

The Role of In Silico Regional Deposition Modelling and Pharmacokinetic Profiling in the Development of a Generic Tiotropium Dry Powder Inhaler

Irene Rossi,¹ William J. Ganley,¹ Olivier Michelet,² Benedicte Grosjean,² Segolene Sarrailh,² Gerallt Williams,² Robert Price¹ and Jagdeep Shur¹

¹ Nanopharm Ltd, Newport, UK

² Aptar Pharma, Le Vaudreuil, France

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INTRODUCTION

The rate and extent of drug absorption is traditionally determined *in vivo* through pharmacokinetic (PK) studies. In order to determine bioequivalence (BE) between a test (T) and a reference (R), clinical trials should be able to detect differences in the lung dose by comparing the area under the plasma concentration time curves (AUC_{0-inf}) and the peak plasma concentrations (C_{max}). Moreover, C_{max} and time to reach C_{max} (T_{max}) can be affected by formulation and device characteristics [1]; for example, if particles are deposited more centrally, slower drug releasing particles will be removed by mucociliary clearance, resulting in a smaller extent of absorption and smaller AUC_{0-inf} . Finally, drug deposition affects C_{max} , as absorption from the alveoli is assumed to be faster due to larger surface area, higher perfusion and thinner epithelial membranes [2]. In PK bioequivalence tests, inter-batch differences are usually assumed small enough to be ignored. However, batch to batch PK differences between marketed batches of an FDA-approved US drug product (fluticasone propionate/salmeterol dry powder oral inhalation product, Advair Diskus 100/50) were recently demonstrated in a study by Sandoz [3]. These differences were large enough to cause consistent failure when Advair Diskus 100/50 was compared to itself, without any correlation to *in vitro* parameters such as fine particle mass (FPM) lower than 5 μm .

In this study, realistic breathing profiles, in silico Regional Deposition Model (RDM) and physiologically-based PK simulation model were employed to compare a tiotropium generic formulation loaded in the Aptar Prohaler[®] with reference Spiriva[®] HandiHaler[®] DPI formulations.

METHODS

A formulation comprising tiotropium bromide (Tio) and lactose as carrier was produced and loaded into a Prohaler® (Aptar Pharma, USA) DPI device. This T was compared with four different batches of Spiriva® HandiHaler® (Boehringer Ingelheim, DE). The Nanopharm Inhalation Flow Profiling system (NIP) was used to record the breath profiles from a healthy volunteer using both devices. The system enabled the capture of the peak inspiratory flow rate and inhaled volume together with the profile of the entire inhalation through the test and reference device. DPIs were characterized in terms of Aerodynamic Particle Size Distribution (APSD) using a Next Generation Impactor (NGI, Copley Scientific, UK). Both devices were activated at a flow rate of 39 L/min for 6.2 seconds (producing a pressure drop of 4 kPa), and for each determination four doses were actuated. Samples collected were then analysed by HPLC and FPM, the Mass Median Aerodynamic Diameter (MMAD) and the Geometric Standard Deviation (GSD) were determined using CITDAS software from Copley Scientific.

RDM was conducted using the The National Council on Radiation Protection and Measurements (NRC) model, which has been modified to accept an aerosol bolus smaller than the total inhaled volume [4]. The model was used to estimate the extent of deposition in the tracheobronchial region (BB), defined as generation 0–8 of the Weibel lung model; the bronchiolar region (bb), generation 9–15 and the alveolar-interstitial region (AL), generation 16–23. For extrathoracic (ET) aerodynamic deposition the modelling is significantly more complex and can only be derived using an empirical basis reflecting the inertial motion of the particles. Due to the heterogenous nature of the respiratory tract and the differences in the physico-chemical properties and thickness of the airway surface lining (ASL) fluid throughout the lung, the local rate and extent of absorption is modelled throughout the entire Weibel A lung model. These absorption processes are modelled, with the inclusion of mucociliary clearance, for each of the 24 generations of the lung model. The local processes within a generation are independent of another and are highly dependent on the deposition pattern in the lung. A two-compartment PK model was utilised for systemic distribution and clearance for tiotropium. Tiotropium bromide a high aqueous solubility of around 25 mg/mL [5]. Systemic exposure is therefore expected to be absorption rather than dissolution limited. As such, dissolution in the model was assumed to occur instantaneously.

RESULTS AND DISCUSSION

Figure 1 shows APSD for T and R products. Prohaler® MMAD was 3.9 μm , impactor size mass (ISM) was 4.2 μg and FPM $<5 \mu\text{m}$ was 3.9 μg . Interestingly variability was found between the four batches of Spiriva® HandiHaler® tested. For batches 1, 2 and 4, deposition was similar and not comparable to Prohaler. Those batches were characterized by a lower FPM and MMAD than the test product. In contrast, the APSD profile of batch 3 of R was comparable to that of Prohaler.

The RDM (Figure 2) suggested that the ET deposition of Prohaler was 55.5% of the emitted dose and for R it ranged from 50.4–61.3%. The BB deposition was 8.3% and 9.1–10.4% for T and R, respectively. Similarly, the bb fraction was similar between T and R. Whilst the AL deposition for the test product was 31.2%, reference batches 1, 2 and 4 had lower AL deposition. Only R batch 3 had similar RDM to Prohaler®.

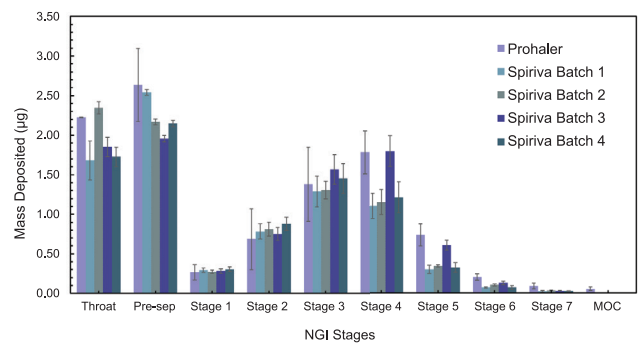


Figure 1. Aerodynamic particle size distribution for reference batches and test products (n=3).

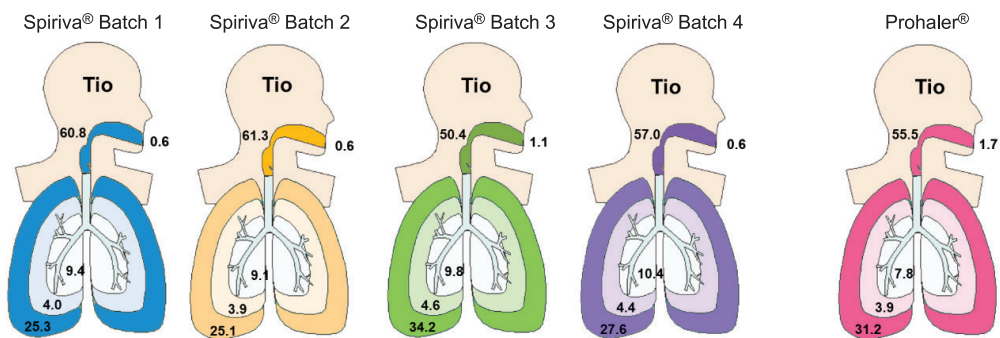


Figure 2. Regional deposition modelling for reference batches and test product (%).

AL deposition is known to impact PK results as in this region the epithelium is well perfused by blood vessels and much thinner than in shallower regions in the lung. AL fraction was similar for T and R batch 3, therefore for equivalent emitted dose R batch 3 would be expected to result in similar systemic exposure as T. This similarity in the predicted PK is shown in Figure 3 and Table 1. R batches 1, 2 and 4 had significantly lower C_{max} , which may be related to their lower predicted regional deposition.

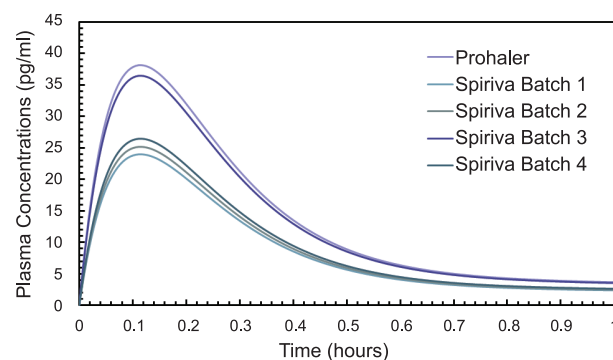


Figure 3. Simulated pharmacokinetic profiles for test and reference products up to 1 hour.

Table 1.

Summary of simulated pharmacokinetic parameters for the test and reference products.

	C _{max} (pg/mL)	AUC _{0–12hr} (pg hr/mL)
Prohaler®	38.14	31.21
Spiriva® Batch 1	24.00	20.65
Spiriva® Batch 2	25.18	21.59
Spiriva® Batch 3	36.50	30.36
Spiriva® Batch 4	26.45	22.81

CONCLUSIONS

Conventional compendial APSD testing can only partially predict *in vivo* product behaviour. In this study, a significant batch to batch variability in the *in vitro* performance of the reference product Spiriva® HandiHaler® was reported. Moreover, in silico modelling of the regional deposition and PK simulations was used to highlight that variability in the peripheral dose deposition will likely impact the PK profile of test and reference products. Once validated with actual PK data these in silico tools will be powerful in ascertaining in vitro and in vivo relationships for dry powder inhalers.

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