On Measuring the Specific Surface Area of inhalation-grade lactose powders

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INTRODUCTION

Measuring and monitoring the specific surface area (SSA) of powders during storage or after processing is a valuable metric that has been associated with changes in the performance of inhaled powder formulations, as it depends on both particle size distribution (PSD), the porosity and the surface roughness of the powders [1,2]. The value is also needed in surface energy experiments using inverse gas chromatography (iGC). Typically, gas-adsorption techniques use inert gases including Nitrogen (N_2) and Krypton to measure SSA; the adsorption isotherm is analysed and if it is of type II or IV, then the Brunauer-Emmett-Teller (BET) theory can be applied to extract the SSA_{BET} [3,4]. However, the widely used N_2 adsorption method is challenging for powders with low SSA, such as inhalation grade α-lactose monohydrate. More recently, iGC has been employed as an alternative method, using n-alkanes (heptane-C_7, octane-C_8) as probe molecules [5–7]. Advances in X-Ray Computed Tomography (XCT) have allowed the 3D imaging of inhalation grade lactose powders, and useful

metrics, such as PSD to be extracted [8,9]. The SSA_{BET} determined by N_2 adsorption and iGC-C_8 has been compared for inhalation grade lactose and XCT has been assessed as a complimentary technique.

METHODS

Inhalation grade α-lactose monohydrate, namely Lactohale 100 (sieved), Lactohale 200 (milled), Lactohale 206 (milled with fines removed) and Lactohale 20X (milled with fines removed) were kindly supplied by DFE Pharma (GmbH). PSD measurements were achieved by laser diffraction, as previously reported [8]. For the iGC SSA_{BET} measurements, the Surface Energy Analyzer (iGC-SEA, Surface Measurement Systems Ltd, UK) was used. Approximately 1.5 g of lactose was packed into silanised iGC glass columns (Analytical Columns, Croydon, UK). Prior to any measurements, the columns were conditioned using helium carrier gas at 10 sccm (standard cubic centimeters per minute) for 2 h at 30 ^{o}C and 0% RH. Methane gas was injected at the start and the end of the experiments for the dead volume calculation. SSA was calculated via the BET theory (SSA_{BET}), based on the C_8 adsorption isotherm data [10]. N_2 adsorption isotherms were obtained via a TriStar 3000 (Micromeritics Instrument Corp. USA). Around 500- 1400 mg of lactose sample were filled into 3/8″ flat bottom cells with filler rods and conditioned under a helium purge at 25 °C for 8-12h. N_2 isotherms were measured at -196 °C. The BET analysis was based on the linear region of the nitrogen adsorption isotherm (from $p/p° = 0.06$-0.2). Measurements were done in duplicate with the exception of LH20X which was measured just once.

LH100 was prepared for XCT scanning by spooning powder into a separate Kapton tube sample mount as described in [9]. A Zeiss Xradia Versa 520-DCT instrument (Carl Zeiss Microscopy) was used for this experiment. Scan settings and image

analysis methodology have been described elsewhere [8]. The SSA was calculated as the ratio of the total surface area within the analyzed sample to the mass of the of the analyzed sample, with the mass calculated as the product of the sample volume and density of 1.54 g /cm^3.

RESULTS AND DISCUSSION

SSA depends on the surface roughness, porosity and the PSD of the particles, which is influenced by the inclusion of milling or classification steps in the manufacturing process. Table 1 shows the SSA results based on the techniques. By measuring, both iGC-C_8 and N_2 adsorption, it was possible to distinguish between the different grades of lactose (milled>milled with fines removed>sieved). Better agreement between the iGC-C_8 and the N_2 was observed for the milled lactose, (LH200), however, a significant difference was observed for the sieved lactose (LH100). This is due to the detection limit of the technique, as it is challenging to measure SSA_{BET} values less than 0.1 m^2/g with N_2. LH100 $SSA_{BET\text{-}N2}$ was 0.064 m^2/g with poor correlation in the measured partial pressure range (R^2 values were 0.984 and 0.959). Krypton adsorption could be employed but due to the experimental setup, there is the potential risk of change in structural form [6].

In order to assess SSA in an indirect way, further analysis of the XCT results was employed. To the best of the authors knowledge it is the first time that an indirect SSA evaluation based on a 3D imaging technique is presented. SSA_{XCT} for LH100 was 0.0854 m^2/g, comparable with the other two techniques. However, due to the image resolution of the instrument used, surface roughness and porosity cannot be sufficiently estimated. This could potentially be addressed with the microstructural

information obtained from higher resolution XCT systems like nanoCT which can achieve voxel resolutions of 16 nm [11].

Table 1 – Characteristics, PSD and SSA values of inhlalation grade lactose via N_2 adsoprtion, iGC and XCT. Errors correspond to duplicate measurements for the N_2 adsorption experiments and for triplicate measurements in one column for iGC.

Sample		**LH100**	**LH200**	**LH206**	**LH20X**
Grade		Sieved	Milled	Milled (fines removed)	Milled (fines removed)
LD PSD [µm] (2.0 bar)	D_{10}	55	13	31	60
	D_{50}	131	77	81	102
	D_{90}	216	143	160	151
SSA [m^2/g]	N_2	0.06 ± 0.02	0.25 ± 0.03	0.14 ± 0.03	0.13
	iGC-C_8	0.18 ± 0.002	0.29 ± 0.003	0.22 ± 0.001	0.24 ± 0.001
	XCT	0.09	-	-	-

CONCLUSIONS

A comparison between the standard N_2-based adsorption and the C_8-based iGC for the measurement of the SSA of inhalation grade powders showed a good agreement between the two techniques for coarse lactose. For sieved lactose that exhibits an SSA value close to the detection limit of the instruments (0.1 m^2/g), XCT was used as an alternative indirect measurement. The XCT value was in good agreement with the two other techniques suggesting that in the future, XCT imaging with built in porosity and roughness parameters will be able to provide SSA values.

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REFERENCES

1. Watling CP, Elliott JA, Scruton C, Cameron RE: Surface modification of lactose inhalation blends by moisture. *Int J Pharm* 2010, 391: 29–37.

2. Depasquale R, Lee SL, Saluja B, Shur J, Price R: The Influence of Secondary Processing on the Structural Relaxation Dynamics of Fluticasone Propionate. *AAPS PharmSciTech* 2015, 16: 589–600.

3. ISO [International Organization for Standardization]: Determination of the specific surface area of solids by gas adsorption — BET method. 2010.

4. Brunauer S, Emmett PH, Teller E: Adsorption of Gases in Multimolecular Layers. *J Am Chem Soc* 1938, 60: 309–19.

5. Duralliu A, Matejtschuk P, Williams DR: Measuring the specific surface area (SSA) of freeze-dried biologics using inverse gas chromatography. *Eur J Pharm Biopharm* Elsevier; 2019, 142: 216–21.

6. Sharif S, Dimemmo LM, Thommes M, Hubert M, Sarsfield BA: A simplified approach to determine effective surface area and porosity of low bulk density active pharmaceutical ingredients in early development. *Adv Powder Technol* The Society of Powder Technology Japan; 2015, 26: 337–48.

7. Jaffari S, Forbes B, Collins E, Khoo J, Martin GP, Murnane D: Evidence for the existence of powder sub-populations in micronized materials: Aerodynamic size-fractions of aerosolized powders possess distinct physicochemical properties. *Pharm Res* 2014, 31: 3251–64.

8. Gajjar P, Styliari ID, Nguyen TTH, Carr J, Chen X, Elliott JA, et al.: 3D Characterisation of Dry Powder Inhaler Formulations: Developing X-ray Micro Computed Tomography Approaches. *Int J Pharm* 2020, In press.

9. Gajjar P, Styliari ID, Burnett TL: Multiscale Tomography : Probing The Nano- , Micro- , And Meso-Scale Resolution Of Inhalation Powder Structure Multiscale Tomography : Probing the Nano- , Micro- , and Meso-scale Resolution of Inhalation Powder Structure. *RDD Eur 2019* 2019, 1: 155–68.

10. Ramachandran V, Murnane D, Hammond RB, Pickering J, Roberts KJ, Soufian M, et al.: Formulation pre-screening of inhalation powders using computational atom-atom systematic search method. *Mol Pharm* 2015, 12: 18–33.

11. Withers PJ: X-ray nanotomography. *Mater Today* 2007, 10: 26–34.