

Investigating the Efficiency of the 3M Conix™ Reverse Cyclone Technology for DPI Drug Delivery

Mike Needham, Phil Cocks and Georgina Fradley
3M Healthcare Ltd., Loughborough, Leicestershire, UK

Introduction

Efficient drug delivery is essential due to the rising cost and increasing potency of active pharmaceutical ingredients (APIs). The 3M Conix™ reverse-cyclone dry powder inhaler (DPI) technology provides one potential way to achieve high efficiency delivery to the lung. This paper will seek to demonstrate, through in-vitro impactor testing, that the Conix™ technology preferentially releases respirable particles from the reverse cyclone vortex system thus reducing pre-separator and throat deposition when compared to a leading commercial DPI device. The robustness of this performance to fill weight, pressure drop and flow volume will also be demonstrated.

It will be shown that this is achieved using the same commercial API/lactose blended formulation and a simple passive system that is readily incorporated into single and multiple use devices.

Theory of Cyclone Delivery

Most dry powder inhaler devices utilize a blend of micronized active pharmaceutical ingredient and coarse carrier particles (usually lactose) to bulk out the formulation, thus making the metering and delivery of the API more reproducible. DPI devices are designed to separate the two types of particles through application of shear forces or induction of particle/particle & particle/surface impaction. These techniques generally result in separation, as the formulation leaves the device and the larger carrier particles subsequently impact on the patient's throat, whilst the smaller API particles are delivered to the lung.

The design intent of the 3M Conix™ DPI system was to approach the deagglomeration process in a different way. The aim of the Conix™ technology is to preferentially release small (API) particles that are potentially respirable whilst retaining larger lactose particles and lactose / drug clusters so that they can continue to be worked on and deagglomerated further. Thus the emitted dose would be reduced whilst the fine particle fraction would be high compared to a more traditional approach.

In Conix™, deagglomeration and aerosolization of the API occurs through reverse flow cyclone technology (Figure 1). Upon inspiration, a flow of air enters the cone and forms a free vortex. In traditional methods of cyclone separation, such as separation of sawdust from air in saw mills, the bottom of the cone is open and particles suspended in the vortex exit to a collection hopper and the cleaned air exits separately. However, in Conix™ the base of the cone is blocked such that when the vortex hits the bottom the flow reverses and is forced through the centre of the incoming air towards the exit orifice. This is known as a forced vortex.

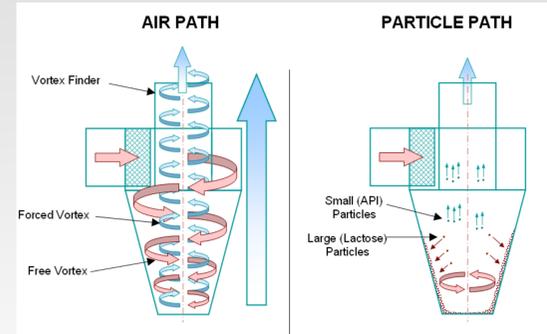
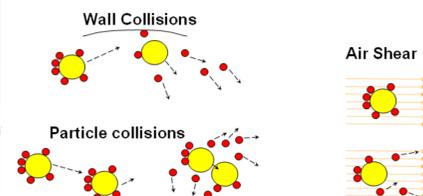


Figure 1 – The reverse flow cyclone principle

The vortex produced by the reverse flow cyclone creates relatively high velocities (and therefore energy) in the air flow which imparts the energy required for deagglomeration through collisions with the cone wall, other particles and through particle shear. Previous work has shown that impaction even are more effective at deagglomerating than airflow shear alone (1).



As deagglomeration occurs, the large lactose particles are flung to the sides of the cone and the lighter API particles are carried along by the air flow and exit the cyclone. Therefore, any API still adhered to lactose particles are re-entrained into the deagglomeration process rather than being emitted, typically to impact in the throat.



Pharmaceutical Performance

The high efficiency of the 3M Conix™ DPI has been demonstrated through assessment of fine particle distribution compared to a marketed albuterol sulfate DPI product. The albuterol sulfate blend was harvested from a commercial DPI (GSK's Accuhaler™, 200 mcg albuterol per dose, blister fill = approx. 240mcg, nominal emitted dose = 200mcg per dose, 12.5mg per blister) product and filled into Conix™ blisters (10 mg per blister, total blister content = approx. 160mg, emitted dose = 100mcg). Testing was performed using test pieces of a recently developed version of the Conix™ cyclone 'engine.' These test pieces were made from injection moulded polypropylene cyclones and rapid prototype (stereo lithographic) air inlet & mouthpiece components which were bolted together. The Conix™ engine represented in these test pieces could readily be incorporated into any one of the Conix™ device family.

The particle size distribution in Figure 2 illustrates the significant difference between the particle size distribution profiles of Conix™ and that of Accuhaler™. The Conix™ device emits significantly fewer large particles and more particles of a potentially respirable size. This supports the theory that the larger particles are retained and re-entrained into the deagglomeration process. This is of benefit, not only as it potentially increases the respirable dose delivered, but also the reduction of deposition on the throat and pre-separator is likely to reduce systemic absorption and may improve patient acceptability through reduced lactose inhalation and systemic API uptake.

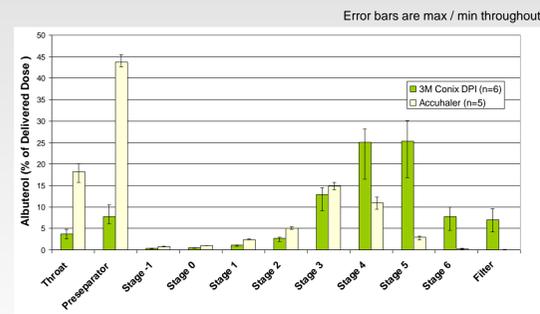


Figure 2 – Fine Particle Distribution for albuterol sulfate DPIs

Figure 3 shows increased fine particle fraction (percent of particles less than 5 microns) for Conix™ compared with the Accuhaler™ DPI. Device efficiency is calculated as the fine particle mass as a percentage of total blister content.

This increase in respirable particles and reduction in the number of large non-inspirable particles is also demonstrated through mass mean aerodynamic diameter (MMAD); Conix™ mean MMAD = 0.97µm, half that from the Accuhaler™ DPI which had an MMAD of 1.99µm.

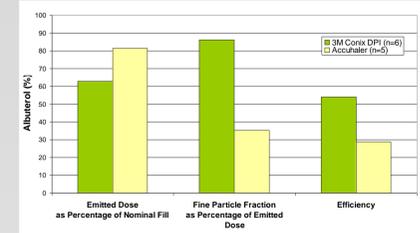


Figure 3 – Pharmaceutical performance summary for albuterol sulfate DPIs

The performance of the Conix™ technology also needs to be robust across a range of fill masses to enable different strengths of a single product to be produced in a simple manner without the need for re-formulation of each variant. This was demonstrated using fill masses of 5 mg, 10 mg and 15 mg with harvested albuterol formulation (GSK's Accuhaler™) and evaluating the in-vitro performance using Andersen Cascade Impaction (ACI) at 4kPa for 4L.

The data, presented in Figure 4, show consistent emitted dose, fine particle mass and lactose retention across the range of fill masses investigated.

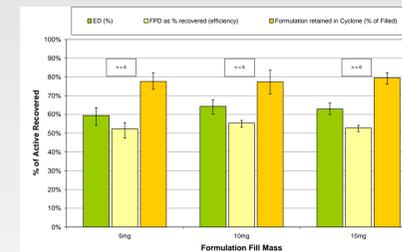


Figure 4 – In-vitro performance for albuterol sulfate formulation across a range of fill masses

The impact of pressure drop and flow sensitivity were also assessed using a 5 mg fill mass and harvested albuterol formulation (GSK's Accuhaler™). The performance of the system was again assessed by ACI, this time run at 4kPa / 4L, 4kPa / 2L and 2kPa / 2L. These data (Figure 5) show good robustness to changes in pressure drop and flow volume with some indication of a slight decline in performance as the pressure drop and flow volume are reduced. The data from the 2kPa / 2L study were also more variable based on these small data sets.

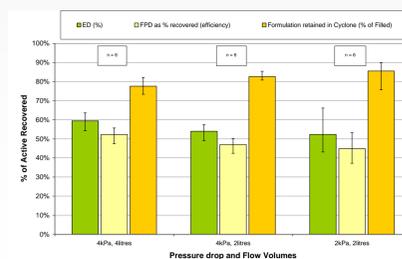


Figure 5 – In-vitro performance for albuterol sulfate formulation at different pressure drops and flow volumes

Conclusions

The 3M Conix™ technology has been designed to address the challenge of deagglomeration in a different manner to most other DPI devices currently available. The initial studies performed here have demonstrated that the original design intent of holding on to large, non-respirable, particles and clusters, so that they can be worked on further, to improve the emitted respirable mass whilst reducing the output of larger particles, has been achieved.

The Conix™ technology brings high efficiency API delivery to the passive DPI development arena using tradition 'simple' API / lactose blended formulations. This increased efficiency is achieved through a novel process which both deagglomerates the formulation in an effective manner but also preferentially retains particles that are still agglomerated such that they can continue to be 'worked upon' until the drug particles are released and are suitable for delivery to the lung. Thus, Conix™ technology should improve delivery to the lung as indicated by increased efficiency, and reduced throat and pre-separator deposition. This is achieved from a fundamentally simple device which is expected to have a competitive cost to produce.

The absolute performance of >50% efficiency across a range of fill masses is also impressive, especially for such an intrinsically simple device. This high efficiency of the Conix™ device brings potential benefit to those wanting to deliver high cost compounds where waste needs to be minimised, and also to those delivering highly potent agents where delivery to the lung needs to be maximised whilst limiting systemic delivery.

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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