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Kaialy, Waseem, Larhrib, El Hassan and Nokhodchi, Ali

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THE EFFECT OF CARRIER PARTICLE SIZE ON ADHESION, CONTENT UNIFORMITY AND INHALATION PERFORMANCE OF BUDESONIDE USING DRY POWDER INHALERS

W. Kaialy,[1, 2] H. Larhrib[1] and A. Nokhodchi[1]

[1]Chemistry and Drug Delivery Group, Medway School of Pharmacy, University of Kent, Kent ME4 4TB, UK
[2]Pharmaceutics and Pharmaceutical Technology Department, University of Damascus, Damascus 30621, Syria

1 INTRODUCTION

Dry Powder Inhalers (DPIs) are the result of the development of two technologies: powder technology and device technology. Particle deposition in the respiratory tract is affected by many aerosol particle properties such as particle size, shape, density, charge, and hygroscopicity.[1] In particular, particle size is of great importance as it is known that particle-particle interactions within DPI formulations are related to van der Waals forces. Therefore, particle size is the most important physical property and design variable of a DPI formulation. Several studies were reported on the effect of drug particle size on DPI performance, showing that the preferred drug particle size is between 1-5 μm.[2] However, in literature, the effect of carrier particle size distribution (PSD) on drug aerosolisation efficiency has received less attention and reported in dissimilar manner.[3] Nevertheless, it should be noted that there is rare studies aimed to show the effect of carrier particle size as a single variable factor on DPI performance. In this study, the effect of lactose particle size distribution on budesonide adhesion, content uniformity and *in vitro* aerosolisation performance was investigated.

2   METHODS AND RESULTS

2.1 Micromeretic, solid state, and flow properties

Commercial α-lactose monohydrate powder was sieved to obtain different lactose samples with different size fractions as follows: A (90-125 μm), B (63-90 μm), C (63-45 μm), D (20-45 μm) and E (< 20 μm). Laser diffraction and scanning electron microscope observations showed that different lactose powders have considerably different size distributions and different surface topographies (Figure 1). Span values indicated narrower size distributions for lactose powders with smaller volume mean diameter (VMD) (r^2=0.9792, Span= 0.417 ln (VMD) +2.6386). Fine particle lactose (FPL$_{<10\mu m}$), which was reported to have dominating effect on DPI performance,[4] was absent in sample A, B, and C whereas sample D and E

contain $5.2\pm0.2\%$ and $36.8\pm2.4\%$ of $FPL_{<10\mu m}$, respectively. Higher specific surface area (SSA_v) was obtained for lactose samples with smaller volume mean diameter, higher span (linear, $r^2=0.9723$), and higher fine particle lactose (linear, $r^2=0.9736$).
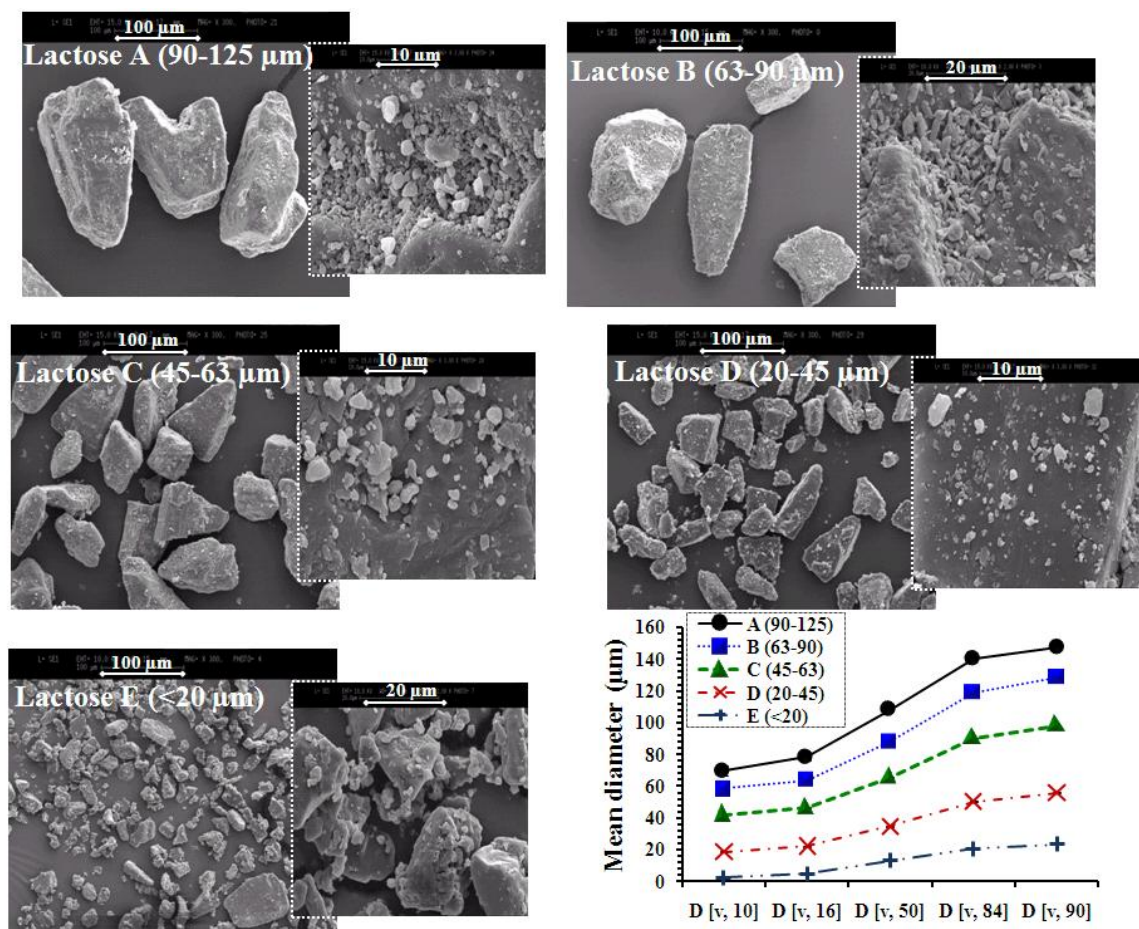

Figure 1 *Scanning electron micrographs (SEM) and PSD of different lactose samples.*
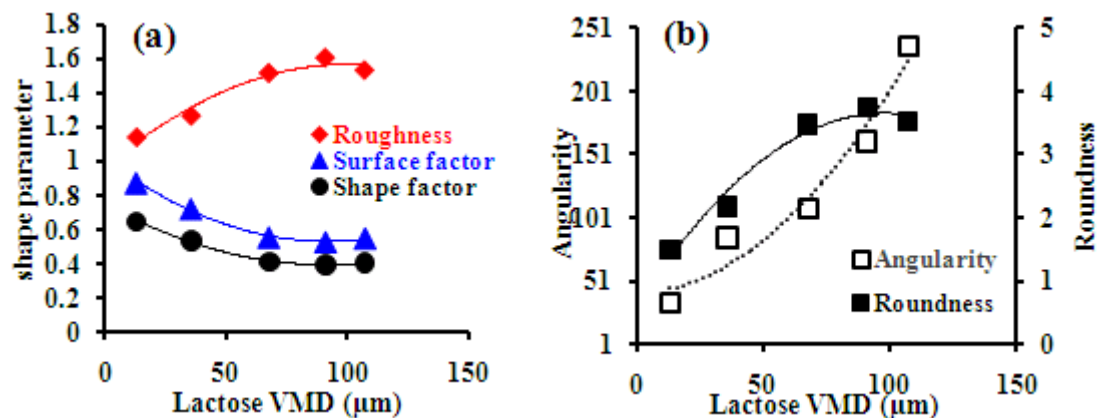
Figure 2 *Roughness, surface factor, and shape factor (a); angularity and roundness (b) for different lactose samples.*

Particle shape image analysis showed that lactose powders with smaller size have higher shape factor, higher surface factor, smaller roughness (Figure 2a), higher roundness, and higher angularity (Figure 2b). This indicates smoother surface and higher degree of shape regularity for lactose particles with smaller size.

Differential scanning calorimeter was employed to characterise the crystalline nature of all lactose samples (Figure 2). All lactose samples showed the typical thermal curve of α-lactose monohydrate consisting of two distinctive endothermic peaks at about 148° C and 219°C and one smaller exothermic peak at about 175 °C corresponding to dehydration of crystalline hydrate water, melting of α-lactose, and crystallisation of amorphous lactose. [5]

Lactose samples with smaller size showed larger exothermic peak at about 175 °C, which is indicative of higher amorphous content. By calculating % amorphous content of different lactose samples,[6] linear relationship was established showing that the lactose samples with higher volume mean diameter have smaller amorphous content (Figure 3).
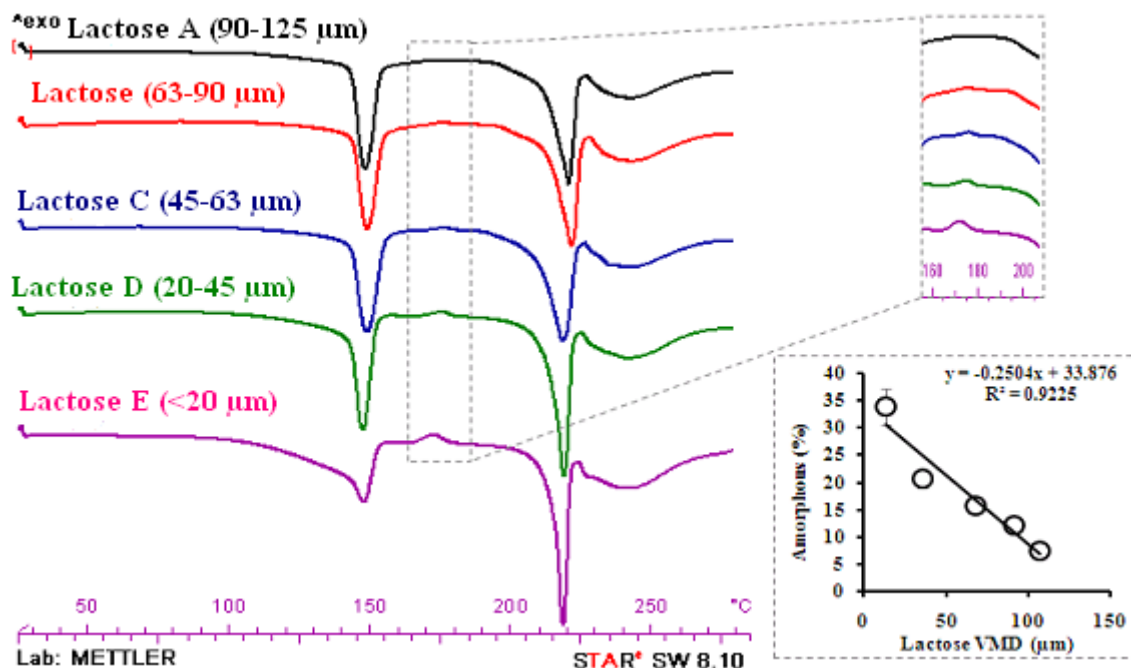

Figure 3 *Differential scanning calorimetery thermograms of different lactose samples.*

True density (D_{true}) measurements provided by helium pycnometery showed that lactose powders with higher volume mean diameter have smaller true density (linear, r^2=0.9932). On the other hand, lactose powders with higher volume mean diameter showed higher bulk density (D_b) (linear, r^2=0.8943) and higher tap density (D_t) (linear, r^2=0.8244). Lactose powders with smaller VMD showed higher Carr's index values (linear, r^2=0.9177) (indicating poorer flow properties) and higher porosity (linear, r^2=0.914).

2.2 Uniformity, adhesion, and *in vitro* aerosolisation performance assessments

Five different formulations were prepared by blending micronized budesonide (median diameter=3.2±0.2 µm) with different lactose samples (A, B, C, D, and E) in a ratio of 1:67.5 w/w in Turbula[TM] mixer for 30 min. From each blend, at least seven samples were collected randomly for quantification of budesonide content using High Performance Liquid Chromatography. All blends showed similar drug content potency ($p<0.05$); however lactose particles with smaller VMD produced higher coefficient of variation (CV%) of budesonide indicating reduced drug content homogeneity (Figure 4a). This can be attributed to poorer flowability and wider size distribution for lactose powders with smaller particle size as shown previously. In fact, direct linear relationships were obtained when plotting coefficient of variation of budesonide against lactose Carr's index ($r^2=0.9275$) or span ($r^2=0.8776$).
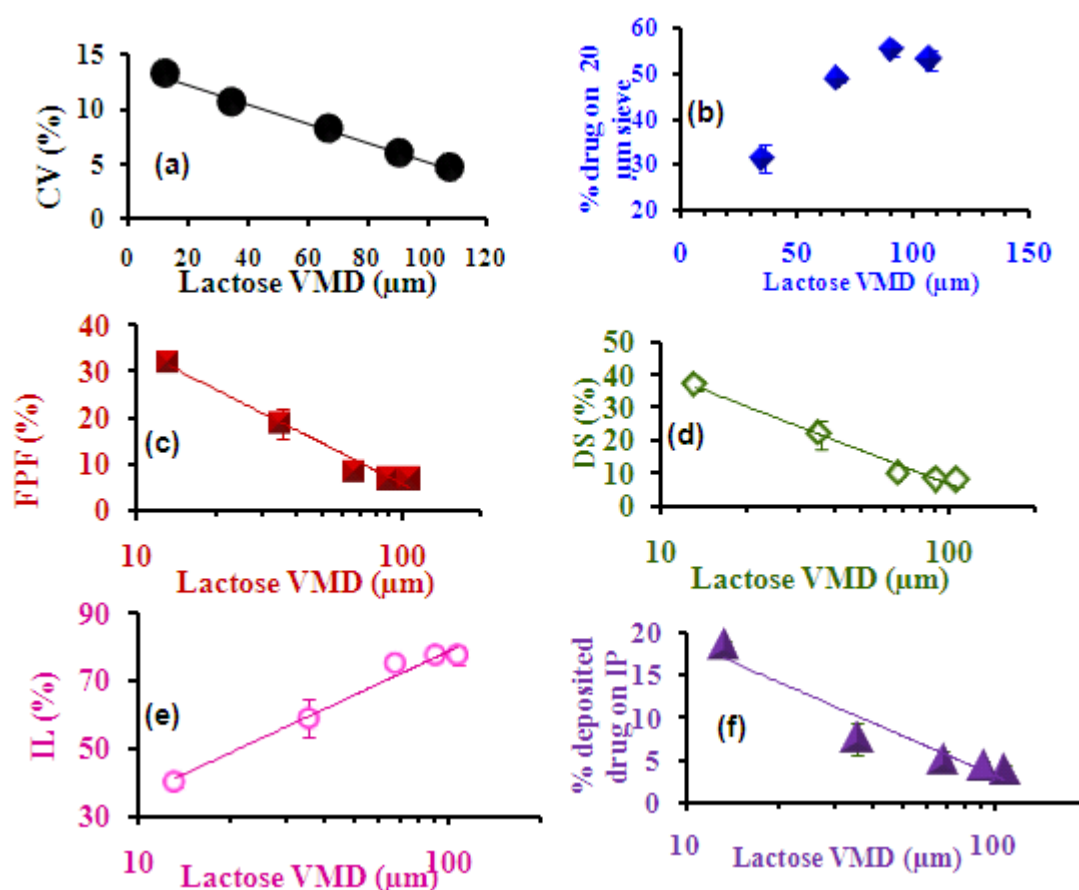

Figure 4 *Relationship between lactose VMD and budesonide CV (a), amount remained on top of 20 µm sieve (b), FPF (c), DS (d), IL (e), and amount deposited on IP (f).*

Air jet sieving was employed to evaluate drug-carrier adhesion properties for all formulations. Less amounts of drug remained on top of the 20 µm sieve was obtained for the lactose particles with smaller VMD (Figure 4b) indicating weaker drug-carrier adhesion. This could be, in part, attributed to higher collision and friction forces during mixing process for lactose powders with higher VMD, which act as adhesive forces.

In vitro aerosolisation performance of different formulations was analysed using Multi Stage Liquid Impinger (MSLI) attached to Aerolizer[®] inhaler device. The results showed that

despite using the same batch of budesonide in all formulations; budesonide aerodynamic particle size was dependent on lactose particle size. Lactose particles with smaller size produced budesonide particles with smaller aerodynamic size upon inhalation. Higher fine particle fraction (FPF) (Figure 4c), higher dispersibility (Figure 4d), and smaller impaction loss (IL) (Figure 5e) of budesonide were obtained for lactose particles with smaller volume mean diameter indicating improved aerosolisation performance. This could be attributed to smaller drug-carrier adhesion for lactose powders with smaller volume mean diameter (Figure 4b) and consequently improved drug-carrier detachment efficiency upon inhalation. However, it was noticed that the smaller the lactose volume mean diameter, the higher the amounts of budesonide deposited on throat (IP) (Figure 4f), which is disadvantageous in terms of increased potential local and/or systemic side effects of budesonide.
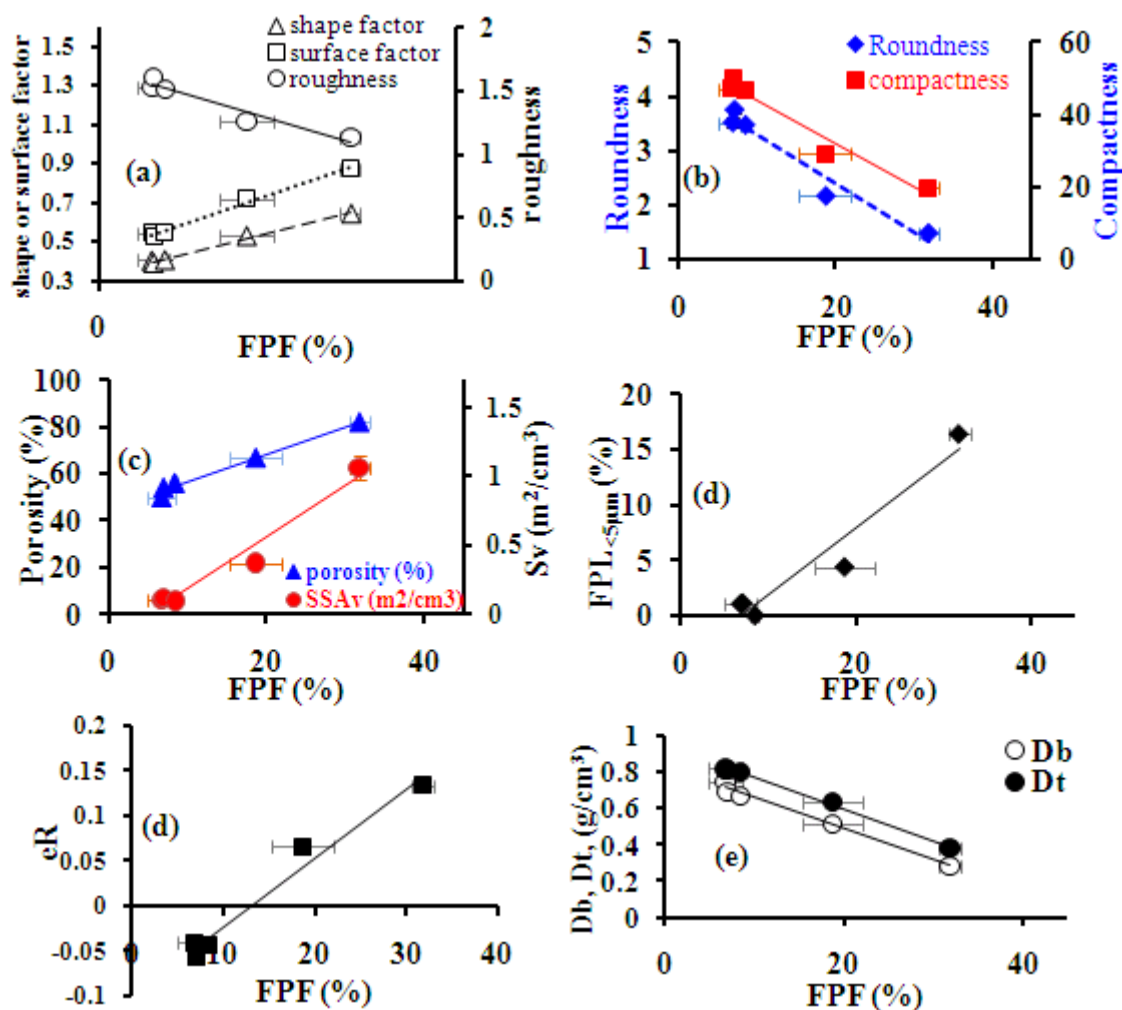

Figure 5 *FPF of budesonide in relation to lactose shape factor, surface factor, roughness, roundness, compactness, porosity, SSAv, $FPL_{<5\mu m}$, e_R, D_b, and D_t.*

Direct linear relationship ($r^2=0.9822$) was established between amounts of drug deposited on throat and fine particle lactose ($FPL_{<10\mu m}$) (figure not shown). Lactose powders with poorer flowability produced higher amounts of budesonide remained in inhaler device and deposited

on throat. It was assumed that high powder cohesiveness for lactose D and E (as indicated by higher Carr's index values) could not be totally overcome during inhalation process, leading to the formation of aggregates remained in the inhaler device and/or deposited on throat. The smaller the volume mean diameter of lactose, the smaller the amounts of budesonide deposited on MSLI stage 1 and the higher the amounts of drug deposited on MSLI stages 2, 3, 4, and filter.Figure 5 shows that higher fine particle fraction of budesonide was obtained when lactose powders with smaller roughness, higher shape factor, higher surface factor, higher roundness, higher compactness, higher porosity, higher specific surface area, higher fine particle lactose, higher simplified shape factor, smaller bulk density, and smaller tap density were used. This indicates that the aerosolisation performance is better when carrier particles with smoother surface, regular shape, higher surface area, higher content of fines and smaller bulk and tap density are used.

3   CONCLUSIONS

This study showed that the smaller the carrier size the better the drug aerosolisation efficiency. However, the use of carrier powders with smaller particle size is disadvantageous in terms of reduced dose homogeneity, higher potential of side effects possibility, and reduced formulation stability and flowability.

Abbreviations

CI:	Carr's index;	CV:	coefficient of variation;
D_b:	bulk density;	DPI:	dry powder inhaler;
DS:	dispersibility;	D_t:	tap density;
D_{true}:	true density;		
e_R:	simplified shape factor;		
FPF:	fine particle fraction;	FPL:	fine particle lactose;
IL:	impaction loss;	IP:	induction port;
MMAD:	mass median aerodynamic diameter	MSLI:	Multi Stage Liquid Impinger;
PSD:	particle size distribution;	SEM:	scanning electron microscope;
SSAv:	specific surface area	VMD:	volume mean diameter.

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