

The Technical Challenges of the Developing Existing Inhalation Drug Products into New Metered Dose Inhaler Designs

Neha Patel¹, Alex Slowey¹ & Lester Harrison²

¹3M Drug Delivery Systems Division (DDSD), Charnwood Campus, 10 Bakewell Road, Loughborough, Leicestershire, LE11 5RB, UK

²3M Drug Delivery Systems Division (DDSD), 3M Center, St. Paul, MN 55144-1000, USA

Introduction

Many of the best-selling inhaler products currently on the market deliver drugs that have been around for decades, yet the complex regulatory pathway required to develop generic inhalers has resulted in few generic inhalers being available on the market. In general, companies have chosen to develop 'branded generic' products using the same drug substances and inhaler design as the reference product on the market using the 505(b)(2) regulatory pathway in the US or Article 10.3 submission in the EU.

An alternative approach is to develop existing drug substances into new inhaler designs that contain the same drug substances currently in the reference inhaler product, but within an entirely new delivery system e.g. developing a new metered dose inhaler (MDI) that delivers drugs which are currently delivered via a dry powder or soft mist inhaler (SMI). This approach may be chosen due to intellectual property considerations, as a product lifecycle management strategy or to provide market differentiation (e.g. using improved inhaler technologies).

The MDI has a prominent place in the market, however there are many inhaled drugs which are not available in this format. There are several benefits from patient use of an MDI including MDIs are essentially functionally uniform, independent of the manufacturer, they are familiar, and the majority of patients will have experience of using an MDI as a rescue inhaler. In addition to this, MDIs provide multiple doses in each device and have a low resistance, which is particularly beneficial for those patients with limited airway capacity. Ultimately the availability of an MDI provides patients and providers with a choice in the case where this may be their preferred format.

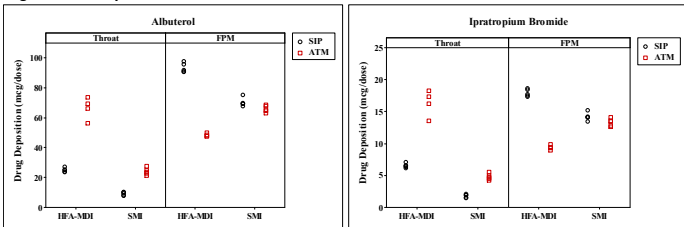
This poster illustrates some of the technical challenges associated with developing existing drug substances into new inhaler designs, with the consideration of more complex in-vitro and in-vivo relationships, in the form of a case study:

Can an HFA MDI be developed to be comparable to Combivent® RespiMat®?

In-Vitro Investigations

- The Combivent® RespiMat® product is an aqueous SMI, which delivers 20mcg of ipratropium bromide and 100 mcg of salbutamol per dose
- It is significantly different compared to an MDI in terms of both the delivery system and the formulation
- Historically Combivent was available on the market in a CFC-containing MDI format - the CFC MDI required essentially double the dose compared to the RespiMat, yet these products were shown to be clinically comparable
- In assessing the viability of an HFA MDI version of this product, the strategy was to target a product that would be comparable to the CFC MDI in-vitro, specifically focused on FPM
- Additionally, clinically relevant testing with an ATM was included to aid understanding of the in-vitro-in-vivo relationship (IVIVR) - the need to employ clinically relevant testing has previously been reported as being critical when in-vitro data are being used to predict in-vivo behaviour of an MDI product, particularly when comparing different inhalation dosage forms¹
- Due to the significant differences between these dosage forms and the expected lack of in-vitro-in-vivo correlation, a proof of concept (POC) Pharmacokinetic (PK) study was carefully designed to establish an IVIVR and to allow interpolation of the data for future product optimisation if required
- 3M HFA MDI product variants were formulated to be comparable to Combivent® CFC MDI in terms of aerodynamic particle size distribution (APSD)
- The inhalers were tested using a Next Generation Impactor (NGI) (Copley, UK) with both a standard induction port (SIP) and a medium anatomical throat model (ATM) (Emmace Consulting AB) at 3M DDSD (Loughborough, UK)
- The NGI test methodology was adapted to ensure its suitability for testing the aqueous SMI, and all testing was performed at a constant flow rate of 30Lmin⁻¹

Figure 1: Aerodynamic Particle Size Distribution - Throat and Fine Particle Mass

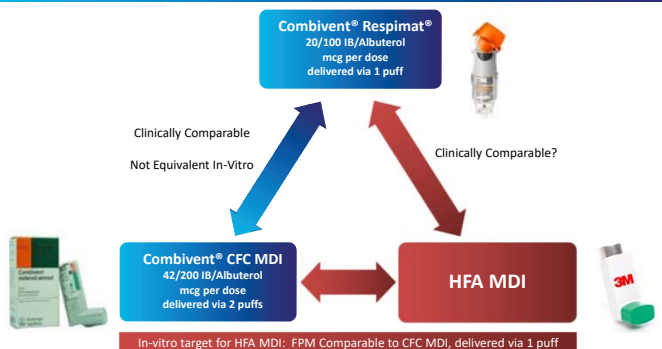


- The data presented in Figure 1 clearly demonstrate that clinically relevant in-vitro testing is key if these data are to be helpful in predicting expected PK or clinical outcomes
- Throat deposition is higher with the anatomical throat compared to the standard induction port for the MDI with a corresponding decrease in the FPM
- Use of an ATM for APSD testing has a major impact in terms of clinical relevance for the MDI in particular
- The FPM of the MDI and the SMI are comparable but not the same when tested with the ATM
- The FPM of the RespiMat SMI is slightly higher than the MDI, which agrees with data recently presented by Wei et al., where it was demonstrated that this ATM provides a reasonable prediction of lung dose for MDIs, but that it overestimates the lung dose for the RespiMat® SMI².
- These data were considered to provide an acceptable in-vitro baseline to progress to a POC PK study to determine the potential for PK comparability between the HFA MDI and the SMI products

References

- Holmes S, Slowey A: *A Comparison of Different Anatomical Throats vs The USP Throat*. Drug Delivery to the Lungs (DDL2017), 2017
- Wei X, Hindle M, Kaviratna A, Huynh B, Delvadia R, Sandell D, Byron P: *In Vitro Tests for Aerosol Deposition. VI: Realistic Testing with Different Mouth-Throat Models and In Vitro-In Vivo Correlations for a Dry Powder Inhaler, Metered Dose Inhaler, and Soft Mist Inhaler*. J Aerosol Med Pulm Drug Deliv. 2018; 31: pp1-14

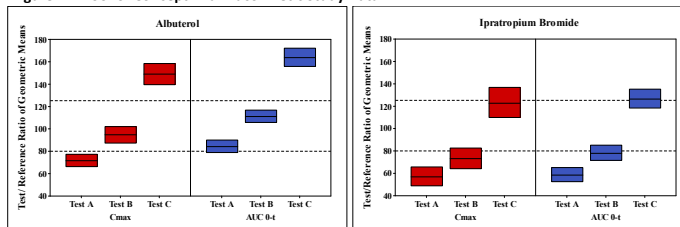
Strategy



In-Vivo Investigations

- The POC PK study was designed to compare the HFA MDI to the Reference (Combivent® RespiMat®) to provide confidence in the ability to define the target dose for HFA MDI
- An FPM range of approximately 80% – 160% compared to CFC MDI target were selected in order to establish an IVIVR
- The study was conducted open label in healthy adult male and female subjects (Novum PRS, Houston TX, USA)
- All subjects received Test Treatments A, B and C and one Reference Treatment, according to a balanced four-period randomized cross-over design:
 - Reference: Combivent® RespiMat®
 - Test A: FPM below-target (approx. 80% compared to the CFC MDI)
 - Test B: FPM on-target compared to the CFC MDI and
 - Test C: FPM above-target (approx. 160% compared to the CFC MDI)
- Subjects were fasted overnight (no food or beverages except water) for at least 10 hours before and until 3 hours following each dose. Subjects were required to demonstrate proper inhalation technique with a placebo pMDI inhaler
- For each study treatment and at each specified time, two blood samples were collected for the pharmacokinetic analyses of ipratropium bromide and albuterol in the plasma
- Pharmacokinetic parameters were calculated for each drug and compared. Subsequent doses were given following 7-14 days wash out
- Acceptance Criteria: The mean C_{max} and AUC_{0-4} for a test product was considered bioequivalent to the respective mean values for the reference product if the 90% confidence interval for the ratio of geometric means is completely contained within the interval 80% to 125%

Figure 2: Proof of Concept Pharmacokinetic Study Data



- The data presented in Figure 2 demonstrate that for albuterol, Test product B, with FPM comparable to previous CFC MDI product, demonstrated bioequivalence for both C_{max} and for AUC_{0-4}
- The corresponding data for ipratropium bromide, demonstrated that Test Product B was slightly lower than the reference product for both C_{max} and AUC_{0-4}
- Whilst the ipratropium bromide component was determined to be slightly lower than the reference product in this instance, the study design allows interpolation of data, based on the established in-vitro-in-vivo relationship, to closely predict a product configuration that can achieve bioequivalence for both drug substances if required
- In-vitro testing of the test products using an ATM in combination with an NGI allowed the FPM and throat deposition to be assessed alongside the marketed reference product, which allowed a meaningful prediction to be made of the potential outcome of a POC PK study

Summary

- POC PK data confirm that an HFA MDI CAN be developed to match a SMI in terms of PK outcomes
- IVIVR challenges are even more complex when developing MDIs to match alternative dosage forms
- With the right POC PK study design, an IVIVR can be established to determine the HFA MDI dose required to achieve PK BE for C_{max} and AUC_{0-4}
- Availability of an MDI format for this and other inhaled drugs would provide increased choice for patients and prescribers who may have a preference for this format