Comparative *in vitro* evaluation of aerosolization behaviour of heterogeneous carriers: Multi Stage Liquid Impinger *versus* Next Generation Impactor

Waseem Kaialy[1,2], Ali Nokhodchi[1]

[1]Chemistry and Drug Delivery Group, Medway School of Pharmacy, University of Kent, ME4 4TB, Kent, UK; [2]Pharmaceutics and Pharmaceutical Technology Department, School of Pharmacy, University of Damascus, Syria; w.kaialy@kent.co.uk

ABBREVIATIONS

Acetone crystallized mannitol, ACM; Bulk density, D_b; Carr's index, CI; Commercial lactose, CL; Commercial mannitol, CM; Cooling crystallized mannitol, CCM; Differential scanning calorimetry, DSC; Elongation ratio, ER; Ethanol crystallized mannitol, ECM; Fine particle dose, FPD; Fine particle fraction, FPF; Fourier transform infrared spectrometry, FT-IR; Geometric standard deviation, GSD; High performance liquid chromatography, HPLC; Impaction loss, IL; Mass median aerodynamic diameter, MMAD; Multi-Stage liquid impinge, MSLI; Next generation impactor, NGI; Particle size distribution, PSD; Salbutamol sulphate, SS; Scanning electron microscopy, SEM; Volume mean diameter, VMD.

INTRODUCTION

Inertial impaction methods performed by cascade impactors are considered as 'the golden standard' for testing of the inhalers, because they are capable to give information about the aerodynamic particle size, which is deeply related to particle deposition in the airways (1). With the previous studies demonstrating the variability of impactor efficiency with respect to drug type and dose, there is increased need to investigate the equivalence, or difference, of *in vitro* aerosolization performance using different cascade impactors. To best of our knowledge, there is no study to compare the drug deposition profiles in the case of carriers with considerably different morphologies using MSLI and NGI. To this end, carriers with an elongation ratio (ER) ranges from 1.6 (subrounded shape) up to 5.9 (needle shape) were selected (Figure 1), and drug inhalation behaviour was analyzed using MSLI and NGI.

METHODS

Five different carriers were used in this study, i.e., commercial mannitol (CM), commercial lactose (CL), batch cooling crystallised mannitol (CCM), acetone crystallised mannitol (ACM) and ethanol crystallised mannitol (ECM) (2). Sieved 63-90 µm carrier particles were then characterised in terms of size (laser diffraction), shape (image analysis and SEM), flowability, density, and solid-state (DSC and FT-IR). *In vitro* aerosolisation assessments were performed using both MSLI and NGI operating at flow rate of 92 L/min using Aerolizer® inhaler device. Amounts of salbutamol sulphate (SS) drug were quantified using HPLC (Waters, USA). Fine particle fraction (FPF) was calculated as the percentage of fine particle dose ($FPD_{\leq 5\ \mu m}$) to the recovered dose. Impaction loss (IL) was the per cent amounts of the drug deposited on the inhaler with mouthpiece adaptor plus throat to the recovered dose.

RESULTS AND DISCUSSION

The differences in carrier shape (Figure 1) resulted in variability of carrier powders in terms of particle size (e.g. VMD), flowability (e.g. CI), porosity, density and solid-state form (Figure 1; Table 1).

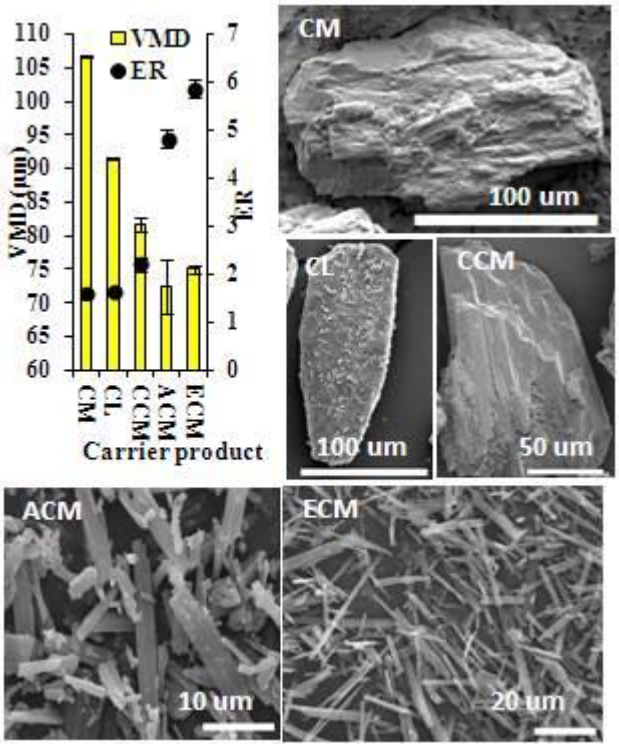

Figure 1. Volume mean diameter (VMD), elongation ratio (ER) and SEM images of CM, CL, CCM, ACM and ECM carriers.

Carrier Product	D_b (g/cm^3)	CI (%)	Porosity (%)	Polymorphic form
CL	0.55±0.00	17.0±2.6	64.0±0.1	α–
CM	0.62±0.01	18.1±1.7	59.8±2.3	β–
CCM	0.44±0.01	19.8±1.3	70.3±0.5	β– + δ–
ACM	0.11±0.01	33.3±4.1	92.6±0.5	α–
ECM	0.06±0.00	38.0±2.0	95.9±0.2	α–

Table 1. Physical properties, i.e., bulk density (D_b), Carr's index (CI), porosity and polymorphic form, of different carrier products investigated.

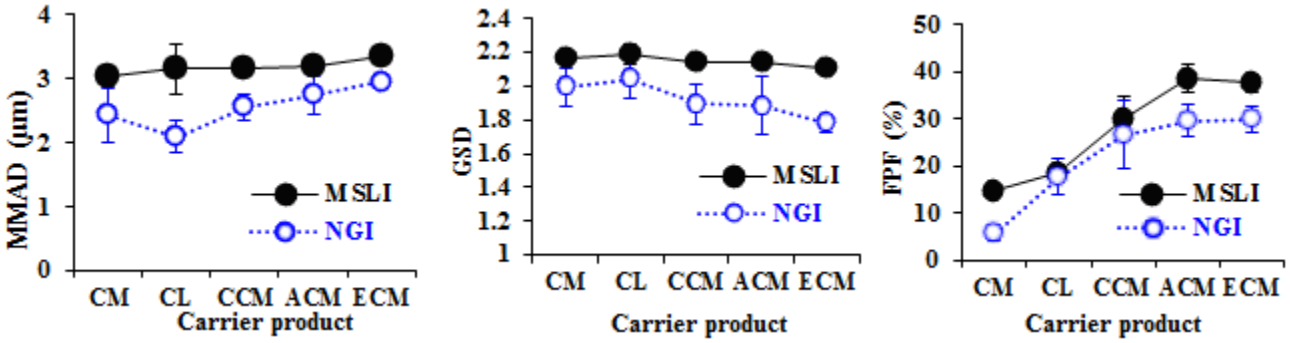

Figure 2. MMAD, GSD and FPF of SS generated by heterogeneous carriers, i.e., CM, CL, CCM, ACM and ECM as analyzed by MSLI and NGI.

Carriers with higher ER demonstrated smaller bulk density, smaller tap density, higher porosity and poorer flow properties (Figure 1, Table 1).

In comparison to MSLI, the obtained PSD data from NGI had bias towards smaller sizes (Figures not shown), due to possible bounce effects and inter-stage loses. NGI provided more accurate size fractionation than MSLI, because it resulted in steeper impaction-stage collection efficiency curves. In comparison to MSLI, NGI demonstrated generally smaller MMADs, smaller GSDs and smaller FPFs (Figure 2).

Both impactors showed good agreement in terms of relative aerosolization behavior such as FPF (r^2 = 0.8884) and IL (r^2 = 0.9745) (Figure 3). However, with increasing the elongation ratio of mannitol carrier particles, the absolute variations between GSDs (△GSDs) and between FPDs (△FPFs) increased whereas the absolute variations between MMADs (△FPFs) decreased (Figure 4).

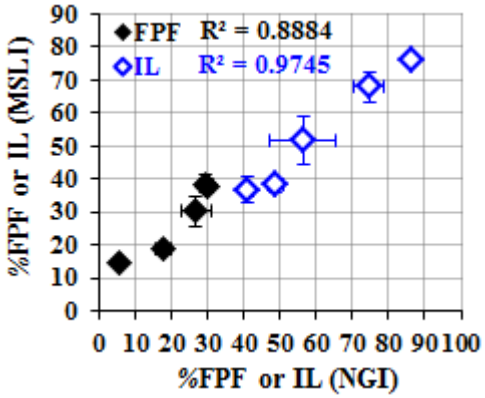

Figure 3. FPF and IL of SS generated by heterogeneous carriers, i.e., CM, CL, CCM, ACM and ECM as analyzed by MSLI in relation to FPF and IL analyzed by NGI.

CONCLUSION

MSLI and NGI demonstrated agreement in terms of relative *in vitro* aerosolization performance of dry powder inhalers formulated with heterogeneous carriers having considerably different morphologies. However, formulators could expect some discrepancies when operating different impactors. For example, in comparison to NGI, MSLI demonstrated higher fine particle fractions. Despite the aerosolization performance has increased with the elongation ratio of carrier particles, there was a concurrent decrease in the absolute equivalency of the deposition data between MSLI and NGI in terms of GSD and FPF.

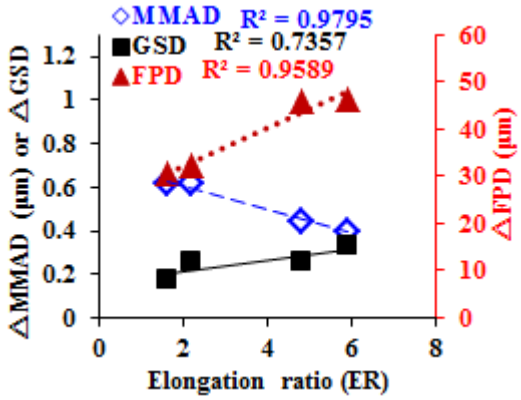

Figure 4. Absoulte difference between MMAD, GSD and FPD in relation to ER of carrier product.

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