Application of SmartTrack™ tools to the investigation of aerosolization and physico-chemical properties of vilanterol dry powder inhalers (DPIs)

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Key Message

SmartTrack™ is a collection of tools, which can be used to fast-track bioequivalence studies. Particularly, *in vitro* release testing was coupled with the orthogonal technique morphological directed Raman spectroscopy to discriminate the release rate of the impactor sized mass delivered by different inhalers and how it correlated to particle size.

Introduction

In vitro and *in vivo* studies are an essential part of bioequivalence (BE) assessment for DPIs. To determine BE it is fundamental to understand the physio-chemical properties of the ingredients of the formulation, which affect pharmacokinetics [1,2]. *In vitro* release testing (IVRT) provides a measure of bioavailability [3]. Previous *in vitro* dissolution models lacked a discriminatory capability due to limitations of aerosol collection [4,2]. Thus, SmartTrack™ IVRT was devised to allow an uniform collection of the impactor sized mass (ISM) over a large filter area, potentially addressing this issue [2].

In a previous study, discriminatory ability of IVRT to highlight differences in particle size distribution was assessed [5]. The difference between test and reference product was very evident when looking at formulation PSD. However, it was not possible to identify the contribution of other physico-chemical properties characteristic such as formulation composition, process and device employed for aerosolization, especially when comparing Relvar Ellipta® versus the in-house blends [5].

Therefore, in this study we investigated the effect of device and formulation composition by IVRR and utilising SmartTrack™ Morphological directed Raman spectroscopy (MDRS) analysis, as morphological characteristics has a well-known effect on IVRR and dissolution [6].

Experimental Methods

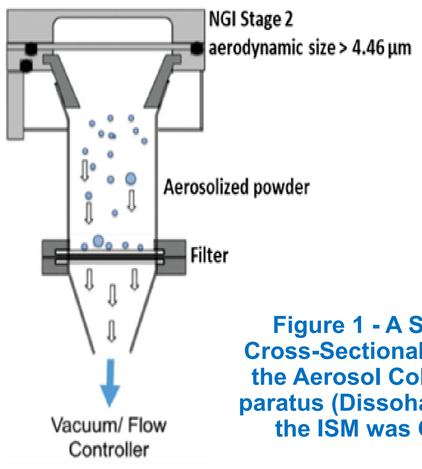

Figure 1 - A Schematic Cross-Sectional Diagram of the Aerosol Collection Apparatus (Dissohale) in which the ISM was Collected

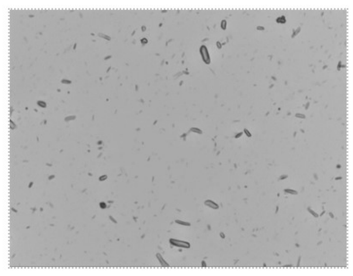

Figure 2 - 50x magnification of particles on filter before MDRS

Figure 3 - Ewerka dissolution machine for IVRT analysis

A Relvar Ellipta® 92/22 µg DPI (GlaxoSmithKline, UK) was dissembled to remove 2 blister strips, containing fluticasone furoate (FF) and the other containing vilanterol trifenatate (VIL). Powder was extracted from each blister strip and blister content identified by high pressure liquid chromatography (HPLC) with ultraviolet (UV) detection. Hypromellose size 3 capsules (Qualicaps Inc., ES) were filled with the either VIL powder comprised in one pocket of the blister or with the amount of one pocket of VIL blister and one pocket of FF blister, these were mixed via vortex and then loaded into a RS01 device (Plastiape S.p.A., IT) and actuated at 60 L/min. The standard device and a modified version containing only the vilanterol blister strip was also tested (a pressure drop test showed no difference in device resistance).

The ISM was deposited with Dissohale system set, on a filter (cellulose nitrate 1.2 µm) then assembled in Nanopharm-designed immersion cell. IVRT study was carried out using USP II apparatus and phosphate buffer pH 7.4 at 37°C as medium. All samples were then analysed by HPLC, IVRR was calculated with the Higuchi model [7]. A filter from each configuration was analysed in a Morphology4-ID (Malvern Panalytical, UK) by automated particle imaging and Raman chemical spectroscopy. VIL was identified and differentiated from other formulation components (such as lactose) against a chemical library and its morphological characteristic extracted.

Results and Discussion

Table 1 – MDRS Parameters for Particle Size Distribution and Morphology of VIL Particles Collected with Dissohale (n=3)

	PSD				*Morphological characteristics*			
Sample	**Circular Equivalent Diameter [n, 0.1] (µm)**	**Circular Equivalent Diameter [n,0.5] (µm)**	**Circular Equivalent Diameter [n, 0.9] (µm)**	**Span**	**Circular Equivalent Diameter median (µm)**	**Elongation Mean**	**Solidity Mean**	**Convexity Mean**
Ellipta VIL	1.34 (0.05)	2.14 (0.06)	3.38 (0.19)	0.95 (0.04)	2.31 (0.09)	0.28 (0.00)	0.91 (0.01)	0.83 (0.01)
Ellipta VIL and FF	1.43 (0.22)	2.25 (0.22)	3.26 (0.43)	0.99 (0.05)	2.43 (0.28)	0.26 (0.00)	0.87 (0.02)	0.72 (0.07)
RS01 VIL	1.19 (0.07)	1.96 (0.03)	3.01 (0.02)	0.93 (0.04)	2.10 (0.05)	0.27 (0.02)	0.90 (0.02)	0.81 (0.02)
RS01 VIL and FF	1.20 (0.07)	1.87 (0.02)	3.08 (0.09)	1.00 (0.01)	2.05 (0.05)	0.27 (0.01)	0.89 (0.01)	0.81 (0.02)

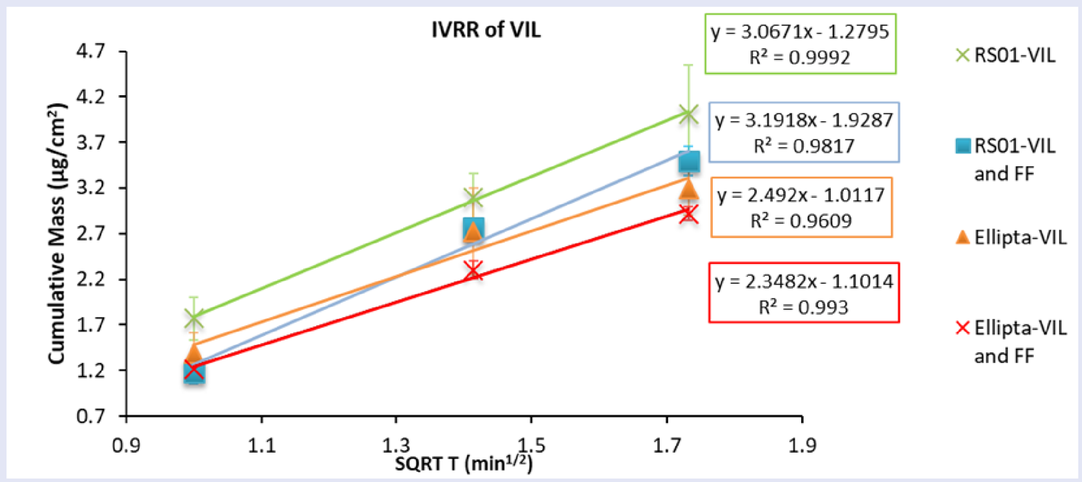

Figure 4 - IVRR of ISM of VIL and VIL/FF aerosolised from Ellipta and RS01 inhalers at 60 L/min (n=3).

The MDRS data (Table 1) showed differences in particle size for the different configurations, despite formulation was coming from the same batch. The span of the particles was slightly affected by chemical composition of the powder. The presence of FF during the aerosolization process resulted in a slight increase of the span of the VIL particles, regardless of the device employed for aerosolization. However, the type of device employed seemed to affect the mean circular equivalent diameter (CED [n,0.5]) which was statistically different across the two devices for each composition ($p < 0.05$). This indicates that a change of device can influence ISM particle size even when the same powder and formulation is employed.

The effect of the device type and formulation composition however, on the previously unmentioned morphological parameters was negligible. The four samples displayed equivalent elongation, solidity and convexity. This outcome showed that in the case studied, neither the device used nor the formulation composition influenced particle morphology, but we could detect differences on the particle size distribution (PSD) of the aerosolized API, deposited within the ISM.

The solubility of VIL (~65 µg/mL) was high leading to a very quick release of API in this medium. In the previous study [5] we had found that the span was the correlating factor when testing blends comprising VIL manufactured with different PSD.

The IVRR (Figure 4) shows that there is a statistically significant difference ($p < 0.05$) between devices used. A capsule-based device increased the release rate (faster release) despite both devices were actuated at 60 L/min [8], showing a high initial release rate and a quicker plateau of the ISM compared to the Ellipta DPI. This outcome may be correlated to the lower CED [n,0.5] observed by MDRS for RS01 device compared to the Ellipta device. Formulation composition seemed, instead, not to be correlated with the observed release rates.

Conclusion

This study focused on understanding how device and formulation composition may play a role on IVRR.

- **Differences in formulation composition determined only slight differences in PSD and no variation on morphology or IVRR.**
- **Device used for aerosolization caused statistically significant differences on the IVRR for both formulation compositions investigated, inversely correlated to the lower CED observed for the capsule-based device.**
- **Generally, the discriminatory ability of IVRT was demonstrated. This allows to pick up differences in particle size and mechanism of aerosolization. Therefore, it may be a useful tool in determining bioequivalence between T and R products.**

References

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