Development Approach for a High-performance Capsule-based DPI Device

The pulmonary route is gaining increasing attraction not only for low-dose locally acting therapies, *e.g.* Asthma and COPD, but also for systemic applications often require higher doses or new formulation technologies.

High-performance devices need to be developed to accommodate the requirements to deliver these new drugs/formulations efficiently. To ensure the best performance, the development of the formulation and the device should go hand in hand.

Dry Powder inhaler devices are used to deliver the medication in powder form to the lungs via oral inhalation. Medication in powder form can be filled in either a capsule, blister, reservoir or cartridge based on the drug product configuration. The device can be either an active or a passive device. In many cases, capsule-based inhalers are preferred solutions for new applications because they offer several interesting features, *e.g.* possibility to use a wide range of different APIs and doses generally ranging from 5 mg to 50 mg. Further advantages include ease of use and a good feedback mechanism for the patient.

Due to the complexity and cost of manufacturing multidose DPI devices, pharma companies want to minimise cost and risks in the new applications by using a simpler and more affordable device.

For some new applications, *e.g.* pain relievers or antibiotics, a reusable dose is beneficial; for others, *e.g.* vaccines, a disposable single-use is required. In both cases, capsule-based inhalers can be a good solution.

Covid 19 has made it imperative that an easy-to-use vaccine is available worldwide and remains stable at ambient conditions. Research continues to happen to deliver the vaccine by the inhalation route.[1]

However, there are some drawbacks associated with current capsule-based DPI devices, *e.g.* Low performance is an inherent feature of many capsule-based DPI devices on the market. Even newly developed integrated solutions for antibiotics, *e. g,* Tobramycin, do not reach a higher FPF than 35%. In order to achieve the therapeutic dose of the antibiotic, the patient has to inhale 4 capsules a day.[2]

Many of the strategies for overcoming the inherent challenges of most existing devices are done by focusing on improved dispersion properties of the formulations. Not a lot of attention was paid to improving the devices either by technological advancements of the device performance (higher deagglomeration and less retention of powder in the device/capsule) or on increasing patient adherence for better handling and thus, higher deposition in the deep lungs.[3]

The novel Presspart DPI device addresses the above problems and challenges of capsule-based inhalers. The most important features of an ideal capsule-based DPI device are, the ease of use with a good feedback mechanism to the patient coupled with a cost-effective design. In addition, dose delivery with high reliability and consistency, and high-performance efficiencies for a wide range of applications are desired.

Device Engine and Development Approach

While developing the novel capsule-based inhaler, the main focus was to create a high-efficiency engine to de-aggregate and aerosolise the powder formulation: a medium resistance and relatively flowrate-independent device. Several prototypes have been tested and studied throughout the development journey.

The airflow through the capsule chamber was designed so that the capsule oscillates. This causes impaction of the capsule within the capsule chamber leading to the breakdown of big powder aggregates inside the capsule and, consequently, an efficient release of the powder from the capsule.

After the initial de-aggregation of the powder in the capsule, the powder evacuates from the capsule and reaches the swirl chamber. Further de-aggregation takes place due to the shear forces caused by the turbulent airflow created in the swirl chamber and the impaction of the powder on the walls of the swirl chamber. The combination of the capsule movement and powder flow in the swirl chamber leads to a highly dispersed powder. This powder exits into the tubular mouthpiece through the mesh.

The powder de-aggregation and dispersion potential in a device are crucial parameters to achieve high efficiencies of the device. Various techniques can be used to study airflow and powder de-aggregation behaviour within a device. Here, a combination of a simulation with CFD (computational fluid dynamics) modelling in a steady state and an experimental approach was used to develop the new device.

In one experimental design CFD was used to study the airflow structures within the device. Two prototypes were tested prototype 1 (Figure 1a) without a flow straightener and prototype 2 (Figure 1b) with an integrated flow straightener in the mouthpiece. The test of fine particle assessment by NGI was conducted on the prototypes. As seen in Figure 1c, the CFD data of Prototype 1 exhibits a swirling flow that proceeds out of the mouthpiece, reflecting a higher deposition and a swirl pattern observed in the induction port of the NGI. However, with the introduction of the flow straightener in Prototype 2, the CFD data shows a high reduction of the swirl exiting the mouthpiece (Figure 1d). This is also in correlation when comparing CFD data with our NGI data (Figure 2). There was a higher deposition in the induction port at both the flow rates for prototype 1, and it was significantly higher @ 30 LPM($p<0.05$). The statistical analysis performed using an independent Student t-test gave probability values of less than 0.05 which was considered as a significant difference. The flow straightener reduced the swirl of the airflow exiting the device, thereby reducing the deposition in the induction port. There was no significant difference in Fine Particle Fraction (FPF) between the two devices indicating that major deaggregation occurs within the device. CFD proved to be a valuable tool for studying the air flow dynamics of the dry powder inhaler. NGI testing provided the supporting data and visual observation of the drug deposition in the induction port, which indicates/simulated probable oropharyngeal deposition.

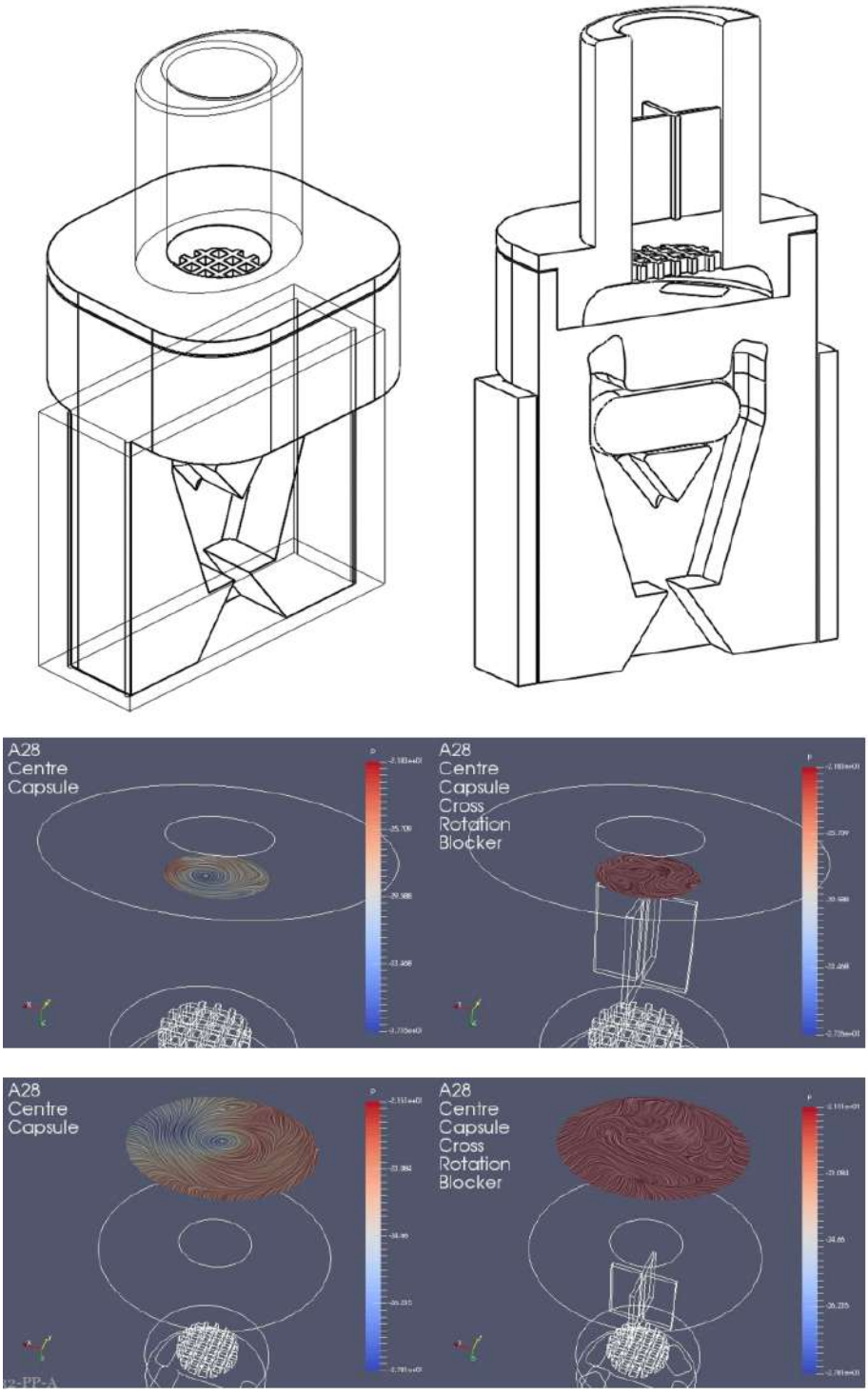

Figure 1a–d: Schematics of DPI device prototypes: (a) Prototype 1 without flow straightener and (b) Prototype 2 with flow straightener configuration. CFD simulations for (c) prototype 1 and (d) prototype 2 configuration.

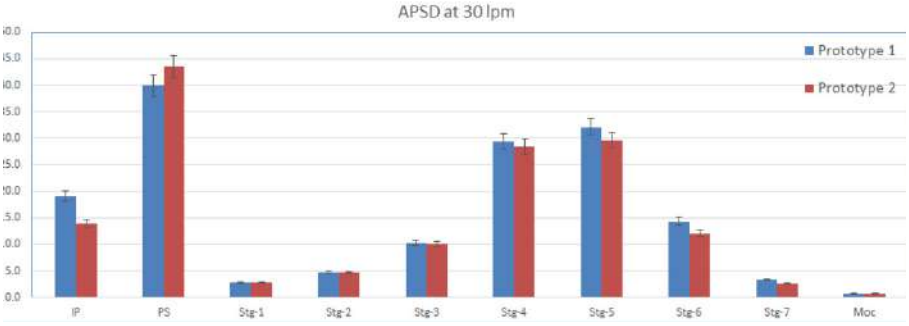

Figure 2: Comparison of NGI deposition of Prototype 1 and Prototype 2 at 30 lpm.

A modular engine set-up during development allowed for adapting small changes in the prototypes. Significant improvements could be achieved by changing different engine parameters. Figure 3 demonstrates the improvement in performance of the test data from Prototype 1 to 4. The NGI testing demonstrated the reduction in deposition in the Induction Port and pre-separator stage and increase in the lower stages of the impactor thereby increasing Fine Particle Fraction as we moved along our design development.

Resistance

The intrinsic resistance of a device is often discussed controversially in the literature. For Asthma/COPD applications, often low-resistance devices seem to be more beneficial for the patient struggling to achieve high flow rates. However, low resistances of a device often come along with a lower deposition of the fine particles of the API in the deep lung. Medium resistances have the big advantage of creating a deeper lung deposition.4 The inspiratory resistance of the new Presspart device was determined to be designed as a medium resistance device.

Another development target was to achieve a relatively flow rate-independent device. The airflow path was designed and optimised such that there was no significant difference in the fine particle fraction for flow rates ranging from 30ltr/min to 90ltr/min (Figure 4).

Evaluation of Different Formulation Types

Two types of formulations were studied a binary mixture and spray-dried engineered particles.

Budesonide a glucocorticoid is known for its property of its sticky nature, and its difficulty to de-aggregate was chosen as the candidate formulation. A binary mixture of a marketed formulation of lactose and budesonide 200 mcg per dose with a capsule fill weight of 25mg was selected to test the prototype. In addition, the performance was compared to a marketed Plastiape RS01 equivalent device. The novel Presspart device exhibited a high fine particle fraction compared to the marketed Plastiape RS01 device confirming the engine's efficiency (Figure 5).

In a study in a corporation with the University of Bonn, the performance of the novel DPI Device was assessed by testing a spray-dried Rifampicin formulation. More detailed information on that can be

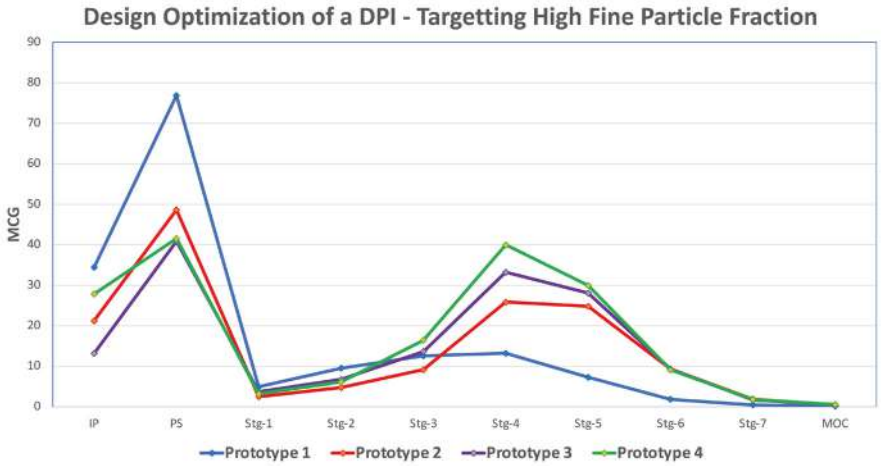

Figure 3: NGI Deposition profile of a Salbutamol Sulfate carrier-based formulation with different prototypes of the Presspart capsule-based device.

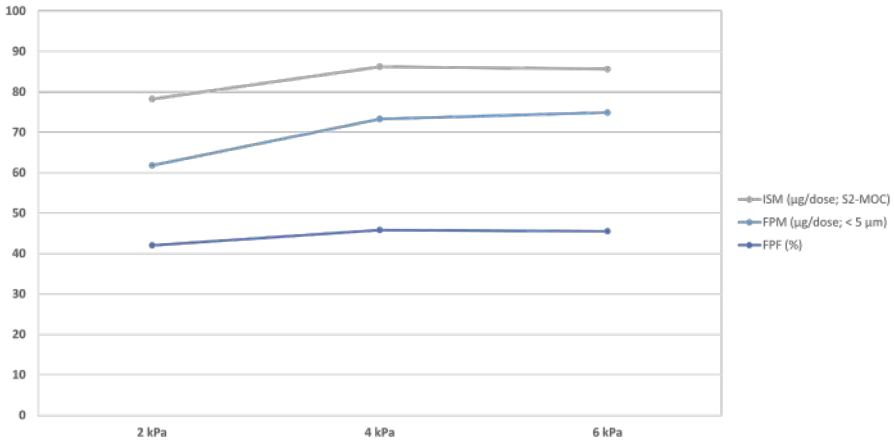

Figure 4: Fine Particle Delivery of Budesonide 200 µg Powder for Inhalation at 2, 4 and 6 kPa.

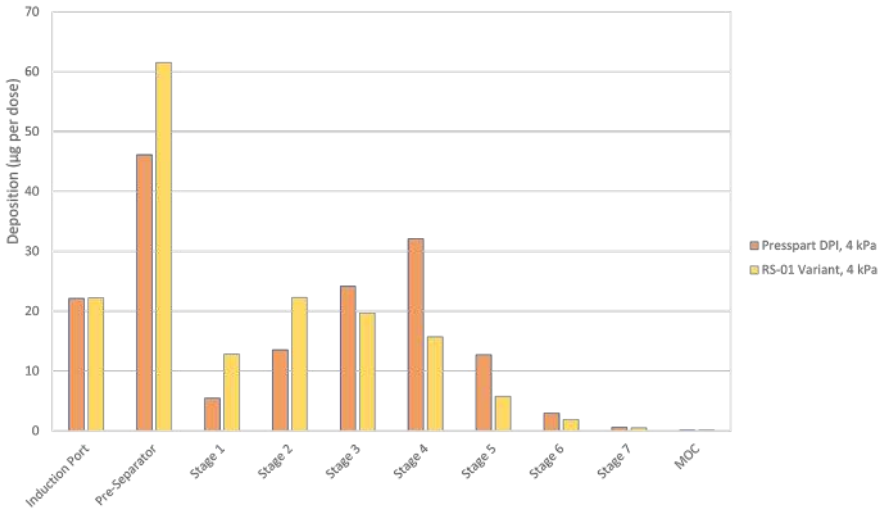

Figure 5: Comparison of NGI deposition profile of Presspart DPI and RS-01 Variant with Budesonide 200 µg Powder for Inhalation.

found in the recently published article.[5] The formulation was used to benchmark the Presspart device performance against devices already well introduced in the market. As shown in Table 1, the FPFs generated are highest for the PP device when compared to the commercially available standard devices Handihaler and RS01 equivalent.

Flowrate	PP-DPI	RS01	Handihaler
50 L/min	73.4 ± 3.2	66.3 ± 5.5	47.8 ± 4.2
100 L/min	63.5 ± 4.2	53.7 ± 4.2	46.6 ± 4.1

Table 1: Comparison of FPF at different Flowrates for Presspart (PP) Device, RS01 equivalent and Handihaler for the Rifampicin particle-engineered formulation.

Conclusion

Several key factors influence the performance of the dry powder inhaler device. The most important ones are the patient's inhalation technique, device handling and the device engine *i.e.* the efficiency of de-aggregation mechanism of the device. Targeting a medium resistance and a relatively flow rate independency were critical factors within the device development approach.

Various complementary techniques were used to study airflow and powder

de-aggregation behaviour within a device. Combining different development approaches of fast-paced prototyping, CFD technique and laboratory data for verification can effectively develop cost-effective high-performance DPIs for the inhalation market. These techniques enabled H&T Presspart to develop a hig-performance prototype independent of the formulation type tested (carrier-based as well as an engineered formulation).

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