

# Characterisation of aerosols from solution-based pressurised metered dose inhalers (pMDIs) when delivered by PreciseInhale®

**Wachirun Terakosolphan<sup>1</sup>, Maria Malmjöf<sup>2</sup>, David Lewis<sup>3</sup>, & Ben Forbes<sup>1</sup>**

<sup>1</sup>Institute of Pharmaceutical Science, King's College London, SE1 9NH, UK

<sup>2</sup>Inhalation Sciences, Hälsovägen 7, Stockholm, Sweden

<sup>3</sup>Chiesi Limited, Chippenham, Wiltshire, SN14 0AB, UK

## Summary

The PreciseInhale® aerosol delivery system was evaluated by determining the similarity of the respirable drug particles emitted from several pressurised metered dose inhalers (pMDIs), compared to when characterised using a compendial testing apparatus, Next Generation Impactor (NGI).

The results showed that the aerosols from each pMDI analysed in each testing apparatus were clearly equivalent in terms of aerodynamic particle size and morphology.

These data confirm that when administered via the PreciseInhale® system, the aerosols were equivalent to those analysed using the NGI.

## Results and Discussion

The aerodynamic sizing of particles emitted from four inhalers are shown in Table 1, including some previously reported data<sup>[2,5]</sup>. The MMAD of **solely BDP particles from Qvar were significantly smaller** than those from Clenil and in-house pMDIs ( $p < 0.001$ ). **The glycerol-containing Clenil produced the largest particles**, compared to those from the other inhalers ( $p < 0.001$ ). There was **no significant difference in the aerodynamic size between the tailored 'red and blue' inhalers** which were engineered to generate aerosols with equivalent aerodynamic performance<sup>[5]</sup>.

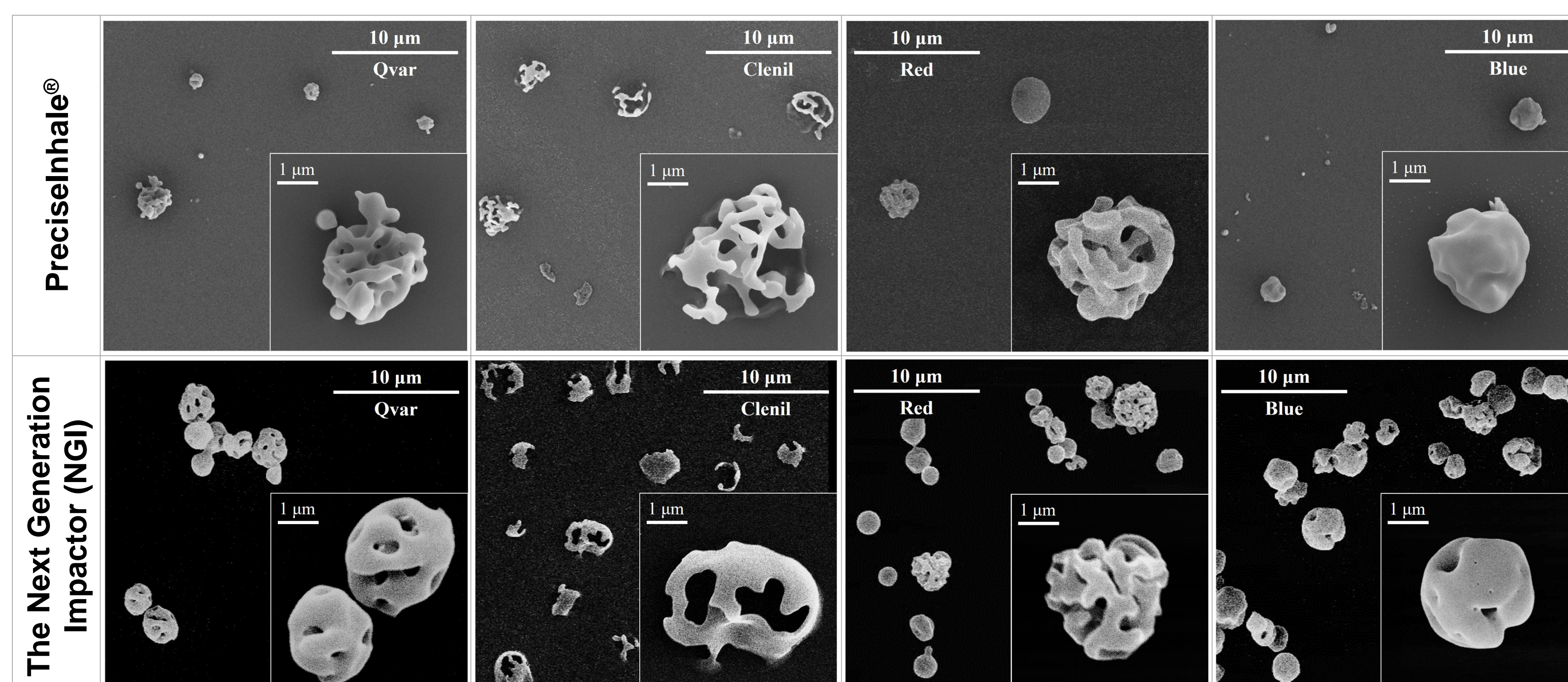
The morphology of the particles emitted from each pMDI and collected in PreciseInhale® and NGI, are shown in Figure 1. **The glycerol-free particles from Qvar and red formulation were mainly spherical and porous**. In comparison to the glycerol-containing inhaler, **Clenil generated larger and more irregularly**

shaped with fractured surfaces which may be a result of the volatile excipients evaporated after the particles formed with a glycerol shell<sup>[5]</sup>. In contrast, **the blue pMDI which also contained glycerol produced smaller and more spherical drug particles with smoother surfaces than those from Clenil**. It may be because the blue formulation contains less glycerol and uses a higher volume metering chamber<sup>[6]</sup>, leading to higher pressure and smaller droplet size during actuation. Hence, glycerol in the smaller droplet may experience different dynamics of volatile excipient evaporation during the formation of particles.

The aerodynamic particle size and appearance of **the particles emitted from each pMDI formulation were alike in all analyses**, verifying that the aerosols delivered from all inhalers through the PreciseInhale® aerosol system were in the form of respirable particles that were identical to those collected and characterised in the compendial testing apparatus.

**Table 1.** Aerodynamic particle size data for the emitted particles of each formulation from different testing apparatus (MMAD ± GSD; n = 3)

Testing apparatus	Licensed inhalers		In-house inhalers	
	Qvar® (glycerol-free)	Clenil® (glycerol-containing)	Red (glycerol-free)	Blue (glycerol-containing)
PreciseInhale® (Weight)	1.20 ± 2.11 µm	3.88 ± 1.65 µm	2.39 ± 1.84 µm	2.39 ± 1.96 µm
PreciseInhale® (HPLC)	1.28 ± 2.15 µm	3.94 ± 1.69 µm	2.42 ± 1.83 µm	2.41 ± 2.04 µm
Next generation impactor (NGI)	1.17 ± 1.88 µm	3.19 ± 2.05 µm	2.01 ± 1.93 µm	2.54 ± 1.96 µm
Andersen cascade impactor (ACI)	1.13 ± 1.98 µm <sup>[2]</sup>	2.77 ± 1.89 µm <sup>[2]</sup>	2.4 ± 2.1 µm <sup>[5]</sup>	2.5 ± 1.9 µm <sup>[5]</sup>



**Figure 1.** Scanning electron microscopic images of particles from each pMDI formulation using different capturing apparatus at lower magnification (bar: 10 µm) to show the typical particle distribution and at higher magnification (bar: 1 µm, inset) to show the morphology of particles.

## Introduction

Glycerol is incorporated in some solution pressurised metered dose inhalers (pMDIs) to modify the particle size distribution of aerosol droplets<sup>[1]</sup>. Nevertheless, evidence is emerging that glycerol may influence the drug kinetics after particle deposition in the lungs<sup>[2]</sup>. To probe this, the PreciseInhale® aerosol system<sup>[3]</sup> will be employed to administer the particles emitted from pharmaceutically-equivalent pMDIs with the presence or absence of glycerol as the only variable.

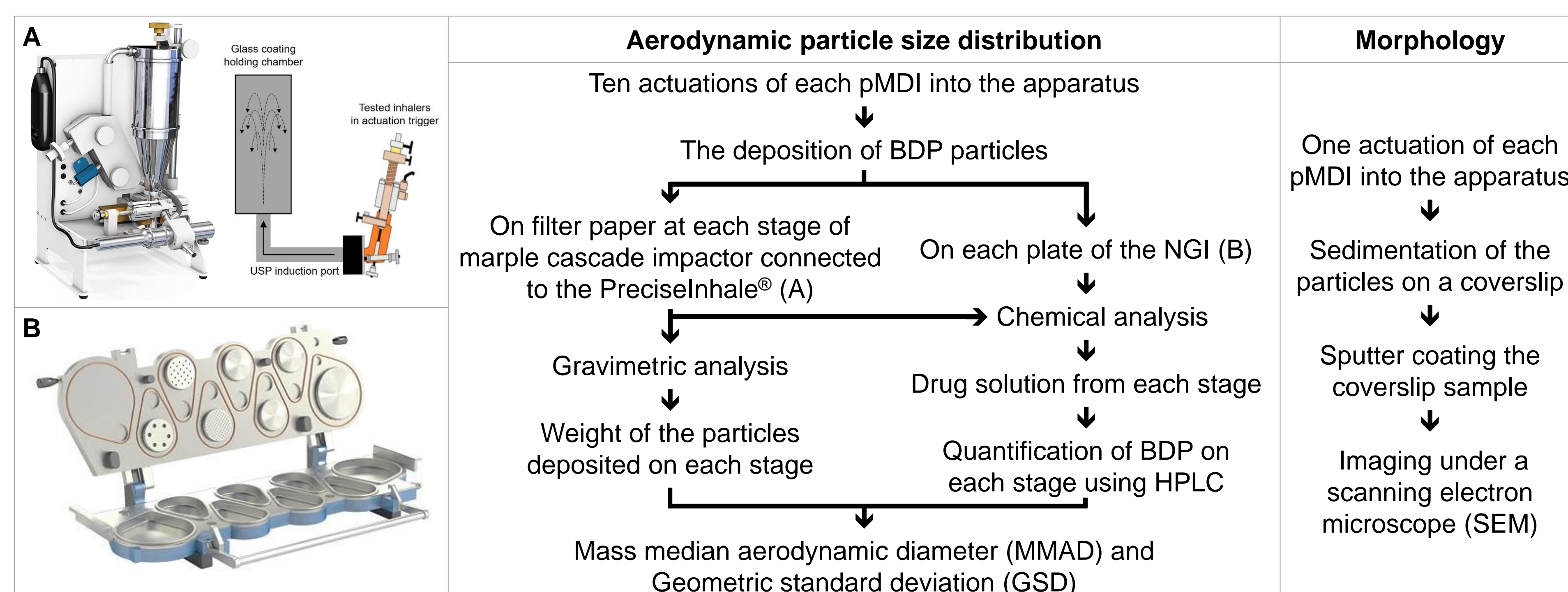
Accordingly, the characteristics of the drug particles aerosolised through PreciseInhale® need to be verified that they are equivalent to those from standard tests for an orally inhaled product<sup>[4]</sup> using a compendial testing apparatus (Next Generation Impactor; NGI).

This work aimed to evaluate the PreciseInhale® aerosol delivery system as a means of delivering drug particles from pMDI formulations for investigating the effect of glycerol on drug delivery via the lungs.

## Materials and Method

Four beclomethasone dipropionate (BDP) pMDIs were selected to generate the particles in this work. Qvar® 100 aerosol and Clenil® Modulite® 100 were from Teva Ltd. (UK) and Chiesi Ltd. (UK), respectively. The in-house inhalers (glycerol-free and glycerol-containing formulations) were manufactured by Chiesi Ltd. (UK).

Aerodynamic particle size and morphology of the drug particles emitted from each pMDI were characterised using two testing apparatus; PreciseInhale® and NGI (Scheme 1).



**Scheme 1.** Scheme of the method for the characterisation of particles emitted from pMDI formulations using PreciseInhale® aerosol system (A) and the next generation impactor (B)

## Conclusion

The properties of the aerosols from each inhaler were equivalent in both PreciseInhale® and NGI, implying that the particles formed and delivered in the Precise Inhale® possess the same properties as those tested using standard *in vitro* techniques. This approach has validated apparatus for *in vivo* pre-clinical studies into the effect of glycerol on BDP pharmacokinetics.

## References

1. G. Brambilla *et al.*, *Int. J. Pharm.* **186**, 53–61 (1999).
2. C. I. Grainger *et al.*, *Mol. Pharm.* **9**, 563–569 (2012).
3. E. Selg *et al.*, *J. Aerosol Med. Pulm. Drug Deliv.* **26**, 181–189 (2013).
4. B. Forbes *et al.*, *AAPS J.* **17**, 837–852 (2015).
5. D. A. Lewis *et al.*, *Eur. J. Pharm. Biopharm.* **86**, 31–37 (2014).
6. M. Haghi *et al.*, *Eur. J. Pharm. Biopharm.* **86**, 38–45 (2014).

