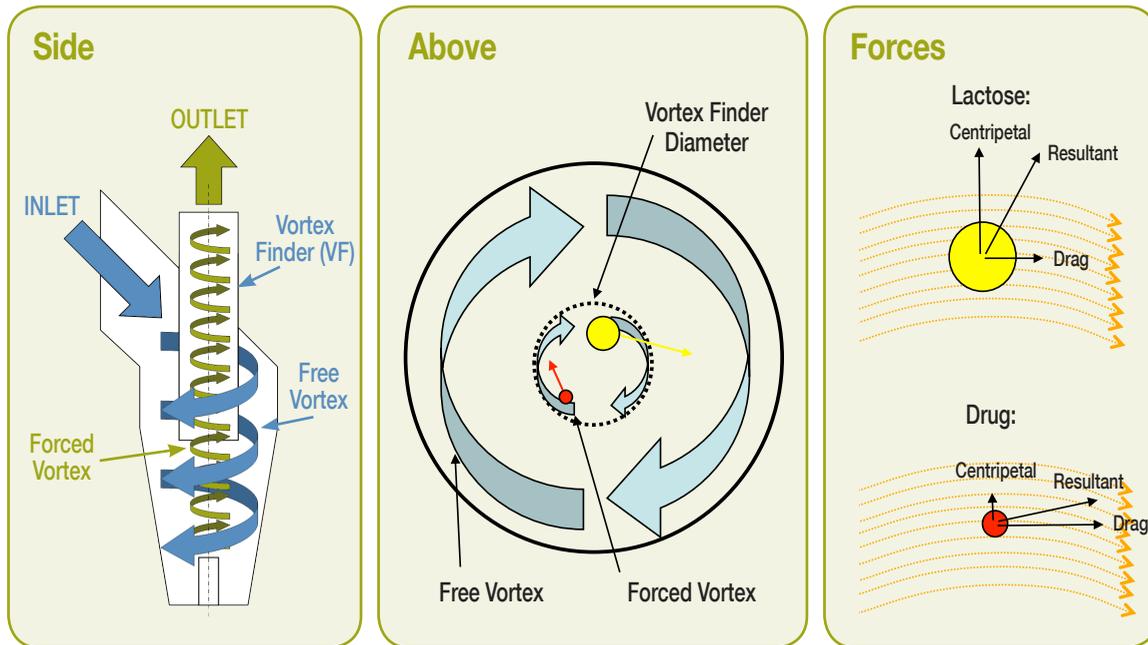
Understanding Reverse-Flow Cyclone Design

Most dry powder inhaler devices utilize a blend of micronized API and coarse carrier particles, typically lactose, to add bulk to the formulation. This approach is intended to make the metering and delivery of the API more reproducible. DPI devices are designed to deagglomerate the powder through application of shear forces or induction of particle/particle and particle/surface impaction. These techniques generally result in deagglomeration, as the formulation leaves the device and the larger carrier particles (and any API that is still agglomerated) subsequently impact on the patient's throat, while the smaller API particles are delivered to the lung.

The 3M Conix™ DPI system, however, uses a different approach for the deagglomeration process. In the Conix device, deagglomeration and aerosolization of the API occur through reverse-flow cyclone technology. As the patient inhales, air is drawn into the cyclone chamber, where a vortex is established. The base of the vortex cone is blocked such that when the vortex hits the bottom, the flow reverses and is forced through the center of the incoming air towards the exit orifice. This is known as a forced vortex. This action results in the preferential delivery of small (API) particles that are respirable while retaining larger lactose particles and lactose/drug clusters so that they can be further exposed to the reverse cyclone action and deagglomerated prior to release to the user. With this technique, a higher fine particle fraction is achieved.

the 3M Conix™ Dry Powder Inhaler IV.

Forces on the Particles



As the patient inhales, a vortex is established in the cyclone chamber. The base of the vortex cone is blocked such that when the vortex hits the bottom, the flow reverses and is forced through the center of the incoming air towards the exit orifice.

How Conix Works

- Based on reverse-flow cyclone design
- Drug/lactose blend contained in cyclone chamber
- Action of device driven by user's inhalation; i.e., a passive system
- Cyclone action separates and releases fine drug particles
- Respirable particles emitted from the device, lactose preferentially remains in cyclone chamber

V Benefits for Patients

This technology results in a number of key patient benefits. Conix delivers a higher percentage of drug dose to the lung, with less drug deposition in the patient's throat and mouth (and therefore fewer taste issues for patients). This targeted delivery to the lung also offers the potential for fewer side effects, as the orally consumed systemic dose (large particles) is reduced.

Beyond its innovative reverse-flow cyclone design, Conix also offers patients a number of practical benefits. It is small, ergonomic, and easy to use, allowing patients to use it discreetly and quickly. These features offer the possibility of improved compliance. Additionally, the breath actuation of the device helps eliminate the coordination issues that can occur with pMDIs.

VI Benefits to the Industry

For the pharmaceutical industry, Conix offers a number of interesting advantages. Its higher efficiency in delivering API requires less drug, creating the potential for cost savings. Additional cost savings are made possible by its simple design, which requires fewer parts. The device provides flexibility in formulation with its use of a drug/lactose blend, and it is available in multiple configurations to meet the needs of each individual application. These configurations include single unit dose designs (both disposable and reloadable) as well as multi-unit dose designs to accommodate various therapeutic needs, including asthma, COPD, migraine, and even mass immunizations and vaccinations.

The inhaler's design allows formulation flexibility and protection from moisture ingress, and is engineered to maximize the effectiveness of energy transfer from the patient's inhalation to the drug formulation. The design is currently developed to achieve a flow rate of approximately 60 L/min at 4kPa; however, the configuration of the core technology can be modified to align with specific patient populations, such as those with COPD.

Examples of Conix Device Designs

Conix 1: Disposable single-dose



Conix 2: Reloadable single-dose



Conix 3: Pre-metered multi-dose



Performance Data

performance data VII

A number of laboratory and clinical studies have confirmed the viability and efficacy of the 3M Conix™ system. This testing has been performed on a range of different laboratory test fixtures and prototypes, as well as a clinical device.

The following summaries highlight key research findings.

Demonstration of Conix Efficiency

A selection of the data generated is presented herein to illustrate the effectiveness of the Conix technology in efficiently generating particles that are likely to be respirable and efficacious. In order to show that this efficiency is due to the Conix device and not the formulation, the formulation was harvested from a commercially available salbutamol DPI (Accuhaler®)* and tested in the Conix device. Further unadulterated examples of the commercial device were also tested under the same conditions as Conix in order to act as a control against which the Conix data could be compared.

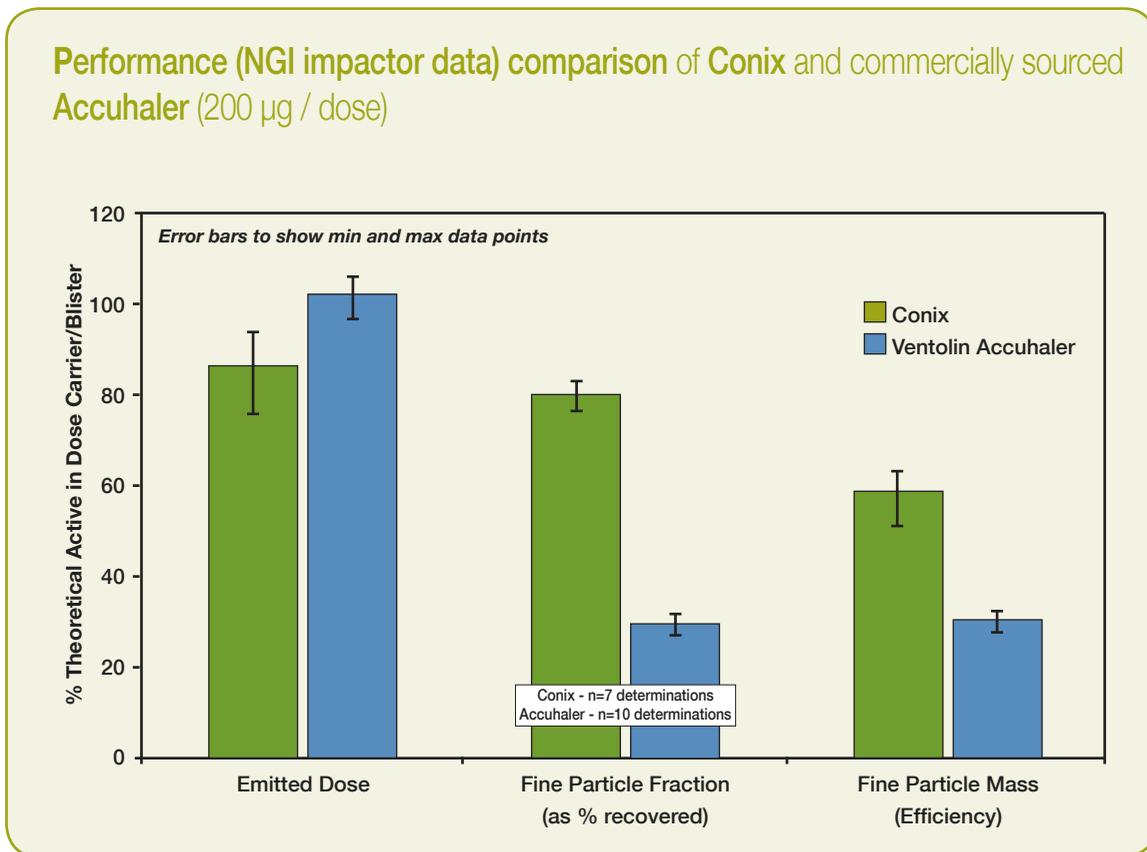
Testing was performed using a Next Generation Impactor (NGI) set-up, which, unless otherwise stated, was run under standard 4kPa conditions. The fill masses used were similar (nominally 13 mg for Accuhaler and 10 mg for Conix) but the data are presented relative to the actual fill so as to correct for any differences.

Key Definitions

- **Fine Particle Dose (FPD)** = Total mass of drug that exits the mouthpiece that is considered to be respirable; i.e., less than a defined particle size, typically 5µm (microns). Here it is expressed as a percentage of the amount of drug in the dose carrier.
- **Emitted Dose (ED)** = Total mass of drug that exits the mouthpiece and is delivered to the patient (or test equipment)
- **Fine Particle Fraction (FPF)** = the percentage of the Emitted Dose that is considered to be respirable; i.e., less than a defined particle size, typically 5µm (microns)

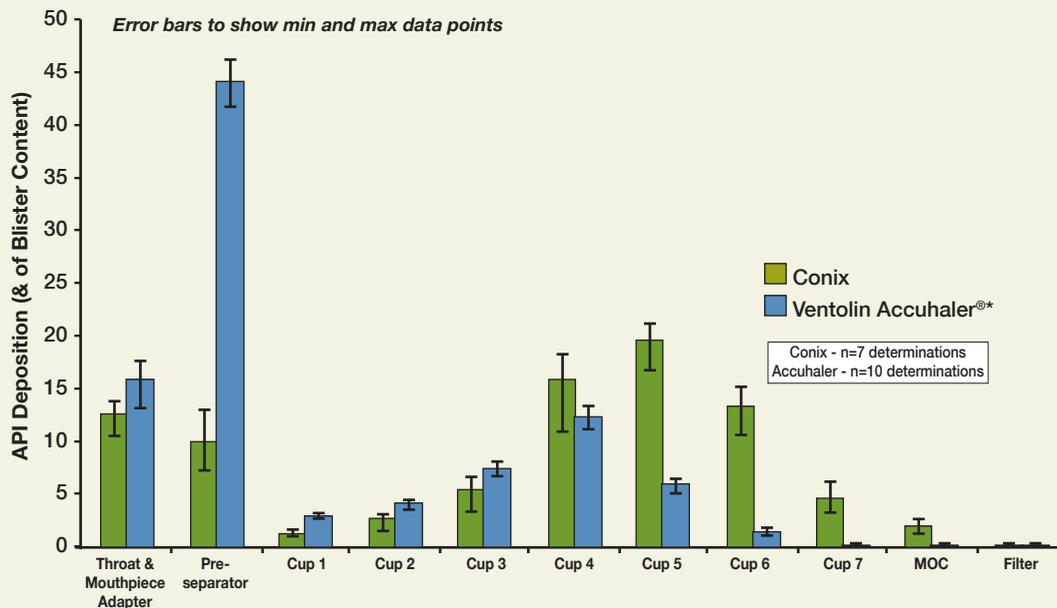
*Accuhaler is a product of GlaxoSmithKline

Results showed that the emitted dose from the Conix device was lower than that of the Accuhaler. However, the fine particle fraction from Conix was significantly higher (> 2.5x) than achieved by the Accuhaler. The net result of this test showed that the fine particle dose delivered in the respirable size range from Conix was double that of the Accuhaler. Thus, using a formulation developed for use in the Accuhaler device, **Conix is twice as efficient as the innovator product at generating particles in the respirable range (< 5µm)**. This data is summarized on the following pages.



This propensity of the Conix technology to deliver a greater proportion of its payload to the respirable range while delivering less API overall to the patient (or test apparatus) is clearly illustrated by a review of the aerodynamic particle size distribution (APSD) from the two devices.

Aerodynamic Particle Size Distribution (APSD) comparison of Conix and commercially sourced Accuhaler (200 µg / dose)



A large proportion of the drug emitted from the Accuhaler product is deposited on the throat and preseparator. In use, this drug would be too coarse to be inhaled into the deep lung; the accepted understanding is that it would impact in the patient's mouth, throat and upper airways, ultimately ending up in the stomach. High non-respirable deposition is not atypical in inhalation products. However, it can lead to unwanted side effects through systemic absorption, limit the upper dose capability with systemically sensitive treatments, and lead to increased cost for the manufacturer, as significantly more drug needs to be loaded into the device than is therapeutically utilized. This last point is particularly relevant where new and/or high cost drugs need to be delivered.

*Ventolin Accuhaler is a registered trademark of GlaxoSmithKline

Conix Performance at Different Flow Rates

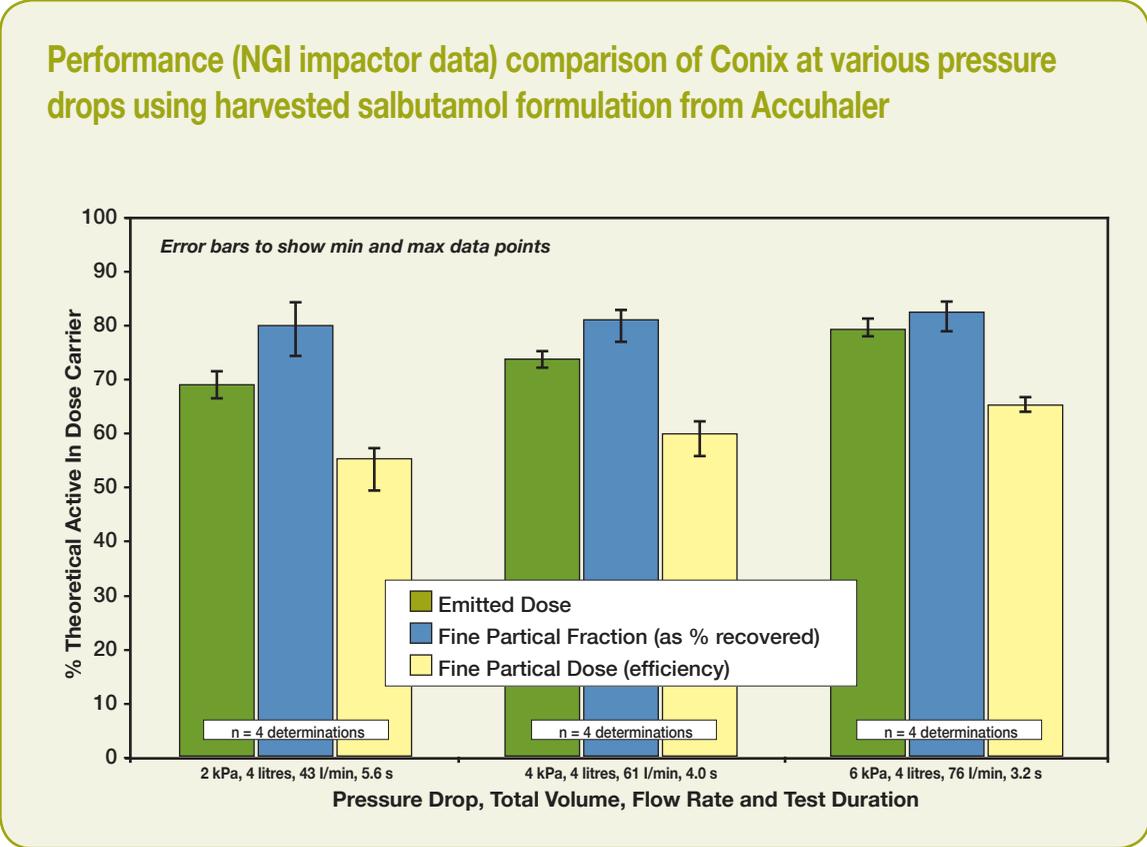
Achieving good performance under one set of standard conditions, as used in the experiments discussed above, is a useful way to compare different delivery systems or even different batches of the device. However, in the real world patients differ in many ways when using an inhaler (health, technique, compliance, environment, etc.). It is also standard practice for suppliers to have several strengths of any given product available to allow the prescriber to tailor the dose to an individual's need. A device therefore needs to be able to perform consistently over a range of conditions, two key ones being a range of pressure drops (and hence flow rates) and a range of fill masses, as this is the simplest way in which to produce multiple strengths of the same product (as apposed to adjusting the formulation concentration).

To evaluate the performance of Conix under a range of air flow/pressure conditions, the NGI testing was repeated at both a low pressure drop (2 kPa) and a high pressure drop (6 kPa). The standard 4kPa condition was also repeated as a control. In order to maintain the different pressure drops, the flow rate was adjusted accordingly. This also meant that the test duration was varied to achieve a constant total volume (4L) through the impactor (all standard DPI test procedures).

Test	Pressure Drop	Flow Rate	Total Volume	Duration
1	2 kPa	43 L/min	4 L	5.6 s
2	4 kPa	61 L/min	4 L	4.0 s
3	6 kPa	76 L/min	4 L	3.2 s

The testing was performed with harvested salbutamol formulation from Accuhaler (200 µg/dose) and a 10 mg fill mass.

The data below show that the performance of the Conix system improves slightly with increasing pressure drop, but the changes are small and the system is relatively insensitive to pressure drop/flow rate over the range evaluated. This result indicates that the performance of Conix is unlikely to vary dramatically when used by patients of differing inspiratory capabilities.

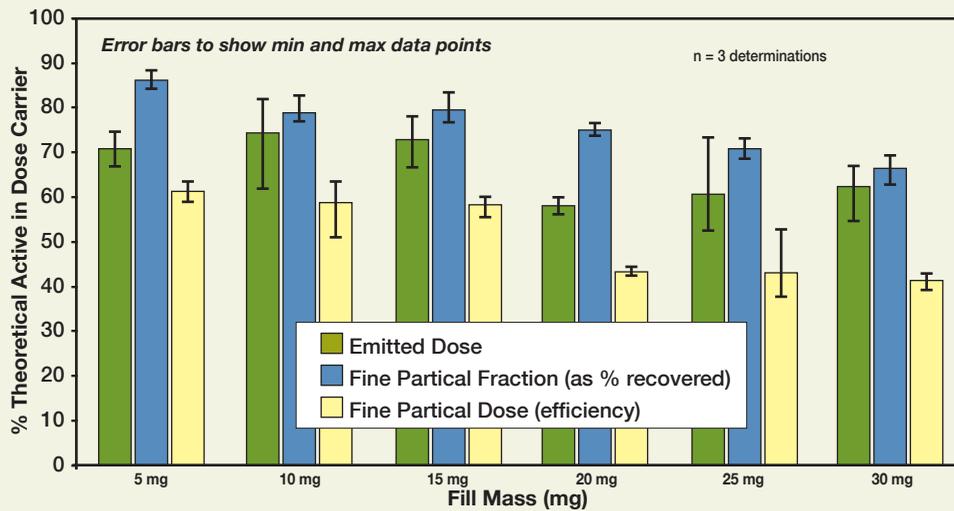


Conix Performance with Various Fill Masses

The assessment of sensitivity of performance to fill was performed in a similar manner using the same Conix system, formulation and test conditions (4 kPa, 4L). Again, the 10 mg fill mass was repeated as a control.

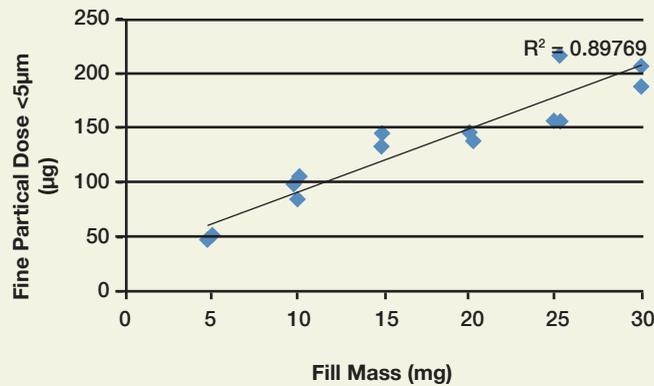
The following data show that the performance of Conix is relatively insensitive to nominal fill mass. Only a small decline in device efficiency is observed at the higher fill masses, and even at the highest fill mass evaluated, an efficiency of over 40% is achieved.

Performance (NGI impactor data) comparison of Conix at various fill masses using harvested salbutamol formulation from Accuhaler at 4 kPa / 4 L



Plotting the fine particle dose (as μg of drug) against the actual fill mass used in each experiment shows the true correlation between the two parameters.

Performance (FPD, μg) comparison of Conix at various fill masses using harvested salbutamol formulation from Accuhaler at 4 kPa / 4 L



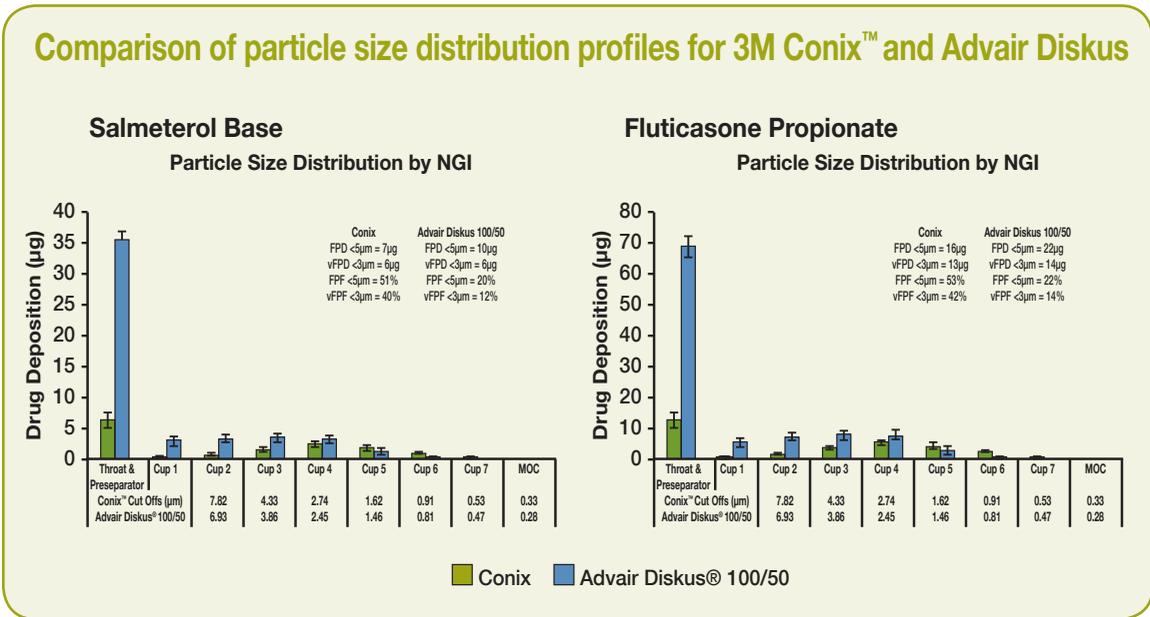
Conix therefore performs consistently across a range of formulation amounts in the cyclone chamber, addressing the pharmaceutical industry's stated desire for a range of dose sizes without the need to reformulate.

VIII

Clinical Testing

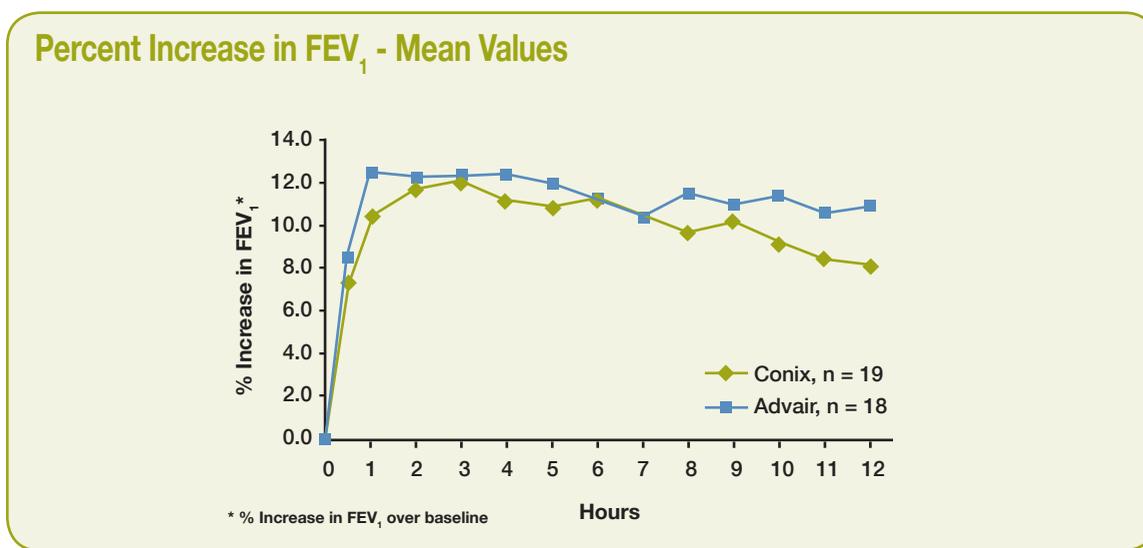
An in vivo study was conducted comparing delivery of a combination therapy (fluticasone propionate and salmeterol xinafoate) from the Conix DPI to Advair Diskus®* 100/50. The study included 19 subjects with mild to moderate asthma. Subjects received two treatments separated by 7-16 days, according to a randomized, two-period crossover design. The reference treatment was one inhalation from an Advair Diskus labeled to deliver 100 µg fluticasone propionate and 50 µg salmeterol base equivalent, and the test treatment was one inhalation from the 3M Conix™ device which contained approximately 10% less of each drug per pre-metered dose in a lactose blend. Pulmonary function and pharmacokinetics were measured over approximately 12 hours.

The inhalation formulation of Conix had a comparable (within ± 15%) in vitro fine particle mass ≤3 µm of each drug using Next Generation Impactor (NGI) testing. This testing also showed that Conix delivered far fewer large particles to the throat than did Advair. The Conix formulation was shown to be stable for 26 weeks under accelerated ICH conditions (40°C / 75% RH).



*Advair Diskus is a registered trademark of GlaxoSmithKline

This study found that pulmonary delivery of a combination formulation from the Conix device was safe and well tolerated, and that Conix successfully produced the expected bronchodilator efficacy for the formulation. FEV₁ was the primary measure of efficacy. The increases in FEV₁ profiles over baseline were found to be comparable for both devices in both peak increase and duration (see figure below). There were no statistically significant differences in these values between the devices.



Pharmacokinetic analyses showed that both drugs were systemically absorbed from each formulation and were consistent with the interpretation of less swallowed drug with Conix. No treatment-related adverse events were reported with either product. Patients reported that Conix was easy to use.

In summary, the Conix device was shown to provide comparable improvement in pulmonary function as compared with the Advair inhaler, while starting with less drug in each pre-metered dose and delivering a lower non-respirable dose to the patient.

Summary

summary

The studies described herein demonstrate how the 3M Conix™ device effectively meets the needs articulated by patients, health care providers and pharmaceutical companies. With a discreet and innovative design, it improves drug delivery to the lung, bringing more efficient API delivery to the passive DPI development arena using traditional “simple” formulations of API and lactose. The Conix DPI is a high performance, cost-effective solution for pharmaceutical companies.

For patients, the device offers a simple-to-use system that has the potential to increase compliance, helping them to manage their health conditions as effectively as possible.

The Conix Dry Powder Inhaler Provides:

Confidence

- Consistent, effective delivery of drug
- High respirable fraction

Compliance

- Simple, easy to use
- Breath-actuated

Convenience

- Small, discreet
- Single & multi-dose designs

Cost-effective

- High efficiency – dose sparing
- Compatible with range of drugs/formulations

easily concealed
delivers feedback
intuitive ergonomic

Partnering with 3M

partnering with 3M

In addition to the DPI device, 3M has a full range of development capabilities, including formulation, testing, product scale-up and manufacturing.

3M Drug Delivery Systems offers more than 50 years of experience and proven success in technology, product development and manufacturing, coupled with global regulatory expertise. We can offer a partnership that ensures a smooth process from start to finish and help you bring your products to market more quickly. Working with us, you get the speed to market that's critical to the success of your new application.

3M DPI Capabilities

- DPI device, design and development
- Lab-scale formulation development, blending and filling
- Analytical testing for all device types
- Commercial scale manufacturing:
 - Micronizing
 - Blending
 - Capsule Filling
 - Capsule Blister Packaging

DPI Product Development Stages

- Paper Feasibility
 - Evaluation of the specific product goals with 3M DPIs
 - Completed Product Definition Form (PDF) required to prepare a PF
- Feasibility Program
 - Lead formulation with initial in vitro data set (and 1 mo. stability), utilizing a 3M DPI and targeting the PDF objectives
- Phase I Clinical Supply
 - Product and supporting CMC documentation for Phase 1 clinical study
- Development Program
 - Through Phase III clinical supply and regulatory submission
- Launch and Commercial Supply



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