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

Ioanna Danai Styliari[1], Thai T.H. Nguyen[2], Parmesh Gajjar[3], Benjamin Tordoff[4], Timothy L. Burnett[3], Philip J. Withers[3], Robert Hammond[2], Kevin Roberts[2] and Darragh Murnane[2]

[1] School of Life and Medical Sciences, University of Hertfordshire, Hatfield, AL10 9AB, UK. i.d.styliari@herts.ac.uk

[2] Centre for the Digital Design of Drug Products, School of Chemical and Process Engineering, University of Leeds, Leeds, UK

[3] Henry Moseley X-ray Imaging Facility, School of Materials, The University of Manchester, Manchester, M13 9PL, UK

[4] Carl Zeiss Microscopy GmbH, Carl-Zeiss-Straße 22, 73447 Oberkochen, Germany

Future Formulations 4
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The basics of specific surface area (SSA)

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SSA of powders has been associated with **changes** in the **performance** of inhaled powder formulation.

SSA depends on the:

- particle size distribution (PSD)
- porosity
- surface roughness of the powders [1,2]

SSA can be measured via gas adsorption isotherms (Figure 1) or through particle sizing and image analysis approaches

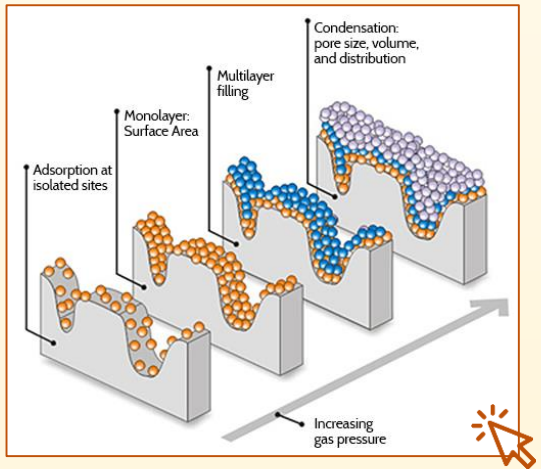

Figure 1: Measurement of SSA by gas adsorption isotherms. The isotherm is analyzed and if it is of type II or IV, then Brunauer-Emmett-Teller (BET) theory can be applied to extract the SSA_{BET} [3,4]

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Measurement by gas adsorption isotherms (Figure 1)

Gas choices:

- Inert gases [Nitrogen (N_2), Krypton]
  N_2 adsorption is challenging for powders with low SSA, such as inhalation grade α-lactose monohydrate and is conducted in low temperatures
- Vapours of n-alkanes (heptane-C_7, octane-C_8) as probe molecules using
  - inverse Gas Chromatography (iGC) [5, 6, 7]
  - Dynamic Vapour Sorption (DVS)

Measurement by particle sizing image analysis

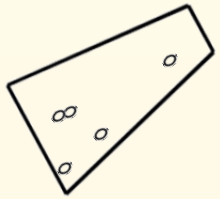
X-Ray Computed Tomography (XCT) allows the 3D imaging of powders [8,9]

Aim: Determine the SSA_{BET} of inhalation grade lactose with multiple techniques and assess the use of XCT as a complimentary technique.

Materials

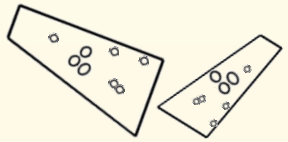
All materials were inhalation grade α-lactose provided by DFE Pharma (Goch, Germany)

Lactohale 100
Sieved



Batch # 101NN16

Lactohale 200
Milled

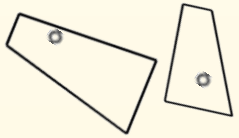


Batch # 1019L43

Lactohale 206
Milled with removed intrinsic fines

Batch #101WSHD

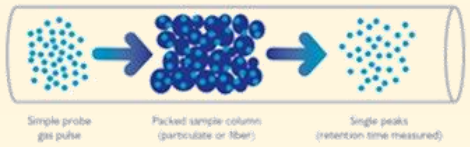
Lactohale 20X
Milled with removed intrinsic fines



Custom batch

Techniques

Inverse Gas Chromatography



Using octane (C_8) as probe [10]

Nitrogen Adsorption

X-Ray Computed Tomography

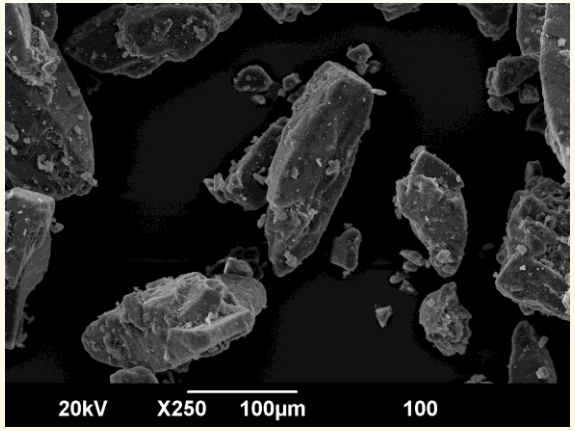
Methods described in recent INFORM2020 Publication

Laser Diffraction

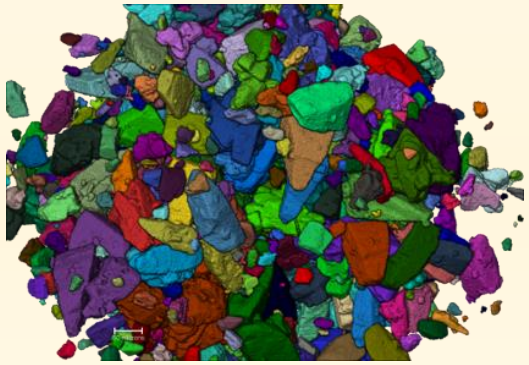
Scanning Electron Microscopy

Results

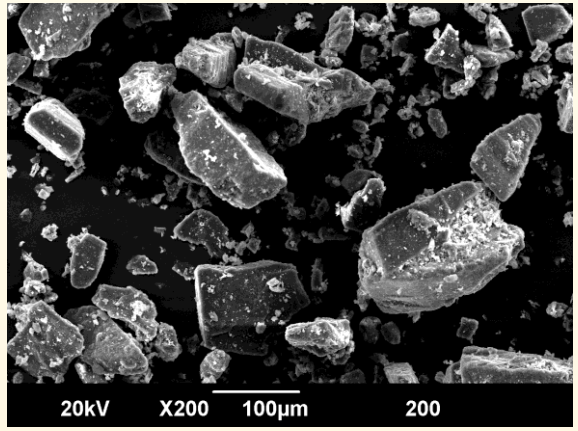
Lactohale 100
Sieved



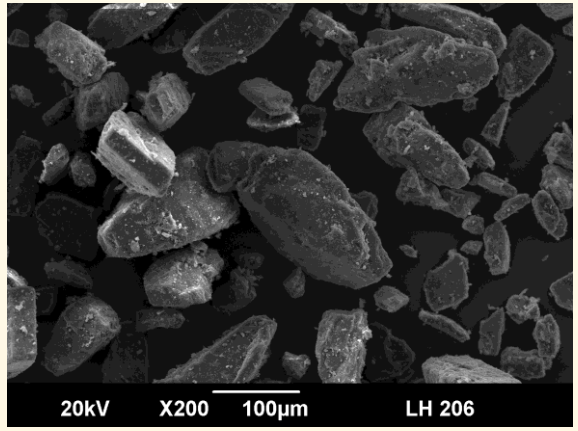
XCT



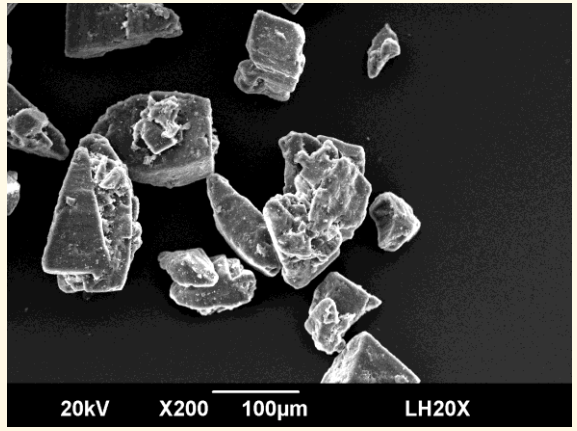
Lactohale 200
Milled



Lactohale 206
Milled with removed intrinsic fines



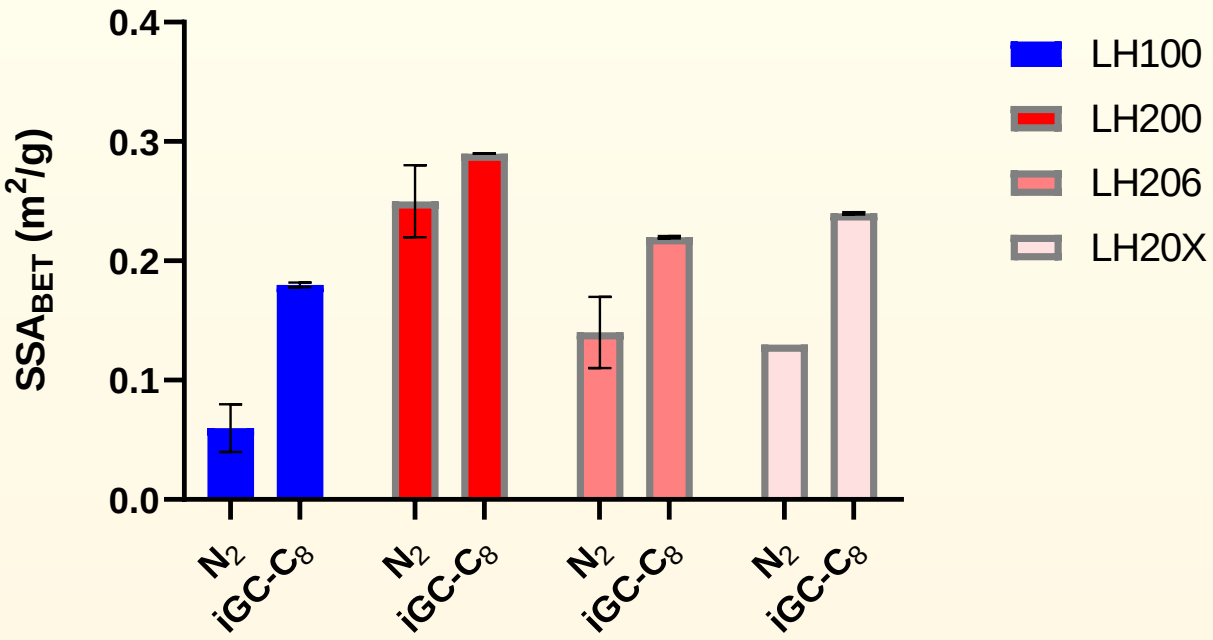
Lactohale 20X
Milled with removed intrinsic fines



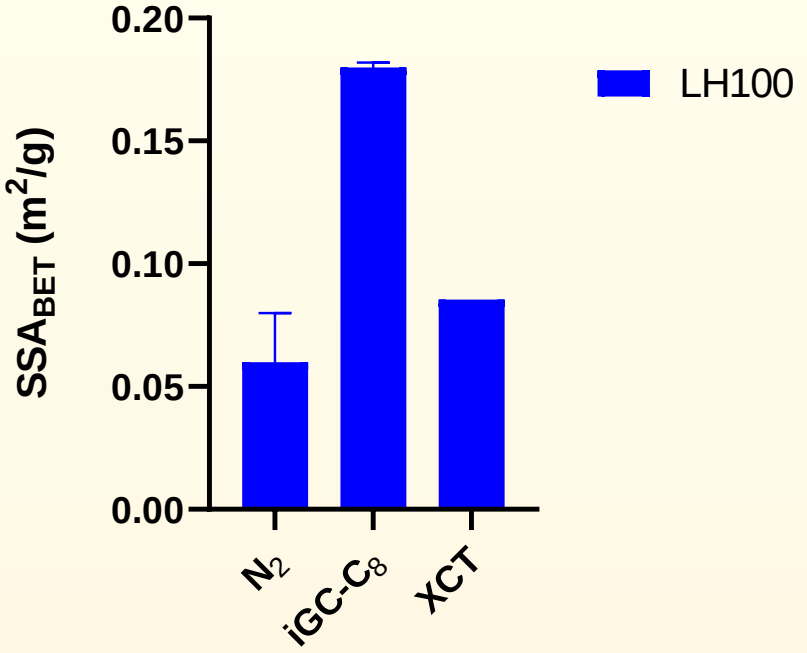
XCT allows the 3D imaging of the powder, providing structural information and number and volume-based PSDs with a 2 µm resolution regardless of the particle spatial orientation.

Laser Diffraction Particle Size Distribution		LH100	LH200	LH206	LH20X
Dispersion at 2.0 bar [µm]	D_{10}	55	13	31	60
	D_{50}	131	77	81	102
	D_{90}	216	143	160	151

Results



Graph 1: Measurement of SSA using N_2 adsorption and iGC-C_8



Graph 2: SSA of LH100 with XCT result included

It is possible to distinguish between grades using both the gas adsorption techniques (milled>milled with fines removed>sieved).

- Better agreement between iGC-C_8 and N_2 observed for milled grades (reds) compared to larger particle and sieved grades
- Significant difference was observed for the sieved lactose (blue)

Particle sizing using XCT image analysis allowed the calculation of the SSA_{XCT} for LH100.

- Accurate SSA determination by gas adsorption is challenging
- The comparability of results to gas adsorption measurement makes XCT a relevant technique for materials with low SSA

Discussion, Conclusions & Future Work

- Poor agreement between N_2 and iGC-C_8 in sieved lactose is due to the detection limit of the N_2 technique (0.1 m^2/g). Krypton adsorption could be employed but there is the potential risk of change in structural form[6].

- Surface roughness and porosity cannot be sufficiently estimated currently using microXCT, due to the micron-size resolution of the instrument. Once microstructural information from higher resolution XCT (nanoCT) addresses this issue, XCT will be able to provide accurate SSA measurements for low surface area powders in a non-destructive way, using small sample amounts, in ambient lab environmental conditions.

Acknowledgments

Questions/
Comments?

We thank Prof. Dr. Regina Scherließ for the N_2 adsorption data of LH100.

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