High Delivered Dose in a Single Inhalation for Carrier-Based Formulations by Retaining Carrier-Fraction in DPI Blister

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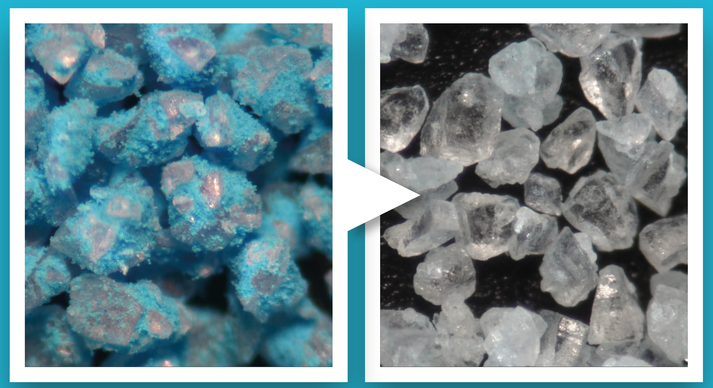
Quattrii detaches the API from the carrier particles and retains the carrier fraction within the blister, delivering only the aerosolised active dose to the lung



Formulation as filled **Fraction retained in blister**

Figure 2: *Micrographs of the formulation as filled in the Quattrii blister (left) and the fraction retained in the Quattrii blister after the test (right). The API mimic (dyed with Brilliant Blue food dye) has been detached from the carrier fraction and delivered, whilst the majority of the inert carrier fraction remains in the blister.*

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References
[1] Claus S, et al., How can we bring high drug doses to the lung?, European journal of pharmaceutics and biopharmaceutics, 86(1) 2013
[2] Hickey A, Why we need to deliver large amounts of powder to the lungs and the concurrent challenges, DDL, Volume 30, 2019

INTRODUCTION

In respiratory medicine there is a growing demand to deliver higher payloads (for example, active doses >5mg) to the lung, driven by an increasing number of lower potency molecules for treating conditions beyond asthma and COPD. [1, 2] These higher payloads present significant challenges for the current delivery technology.

The emitted mass from an inhaler is inescapably limited by the cough response of the patient. Two approaches to mitigate this for high active dose applications using a traditional inhaler are: A) formulate as a carrier-free formulation, or B) split the dose across multiple patient inhalation manoeuvres (Figure 1, A & B).

CLASSIFICATION IN THE BLISTER

Quattrii™ is a novel, blister-based inhaler developed by CHI. Quattrii detaches the API from the carrier particles within the blister and retains the coarse carrier particles in the blister (Figure 2). This mechanism is known as "classification" – the separation of different size fractions, and the retention of coarse particles.

The aim of the study was to evaluate the performance of Quattrii for delivering high payloads of carrier-based formulation to the lung compared to the ultra-high resistance (UHR) Berry RS01 capsule-based inhaler, a widely used "traditional" inhaler. In particular, the classification performance of Quattrii was evaluated.

METHOD

The data was acquired using a Next Generation Impactor (NGI). A spray-dried mannitol API-mimic, containing ~1.25% Brilliant Blue food dye, was produced by Nanopharm. This was blended with lactose by CHI, producing a 9.77% w/w API-mimic blend. The blue food dye enables visible spectrometry to be used to quantify the distribution of the mannitol API-mimic across the NGI stages and the device. A micrograph of the formulation is shown in Figure 2 (left).

Back-to-back testing was conducted with Quattrii and the UHR Berry RS01, which has a similar resistance to Quattrii, allowing NGI stage distribution to be directly compared.

The RS01 nominally emits the entire fill mass, therefore, in clinical trials or real use settings the fill mass must be low enough to avoid the risk of cough. Size 3 capsules were used and filled with 20 mg for each test. Therefore, the total 60, 80 and 100 mg fill mass had to be split across three, four and five shots, respectively (option B in Figure 1). For Quattrii the entire fill mass is filled into a single blister and the delivered dose is emitted in one evacuation.

DISCUSSION & CONCLUSION

The active mass distributions are presented in Figure 4, as a percentage of the filled active mass. For Quattrii, with a gross fill mass of 60 mg to 100 mg, approximately 50% of the filled active mass is respirable (aerodynamic diameter of less than 5 µm). With a gross fill mass of only 20 mg, the RS01 achieves a similar respirable fraction of 55%.

Quattrii delivers approximately equivalent FPD as RS01 but delivers the dose in one inhalation (verses three to five for RS01) and requires the patient to inhale much less emitted mass overall, improving patient comfort and convenience, which may also lead to improved adherence.

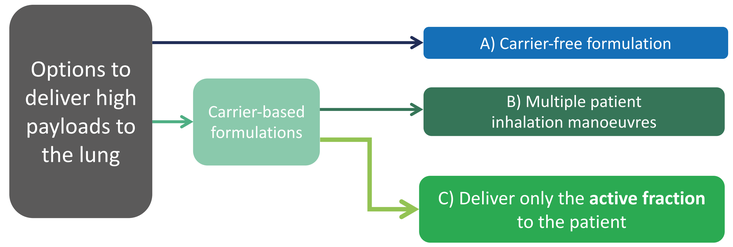

Figure 1: *Three options for delivering high doses to the lung (for example, an active dose of > 5 mg). Option C is the subject of this poster*

RESULTS

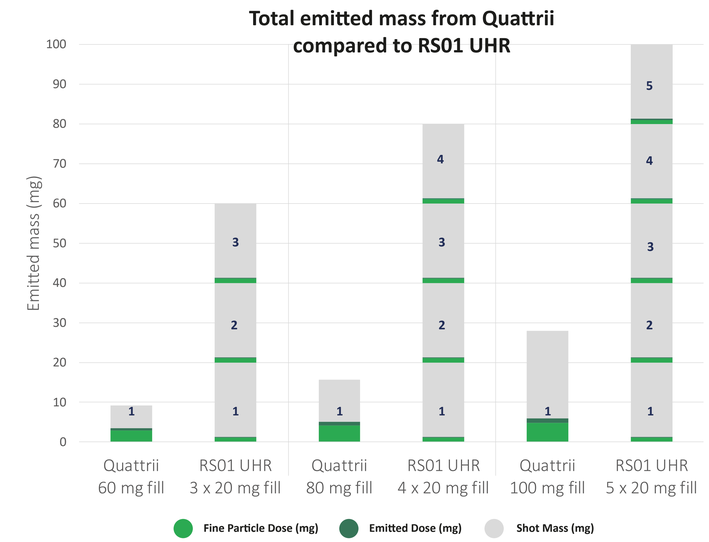

Figure 3: *Emitted mass for Quattrii and RS01 UHR at 60, 80 and 100 mg fill mass, 9.77% API fraction, at 4 kPa. For Quattrii the entire fill mass is filled into a single blister and the delivered dose is emitted in one evacuation. For RS01, size 3 capsules were filled with 20 mg, splitting the total dose across 3, 4 and 5 capsules. Data presented is the mean of three repeat runs.*

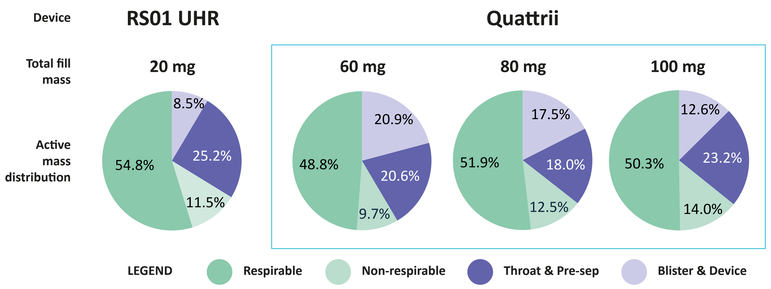

Figure 4: *The active mass distributions as a percentage of filled active mass, for Quattrii at 60, 80 and 100 mg fill mass compared to a fill mass of 20 mg in RS01 UHR. Data presented is the mean of three repeat runs.*