INFORM 2020 – Molecules to Manufacture

Formulation and process engineering of inhaled particle therapies

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INFORM 2020 project team

Academic principal investigators and commercial partners/supporters

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Presenting today

Dr Thai Thu Hien Nguyen (Leeds)

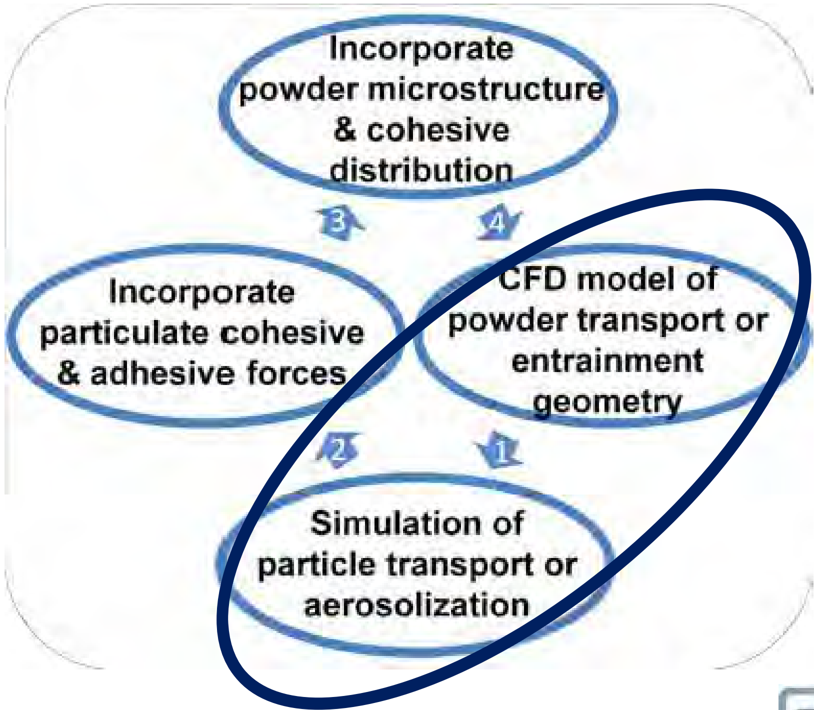
Dr Ioanna Danai Styliari (Hertfordshire)

Dr Parmesh Gajjar (Manchester)

Computational pharmaceutical engineering approach

Hypothesis 4

Incorporating powder microstructure and cohesion into computational models will improve understanding and engineering of formulation processing and performance.



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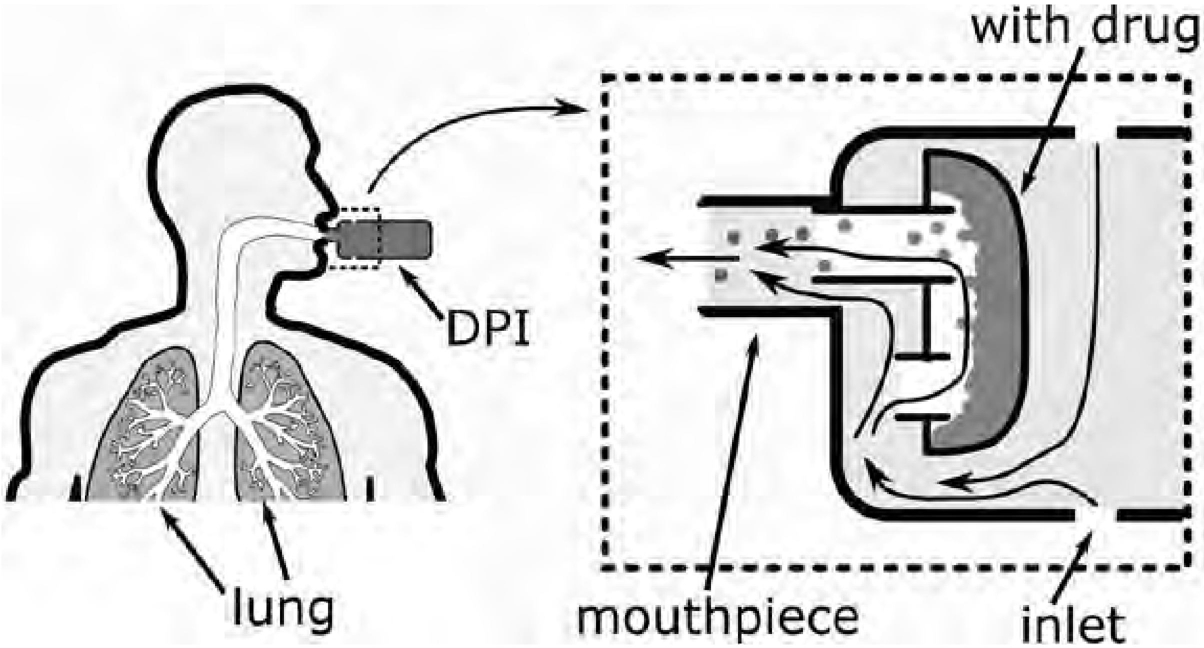
Studying powder emission from a ‘leaky’ blister-type inhaler



Emitted mass versus scaled inhalation volume curves enable us to study device engineering to minimize inter-manoeuvre emission variability

Kopsch, Murnane, Symons (2016) Pharm. Res. 33: 2268-2279; Kopsch (2018) PhD Thesis Univ. Cambridge

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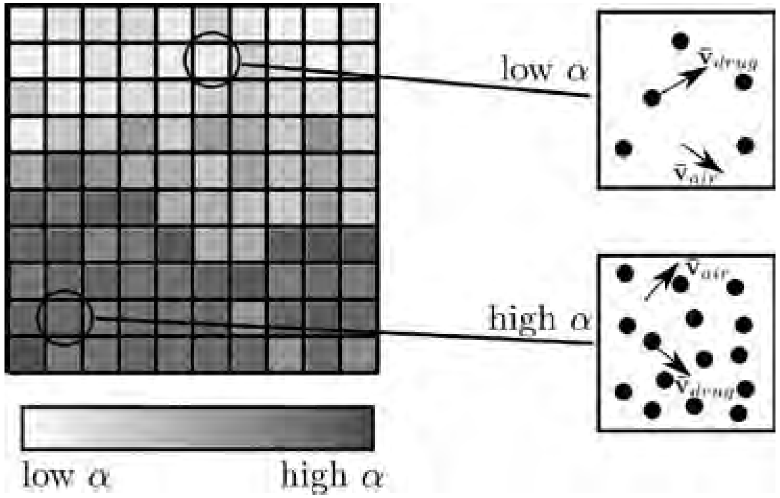
Physiologically-based inhaler design for DPIs
CFD Assessment of emission process within design element

Applied Eulerian-Eulerian CFD to cope with high drug particle concentration

Calculate density and spatial distribution of a granular phase in a gaseous phase



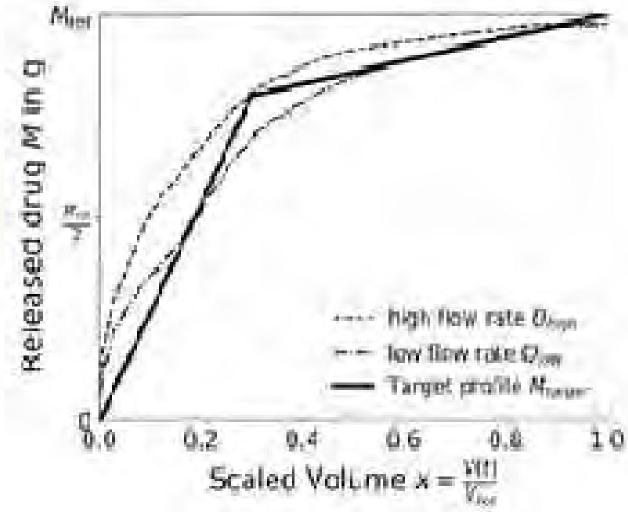
Model/ Parameter	Lactose 16% fines
Average diameter of particles	7.0×10^{-5}m
Initial α in compartment	0.49
CFD solver	OpenFOAM twoPhaseEulerFoam
Boundary Conditions Inlet Outlet Transient condition library	 Atmospheric P (101,325 Pa) A transient flow rate profile $Q_e(t)$ swak4Foam:
Turbulence Modelling & RAS modelling	$k - \varepsilon$
Granular Viscosity Model	Gidaspow
Conductivity Model	Gidaspow
Frictional Stress Model	Johnson Jackson
Granular Pressure Model	Lun
Radial Model	Lun Savage
Drag Model	Gidaspow Ergun Wen Yu

Kopsch, Murnane, Symons (2016) Pharm. Res. 33: 2268-2279

Physiologically-based inhaler design for DPIs

Studying entrainment rates of powders using EE CFD approach

Entrainment geometry optimized for early bolus delivery, emitted to a similar lung region in patients with differing inhalation performance



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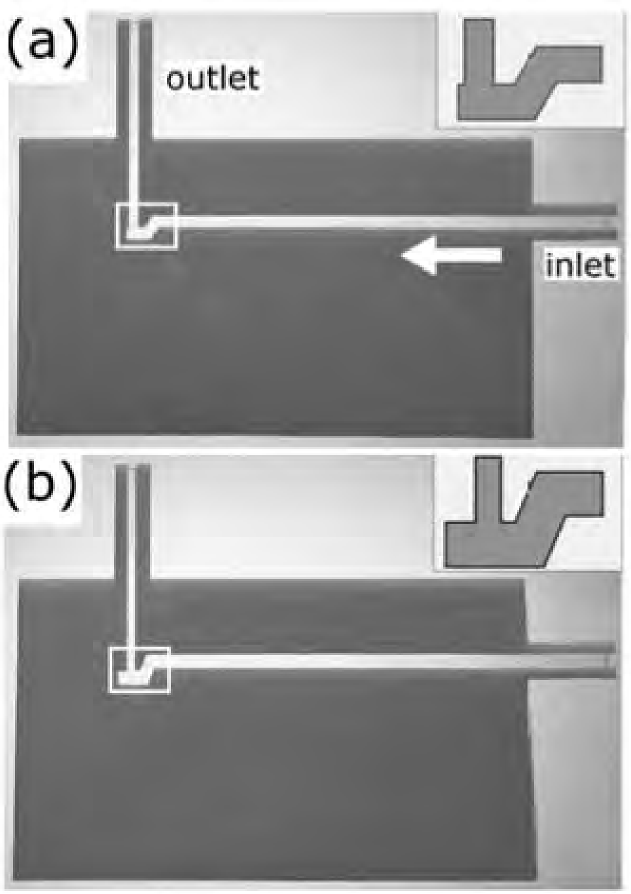
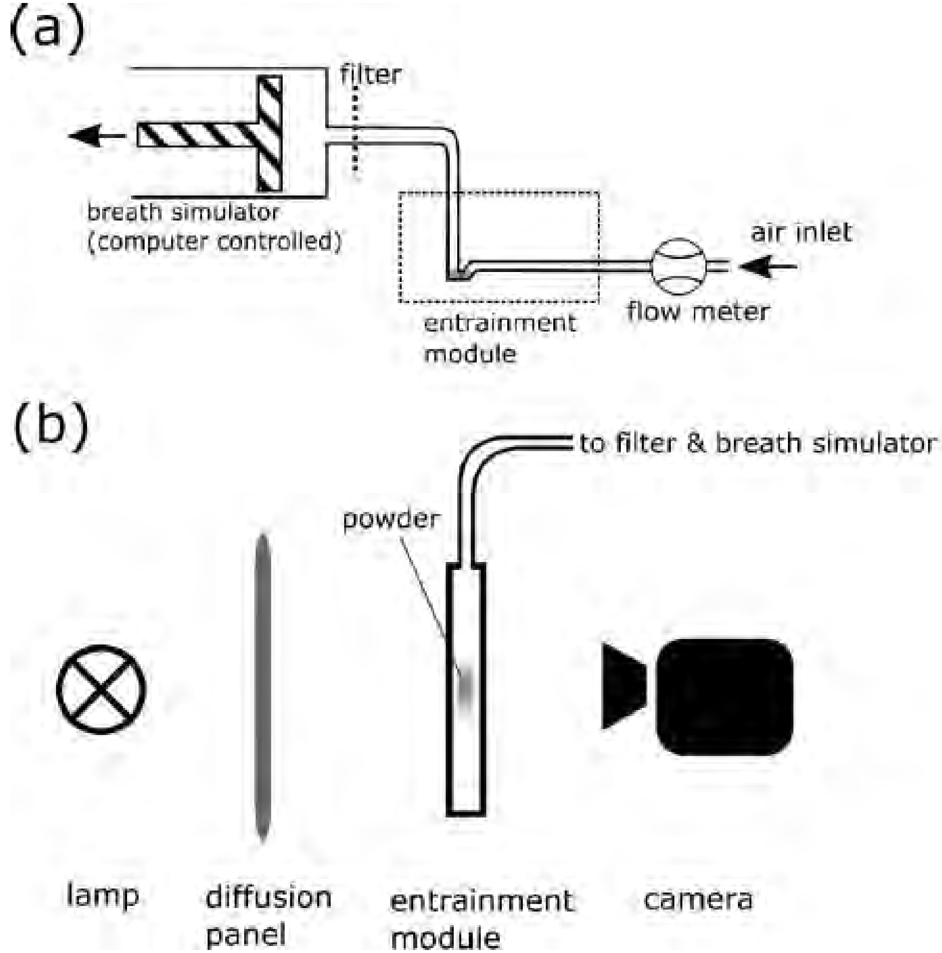
Kopsch, et al. (2016) Pharm. Res. 33: 2268-2279; Kopsch et al. (2018) PhD Thesis, Univ. Cambridge

Validation of numerical CFD optimization approach



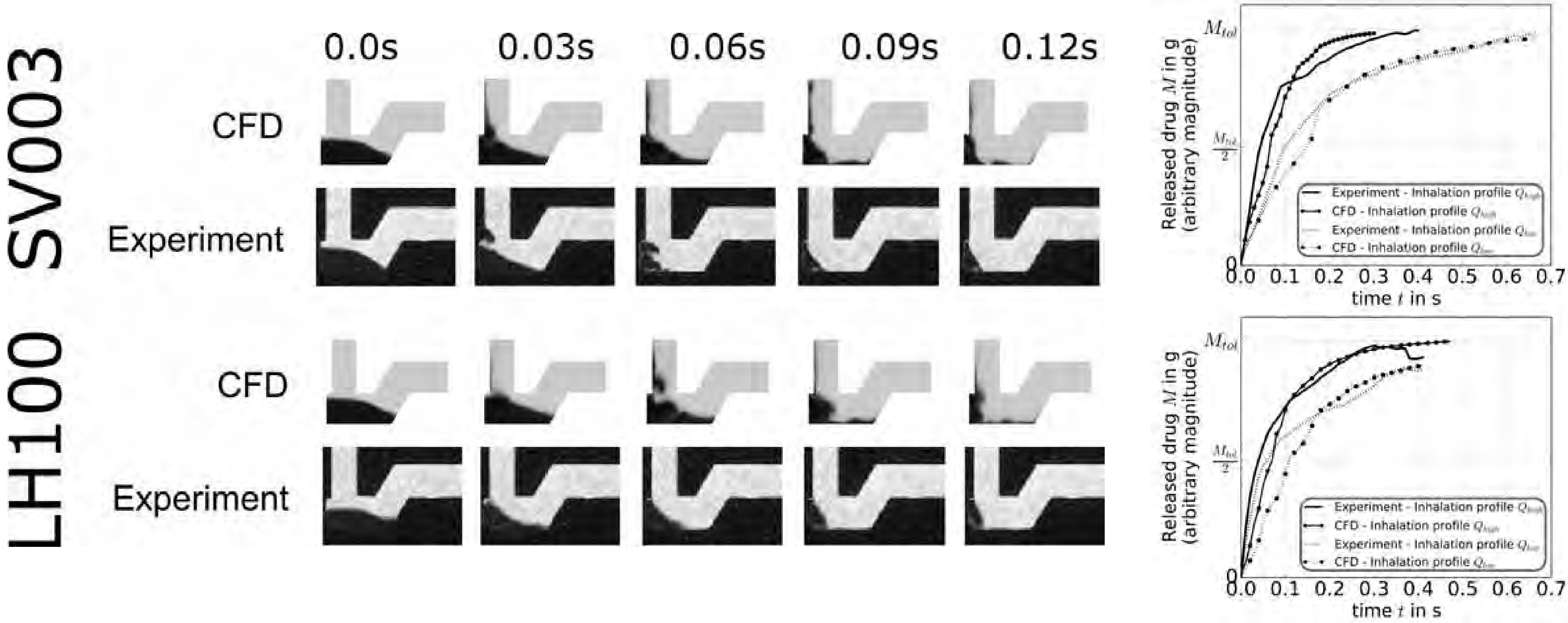


Kopsch et al. (2018) PhD Thesis, Univ. Cambridge

Validation of numerical CFD optimization approach

Emission of large particle carrier lactose

Good agreement between CFD predicted and actual emission rates using carrier lactose as probe material.



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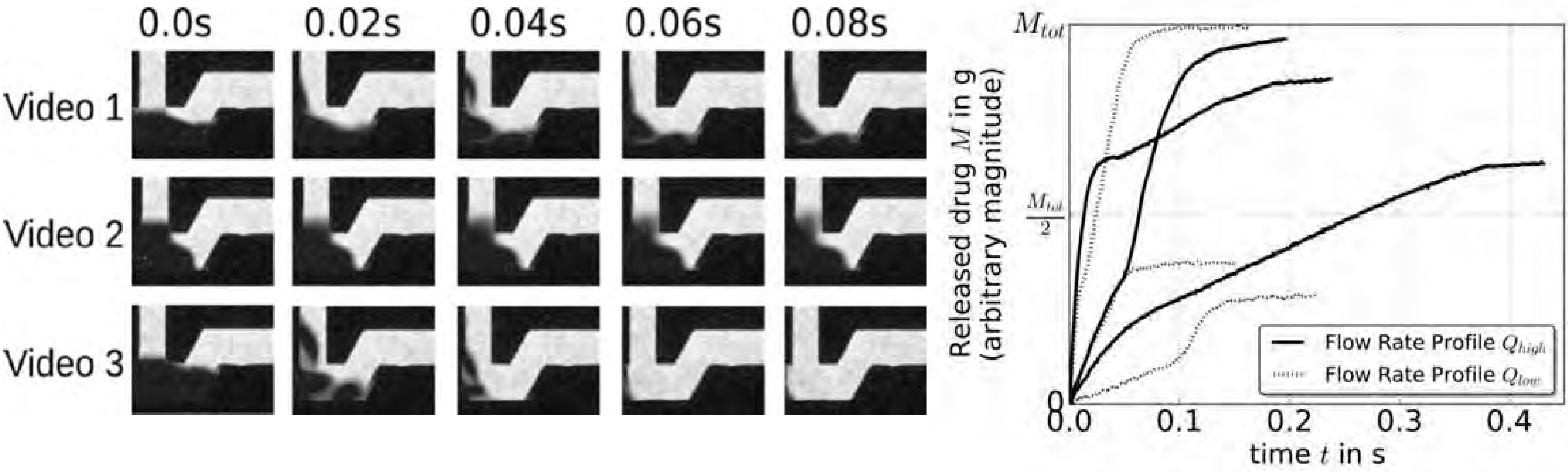
Kopsch et al. (2018) PhD Thesis, Univ. Cambridge

Validation of numerical CFD optimization approach

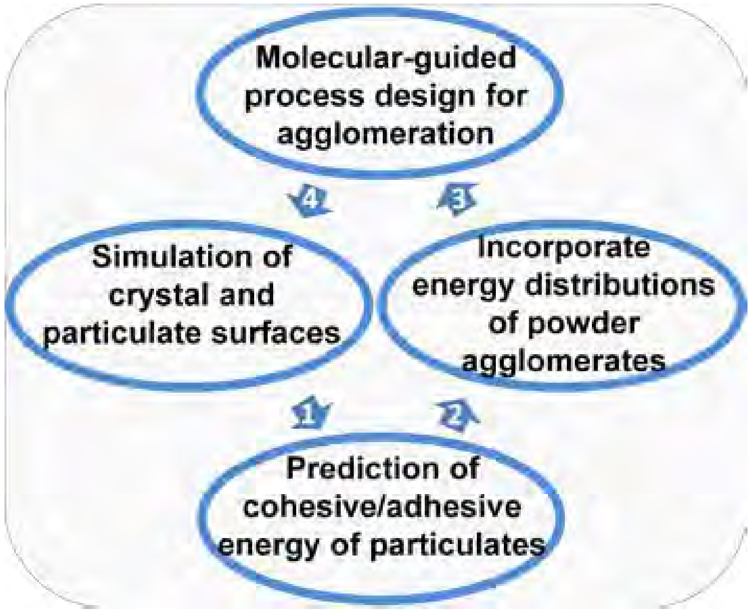
Some challenges that remain to be addressed: Lactohale 200



Computational modelling of emission and aerosol formation was less successful in the presence of fine particles. Next steps to address this require incorporation of microstructure & cohesive forces into the model.

Computational pharmaceutics approach
Key Challenges for Year 1

Hypothesis 1
Computational engineering provides an *in silico* modelling approach to calculate particle surface energy and inter-particulate forces predictive of agglomeration in molecular, ionic and solvated crystals



1. **Validate synthonic modelling of salts & hydrates**

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Modelling Strategy for INFORM2020

Can molecular modeling enhance the understanding of powder cohesion and surface interaction forces at particle-particle contact points in agglomerated powders to provide a strategy to engineer inhalation performance?

Crystal structure
α -Lactose Monohydrate (α-LMH) (Excipient)
Terbutaline sulfate (TBS) (API)

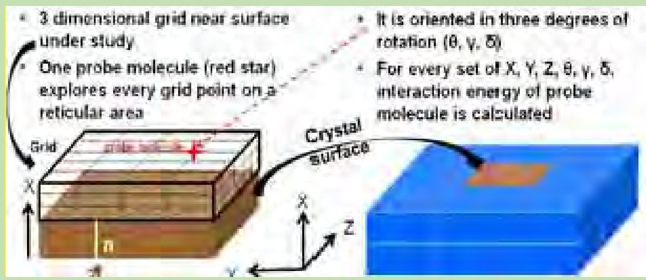
Empirical method **HABIT98**
Bulk (intrinsic) interactions

- **Strength & directions of intermolecular interaction**
- **Lattice energy**
- **Attachment energy; Predicted morphology, index crystal faces**
- **Surface Area & Crystal Surface Energy**

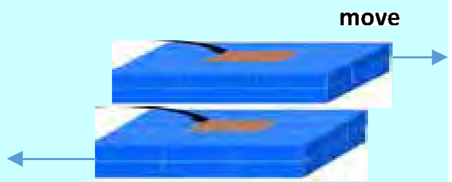
Surface (extrinsic) interactions using Systematic Search to calculate the possible interactions energies of probe molecule & another molecule/crystal surface

Molecular level: **interaction between α-LMH& TBS**

Molecule-Surface binding:
Probe molecule: excipient /API molecule
Surface can be excipient /API crystal surface



Crystal- Crystal interaction:
Allows to quantify cohesive/ adhesive interactions



QM method with PBC to calculate surface charge & surface energy for ionic system

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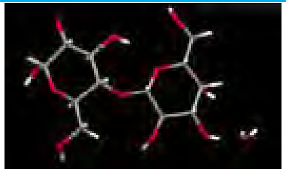
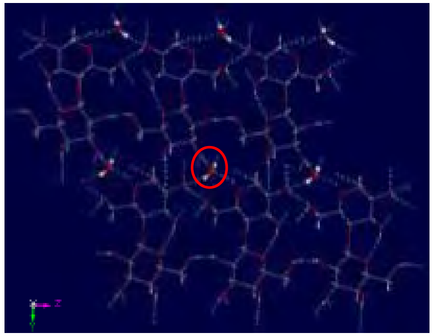
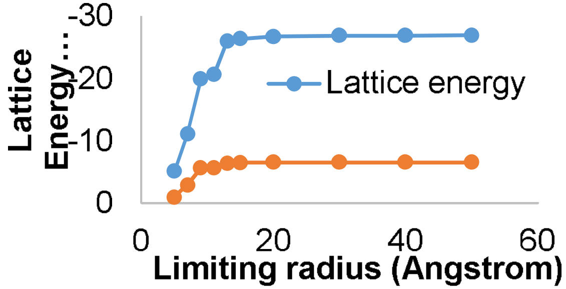
Intermolecular Packing, Lattice Energy and Predicted Crystal Morphology for α-Lactose Monohydrate

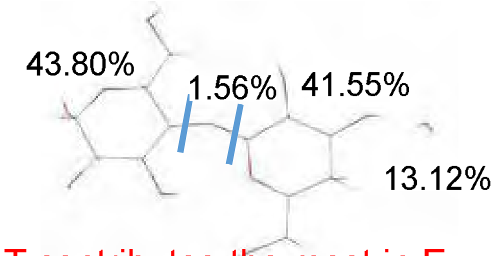


$C_{12}H_{22}O_{11}.H_2O$
CCDC ref code: LACTOS11
Space Group: $P2_1$
a = 4.78; b = 21.54; c = 7.76
β=105.91°; V= 768.8
Z' = 1; Z = 2



4 Lactose (LT) interact with a H_2O

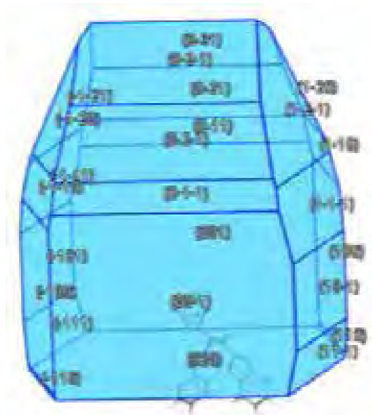




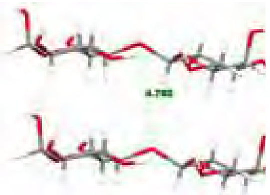
LT contributes the most in E_{latt}

Synthon	Molecules Involved	Inter-Ion Dist. (Å)	Attractive/Repulsive (kcal/mol)	Coulombic (kcal/mol)	Total Interaction (kcal/mol)
A	LT/LT	4.78	-9.30/ 5.17	-0.96	-5.09
B	LT/LT	7.92	-37.69/ 34.90	-1.46	-4.25
C	LT/LT	7.76	-33.39/ 30.52	-1.11	-3.99
D	LT/LT	11.24	-14.10/ 11.95	-0.43	-2.59
E	LT/water	6.19	-14.27/ 12.93	-0.46	-1.80

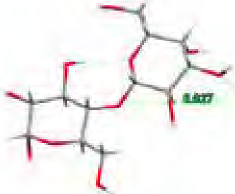
Face {hkl}	E_{att} (kcal/mol)	Surface Energy (SE) (mJ/m²)
{020}	-9.21	93.22
{001}	-12.67	85.08
{01-1}	-15.31	97.68
{02-1}	-17.09	95.60
{031}	-19.22	91.54
{100}	-15.64	70.11
{1-10}	-17.11	74.99
{10-1}	-15.53	63.72
{1-20}	-18.76	76.97
{11-1}	-16.14	64.91
{12-1}	-17.60	66.96



Synthon A



Synthon E



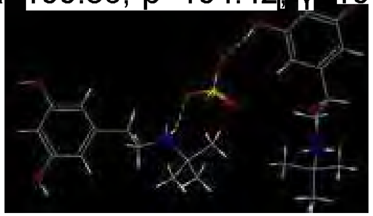
Electrostatic ~10%-20% of E_{att}; relatively low

Strongest synthons: LT-LT pairs > LT-H_2O > H_2O-H_2O; reflecting dominant interactions result from vdw forces

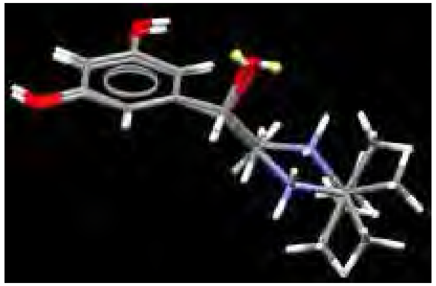
Measured total SE: 77.6 mJ/m² (dispersive SE: 65.3 mJ/m² & specific SE: 12.3 mJ/m²)
(Ramachandran, V. et al. Mol. Pharmaceutics 12, 1, 18-33)

Intermolecular Packing, Lattice Energy and Predicted Crystal Morphology for Terbutaline Sulphate

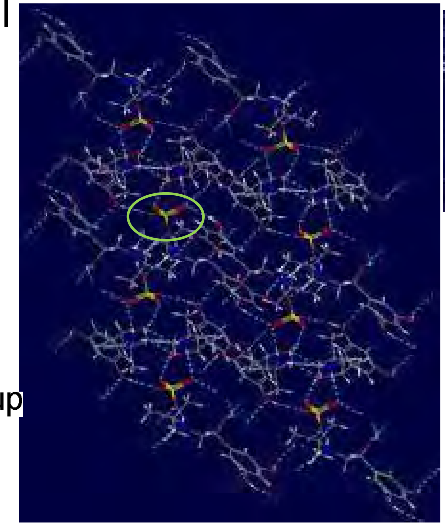
$2[C_{12}H_{20}NO_3]^{+}.SO_4^{2-}$
Triclinic Space group: $P\bar{1}$
a = 9.968; b= 11.207; c = 13.394
α=100.86; β=104.42; γ=101.63

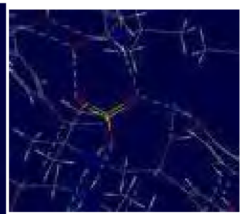


Overlay terbutaline cation I and cation II

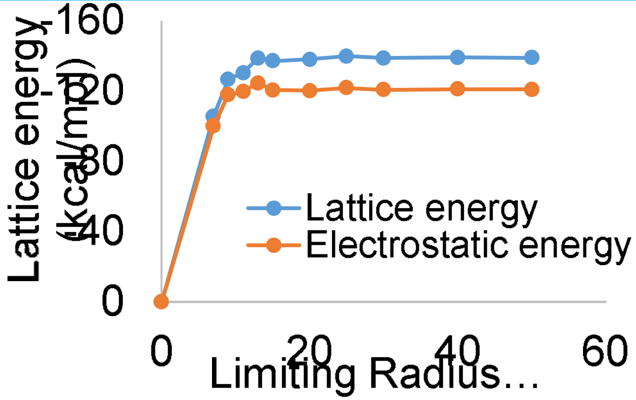


Difference in rotation of $-NH_2$ group



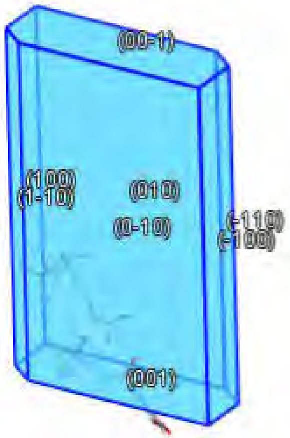


Each SO_4^{2-} forms 6 H-bonds

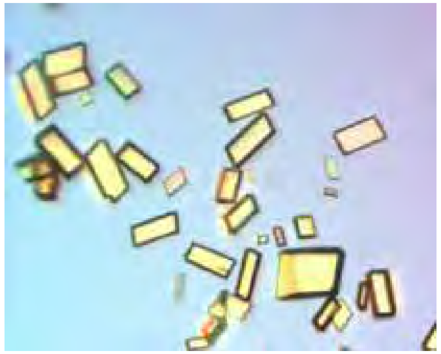


E_{att} converged at −139 kcal/mol
Columbic interactions ~ 85% of the E_{att}

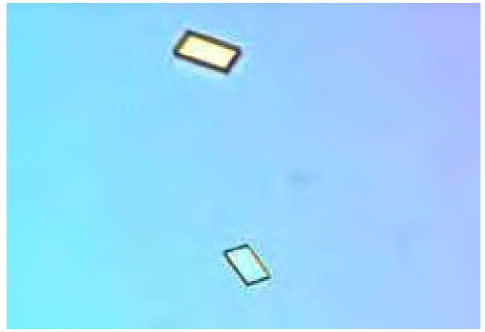
Crystal face	E_{slice}(kcal/mol)	E_{att}(kcal/mol)	Surface Energy (mJ/m²)
{001}	-121.7	-17.16	109.0
{010}	-133.7	-5.16	27.7
{01-1}	-116.2	-22.73	107.5
{100}	-128.2	-10.73	50.6
{10-1}	-111.9	-26.99	120.9
{1-10}	-127.8	-11.07	45.6
{011}	-115.9	-22.93	84.2
{1-1-1}	-110.4	-28.45	101.5
{1-11}	-113.2	-25.72	78.9



TBS grown in 70% H_2O & 30% EtOH @5° C



TBS crystals grown in 15hours



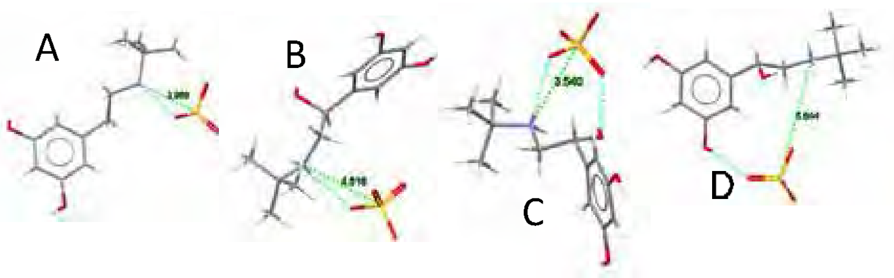
- Plate-like morphology with the {010} being the dominant face, with smaller {100}, {1-10}, {101} & {001} surfaces.
- Predicted morphology agrees with experimental morphology.

Synthon Analysis for Crystal Surfaces

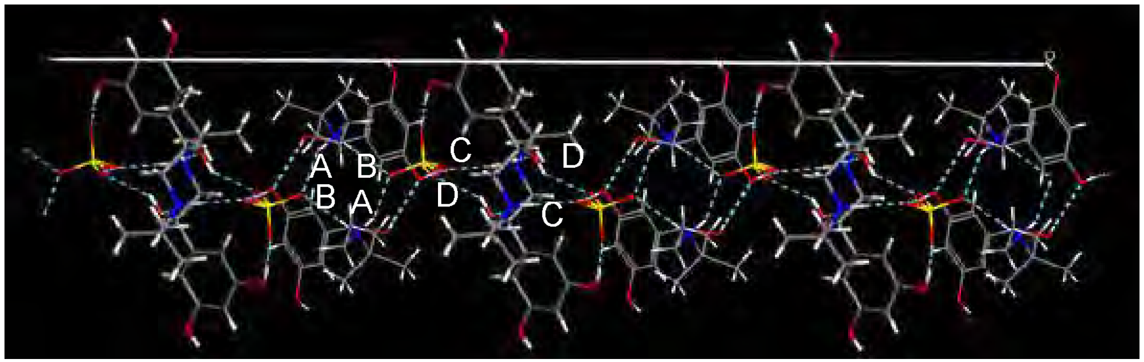
Synthon type	Molecules Involved	Inter-Ion Distance (Å)	Interaction energy (kcal/mol)	{001} (smallest face)	{010} (largest face)	{100}	{1-10}
A (strongest)	SF/TB2	5.48	-87.63	SL	(SL)	(SL)	(SL)
B	SF/TB2	4.36	-82.24	SL	(SL)	(SL)	(SL)
C	SF/TB1	5.04	-78.99	(ATT)	(SL)	(SL)	(SL)
D	SF/TB1	4.81	-75.28	(SL)	(SL)	(SL)	(SL)
E	SF/TB1	6.56	-48.45	(SL)	(SL)	(ATT)	(ATT)
F	SF/TB2	8.57	-41.37	(SL)	(ATT)	(SL)	(ATT)
G	SF/TB2	7.50	-39.00	(SL)	(SL)	(+/-)	(+/-)

SF: Sulphate

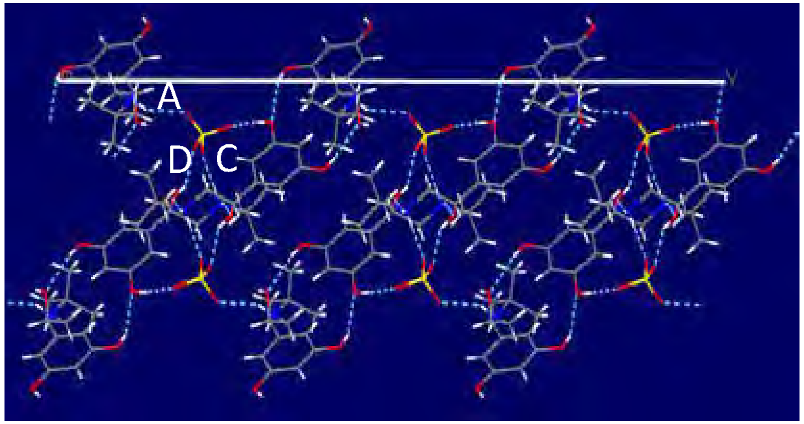
TB: Terbutaline cation



- **Eatt ~ Growth rate of crystal surface (R_{hkl})**
- **Analysing the strongest interaction contributing to E_{att}, explaining the order of the important dominant face: {010}**



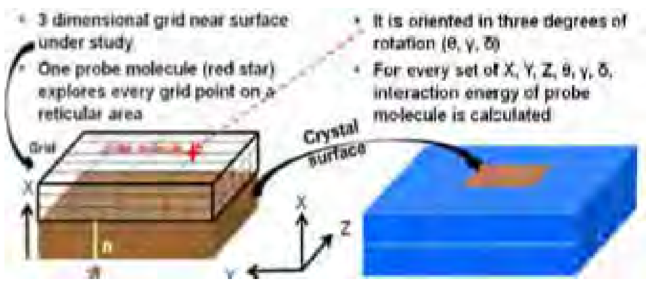
The {010} face: less polar → the most dominant face



The {001} face has more unsaturated H-bonds across the surface →the smallest face)

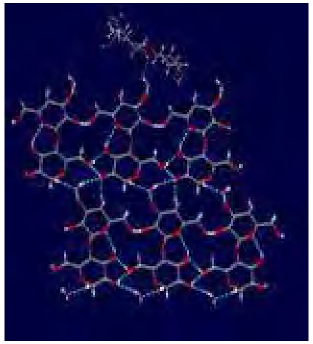
Link surface chemistry (function groups exposed on crystal surfaces, extrinsic synthons) to the surface properties

Cohesive Energy Prediction using Minimum Interaction Energy calculated from Systematic Grid Search

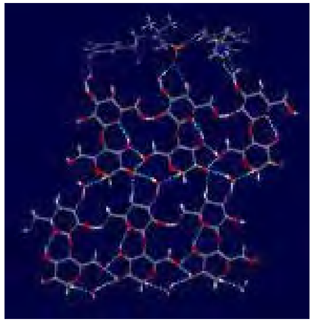


Probe molecule: excipient (α-LMH)/ API (TBS)
Surface: excipient /API crystal surface

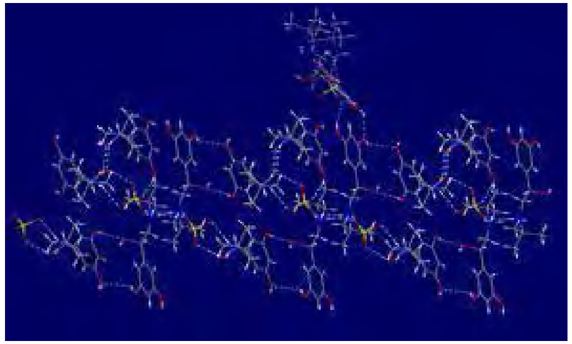
α-LMH binding on (010) face α-LMH

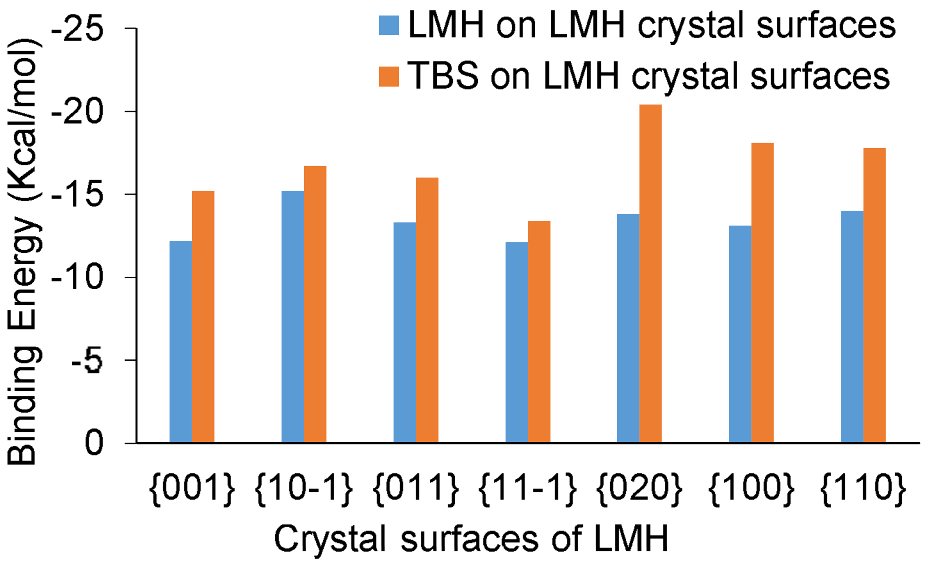


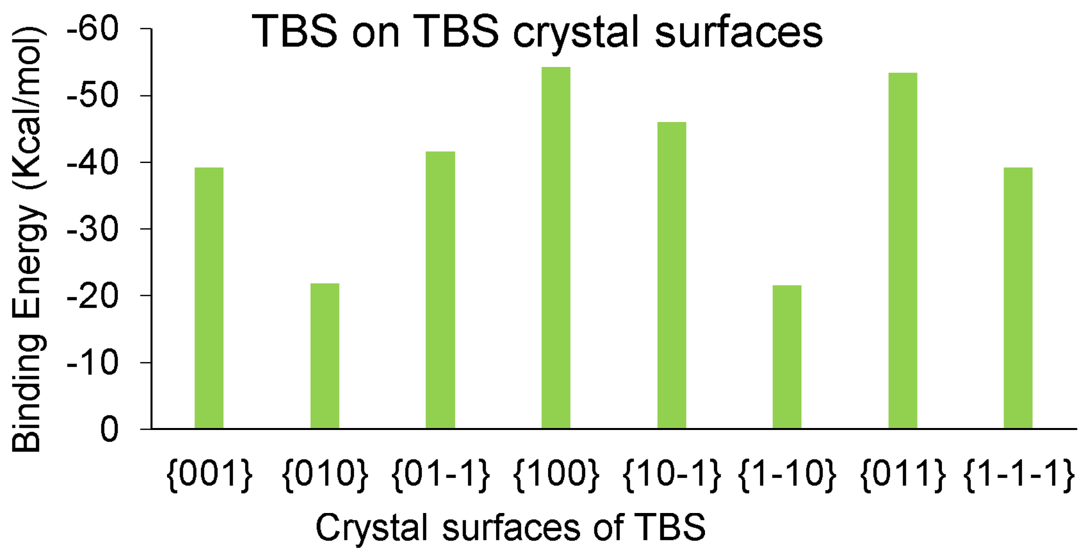
TBS binding on the (010) face of α-LMH



TBS binding on the (10-1) face of TBS



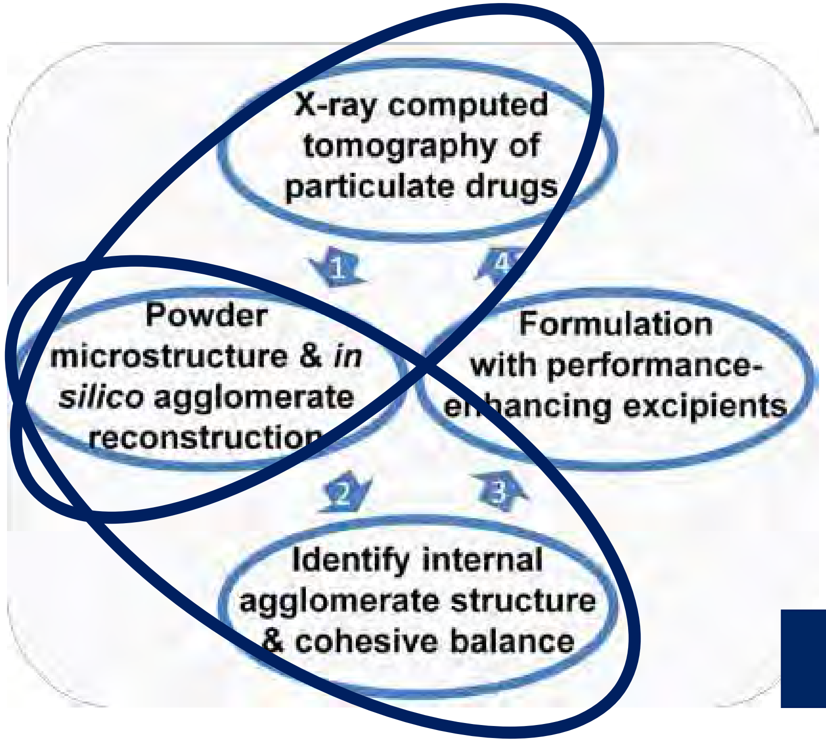




Interaction (Binding) Energy: TBS-TBS >TBS-αLMH> αLMH-αLMH

Enhanced Mechanistic Understanding of Inhaled Formulations

Hypothesis 3
Understanding powder microstructure combined with measurements of agglomerate forces will enable the rational design of formulations achieving uniform aerosolization



(1) Employ imaging techniques to generate nano-, micro- and meso-scale resolution of inhalation powder structure.
(2) X-ray microCT to generate powder structures with single-particle resolution
(3) Single particle microscopy to identify shape and topographical factors for WS1

Validation of computational predictions

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X-ray tomographical insight into inhaled pharmaceuticals from INFORM2020

Parmesh Gajjar

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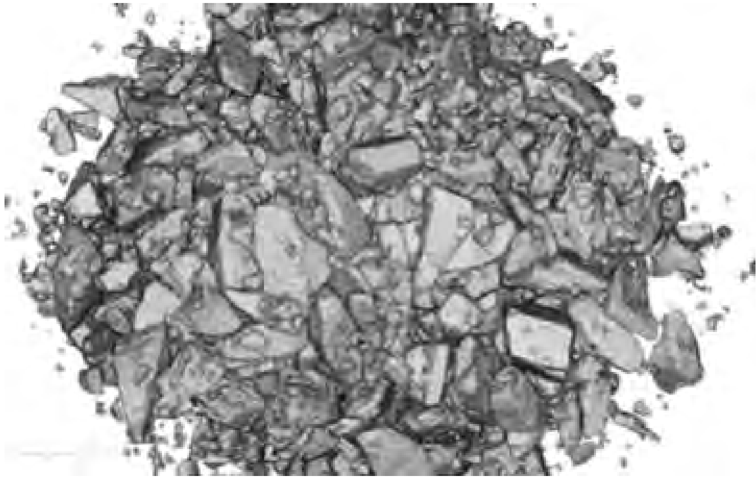
The University of Manchester
parmesh.gajjar@manchester.ac.uk



Phil Withers
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Ioanna Danai Styliari
Kevin Roberts
Hien Nguyen

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X-ray CT of Lactose Particles

Samples mounted in Kapton tubes

Zeiss Xradia Versa 520 with DCT

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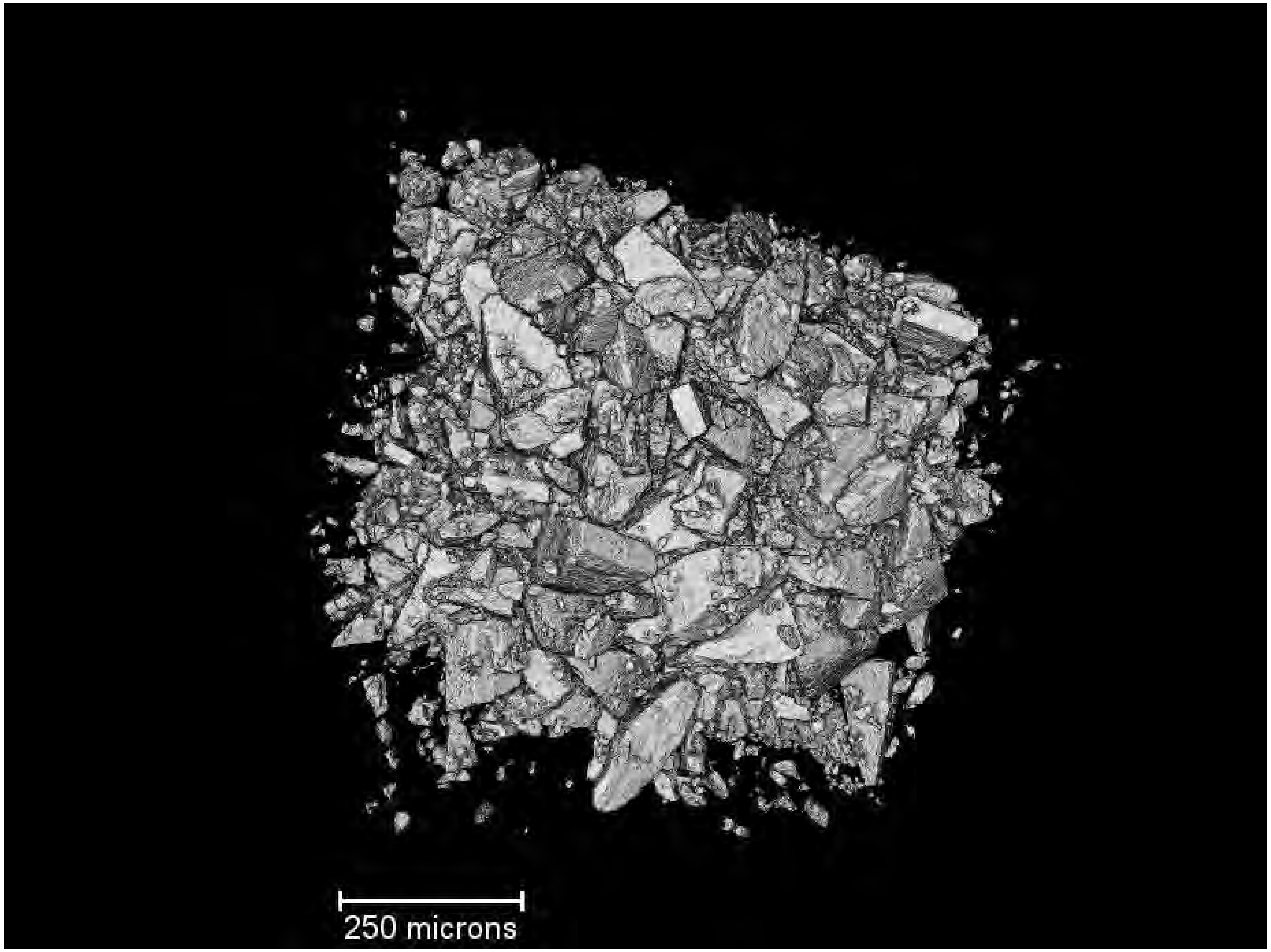
X-ray CT of Lactose Particles



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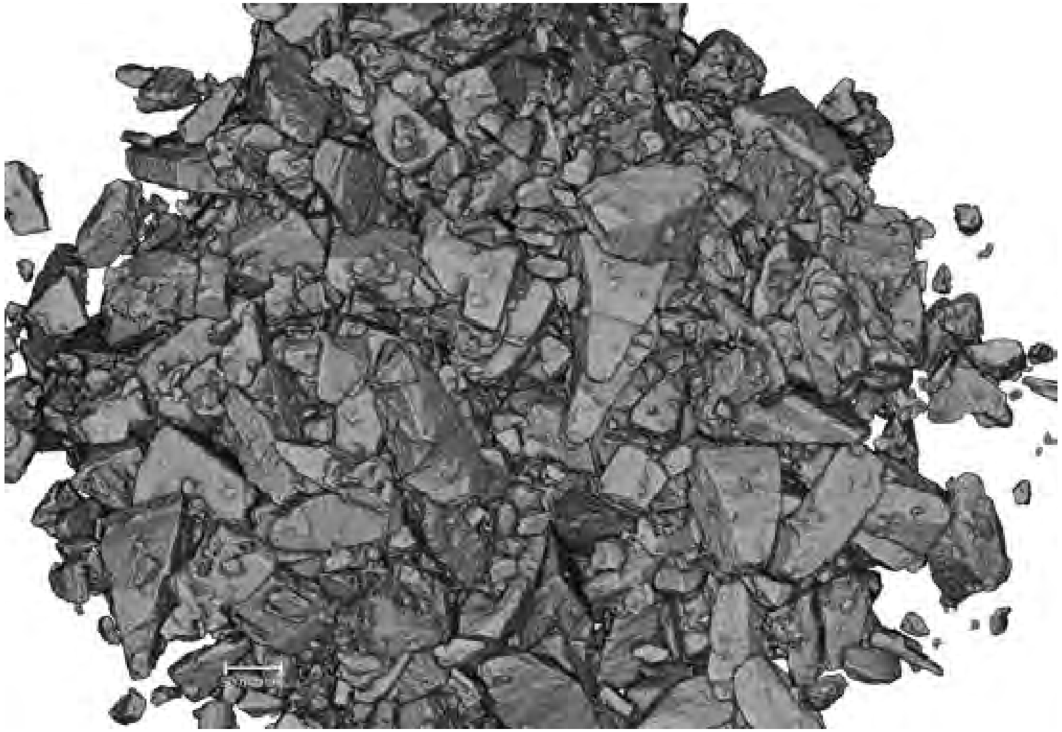
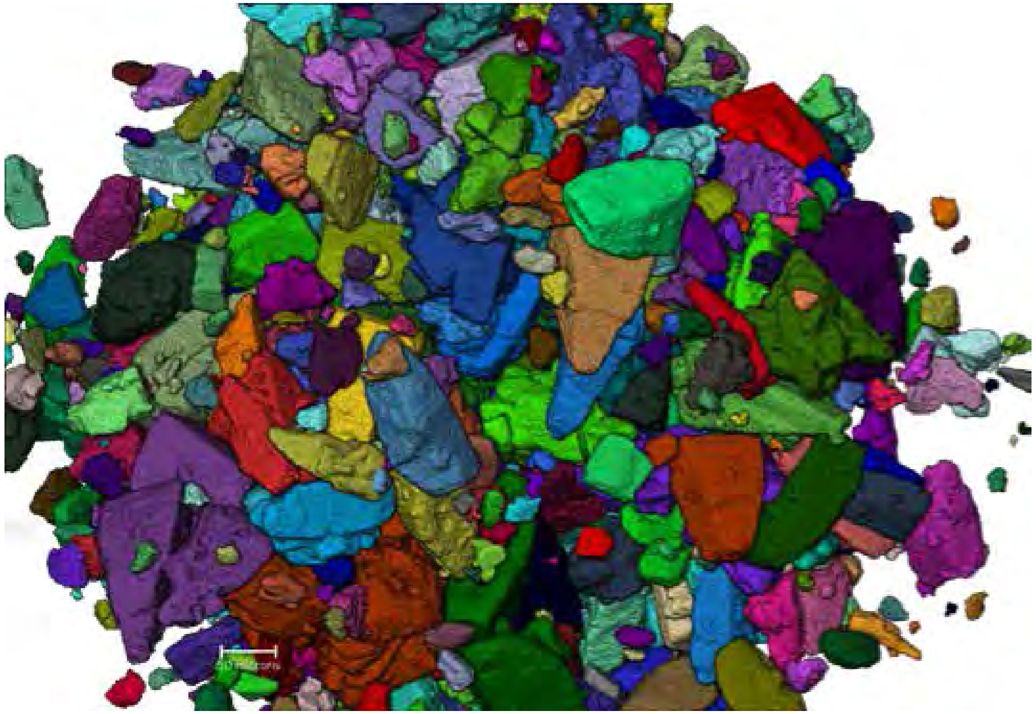
X-ray CT of Lactose Particles





LH100

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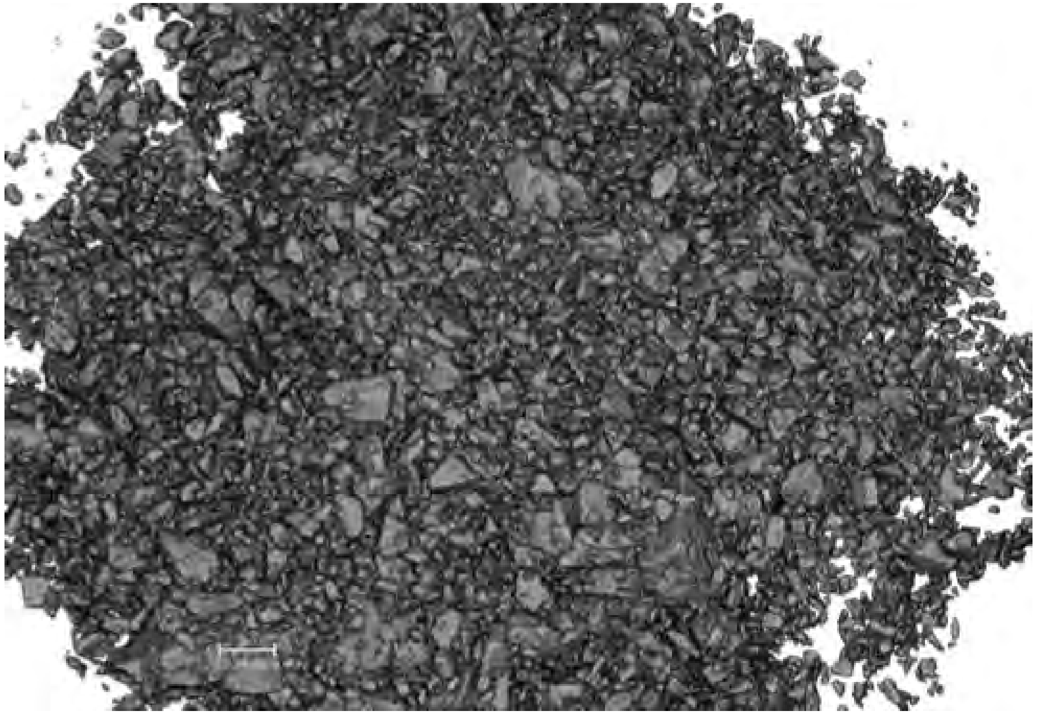
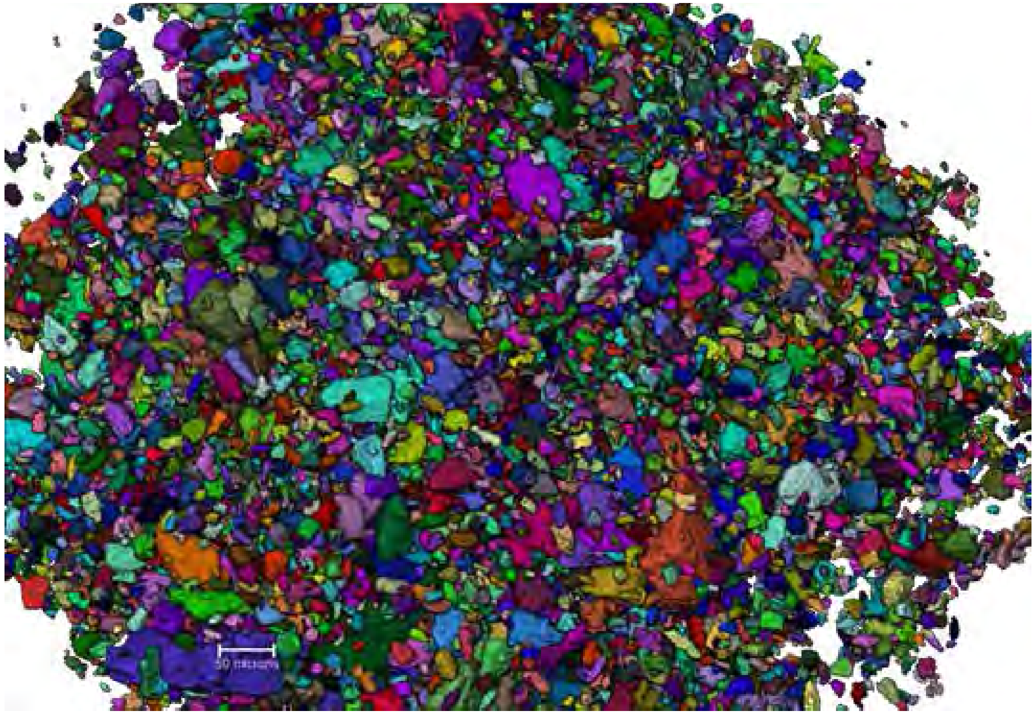
X-ray CT of Lactose Particles





LH200

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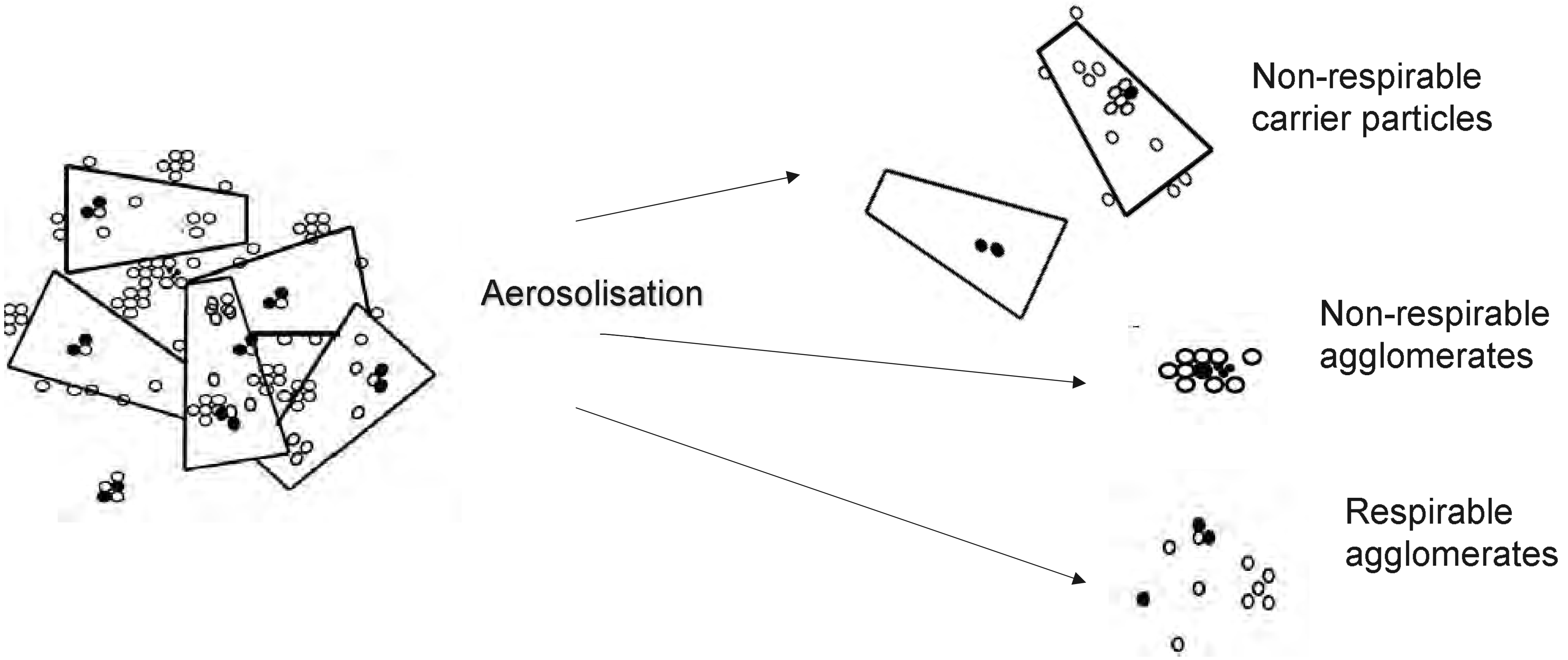
Key Challenges for Year 1

1. **Quantify the powder microstructure to measure density and understand particle-particle interaction geometry (e.g. which crystal face)**
   - **Study 'ultra-clean' lactose monohydrate to develop methodologies**
2. **Serious challenges to couple nano- and microCT of 10^{-9}-10^{-3} m powders**
   - **Develop methodology to study agglomerated microparticles**

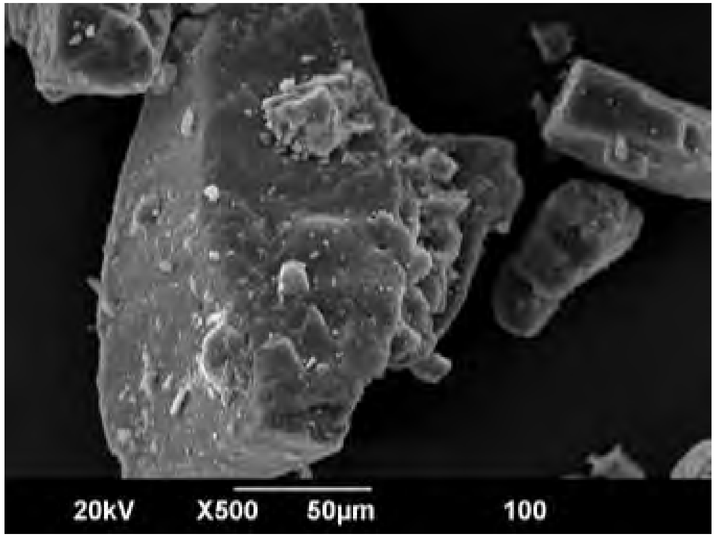
The issue we face in inhaled formulation development
Studying the influence of powder microstructure on performance?

- **Problem**: Intrinsic fines influence the formulation.
- **Solution**: Remove them and produce "clean" lactose carriers.

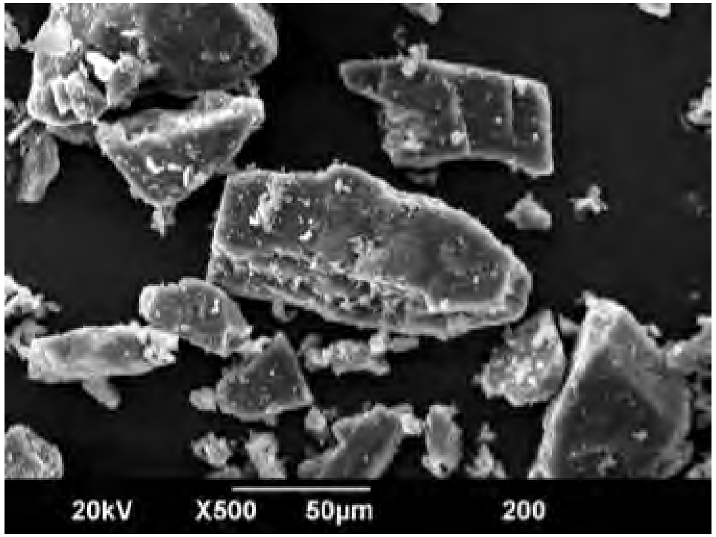


Inhalation grade lactose monohydrate

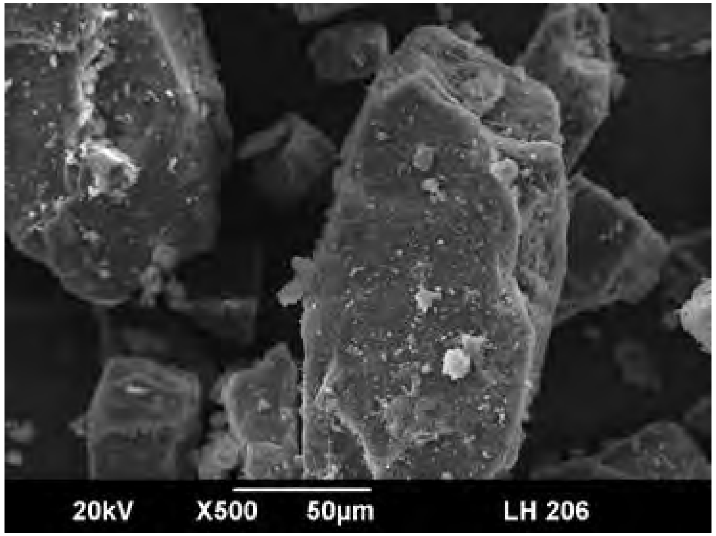
DFE pharma



Lactohale 100
(sieved)



Lactohale 200
(milled)



Lactohale 206
(milled with removed fines)

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Wet decantation technique

Previously reported to remove fine particle lactose

Acetone

Acetonitrile

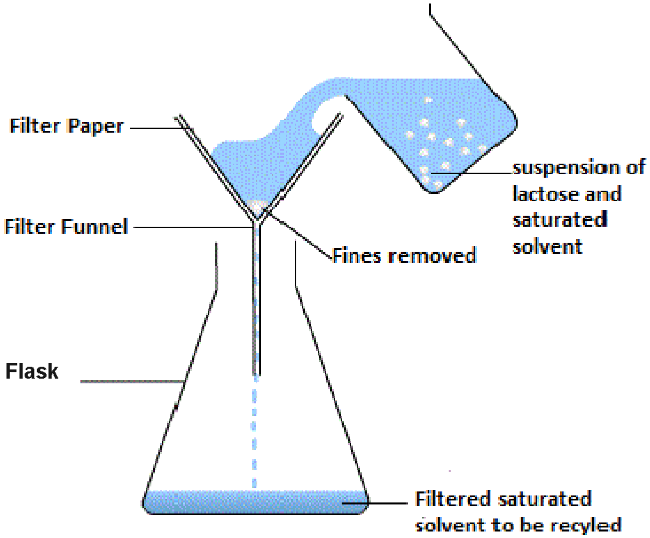
Dichloromethane

Ethanol

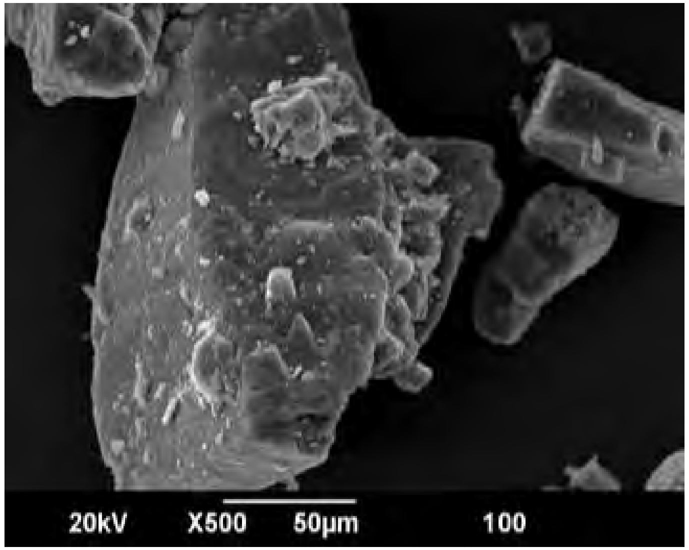
Isopropanol

Methanol

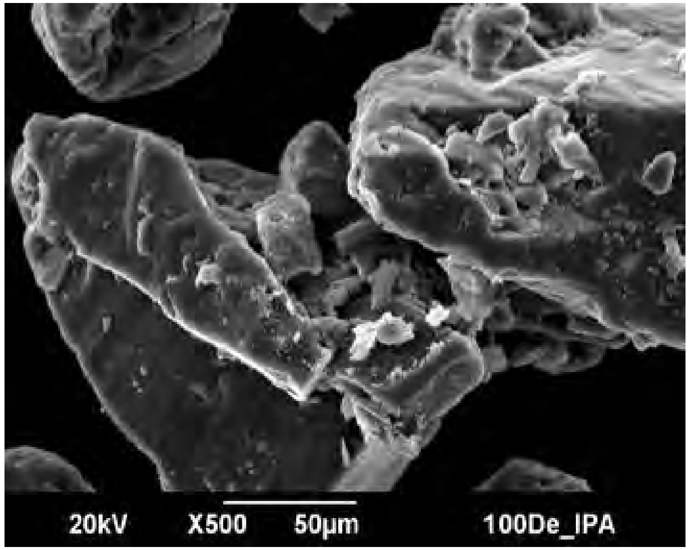
Tetrahydrofuran



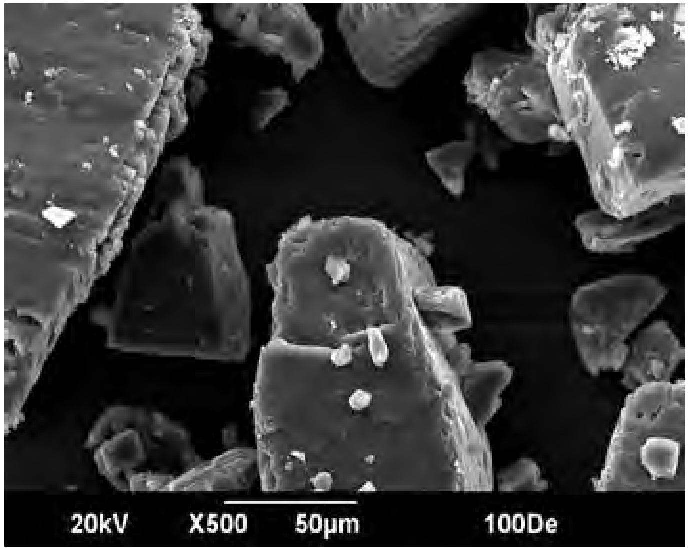
Wet decantation technique
The influence of solvent choice



Lactohale 100
(sieved)



Lactohale 100
Isopropanol



Lactohale 100
Ethanol

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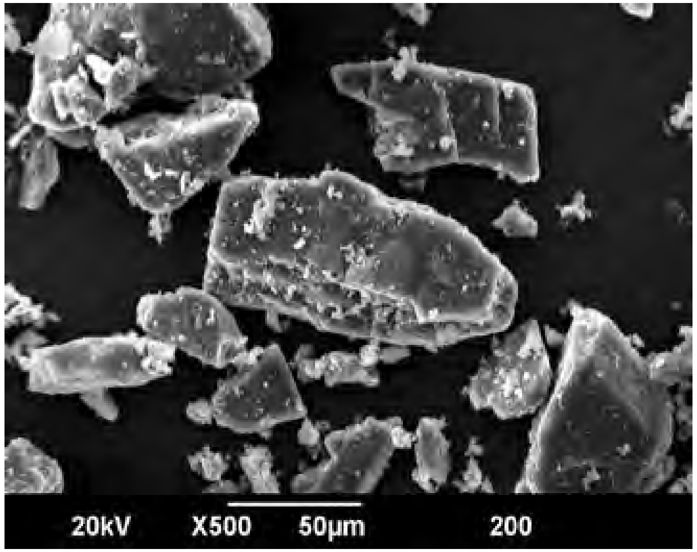
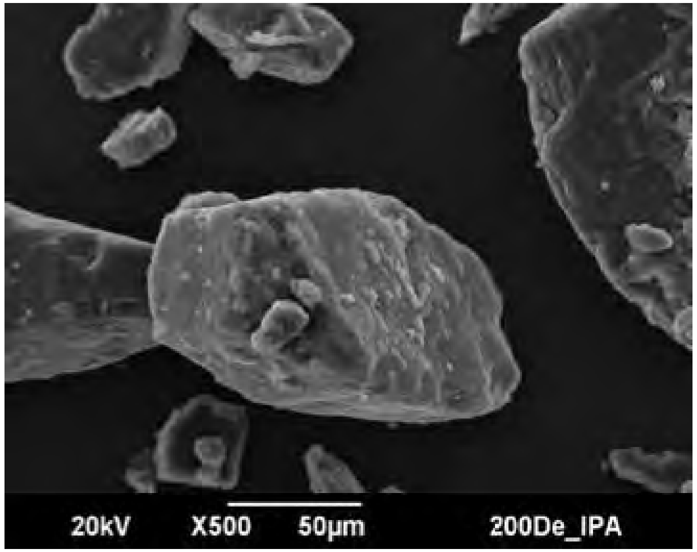
Wet decantation technique

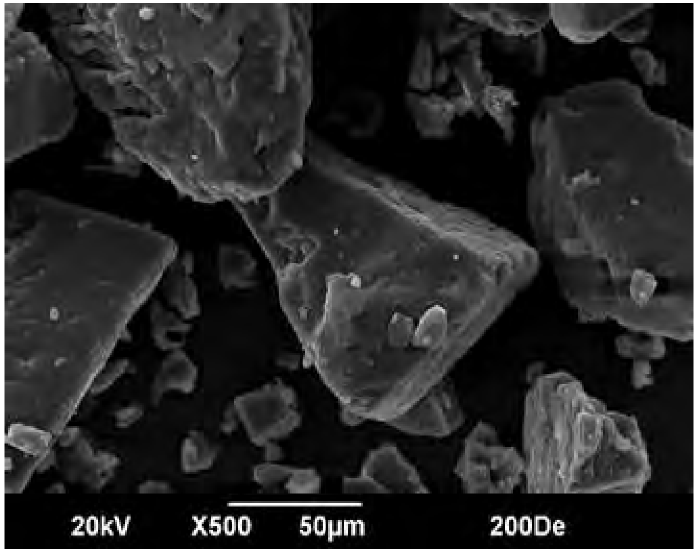
The influence of solvent choice



Lactohale 200
(milled)



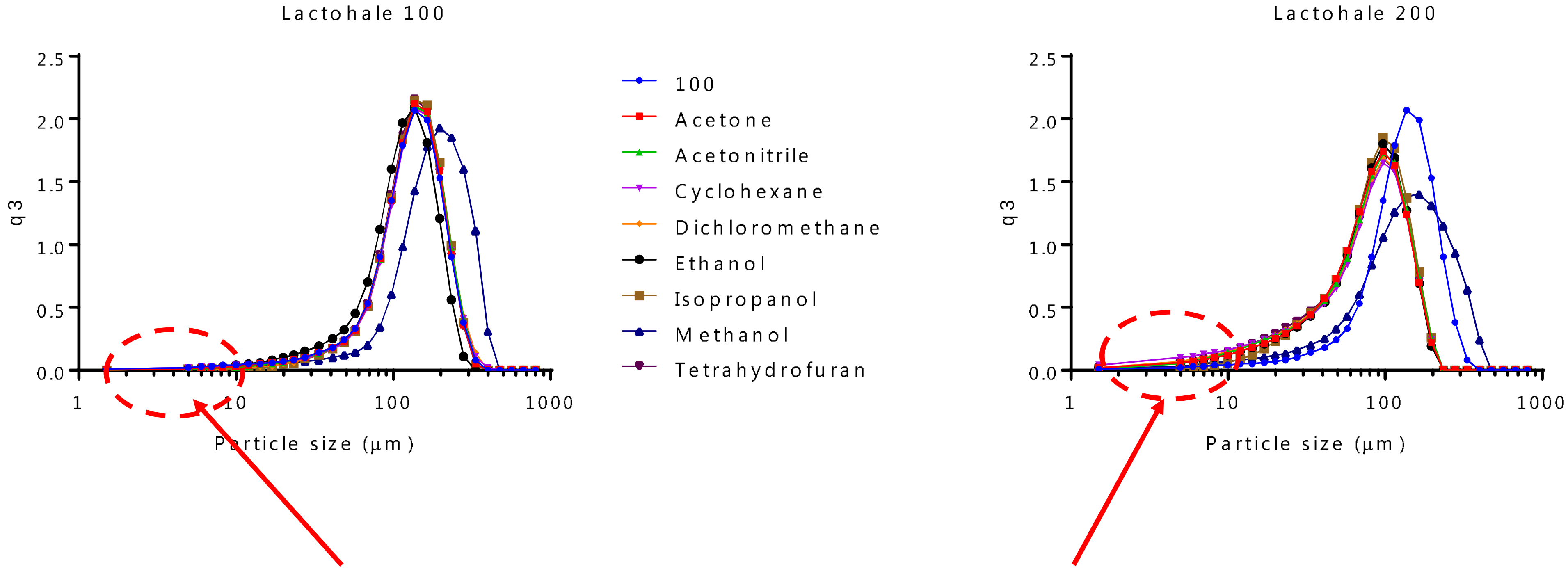
Lactohale 200
Isopropanol



Lactohale 200
Ethanol

Airflow titration

Laser diffraction analysis to assess removal of fines



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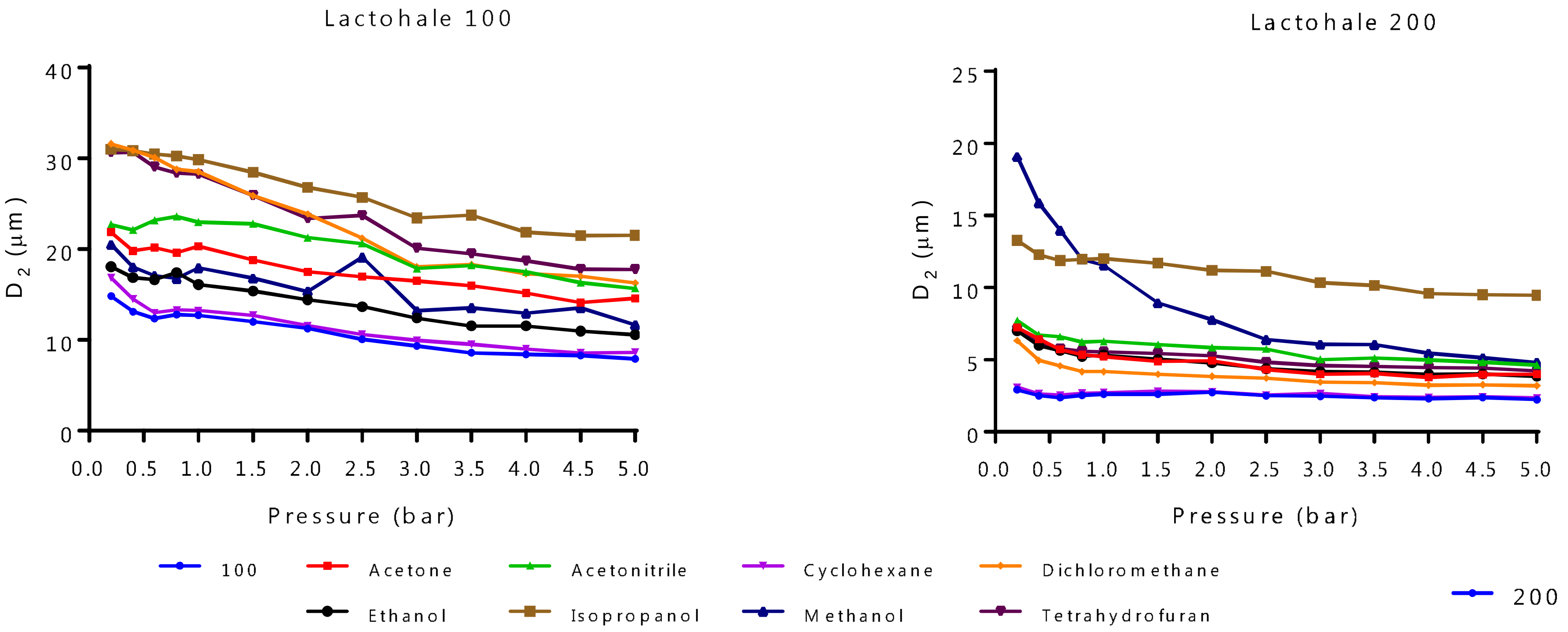
Airflow titration

Laser diffraction analysis to assess removal of fines



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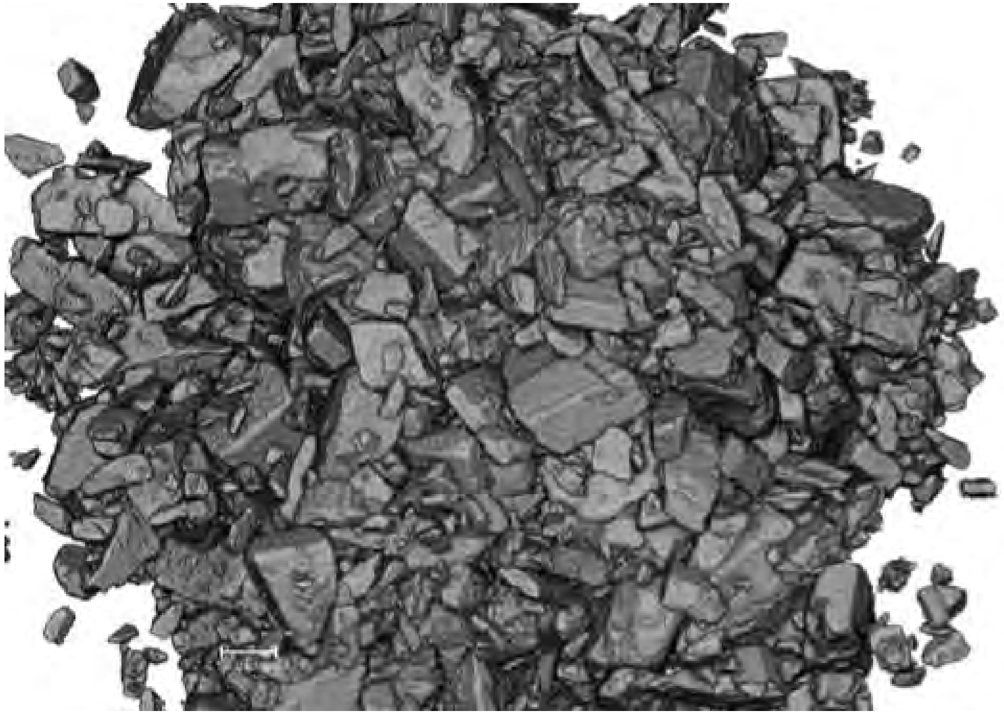
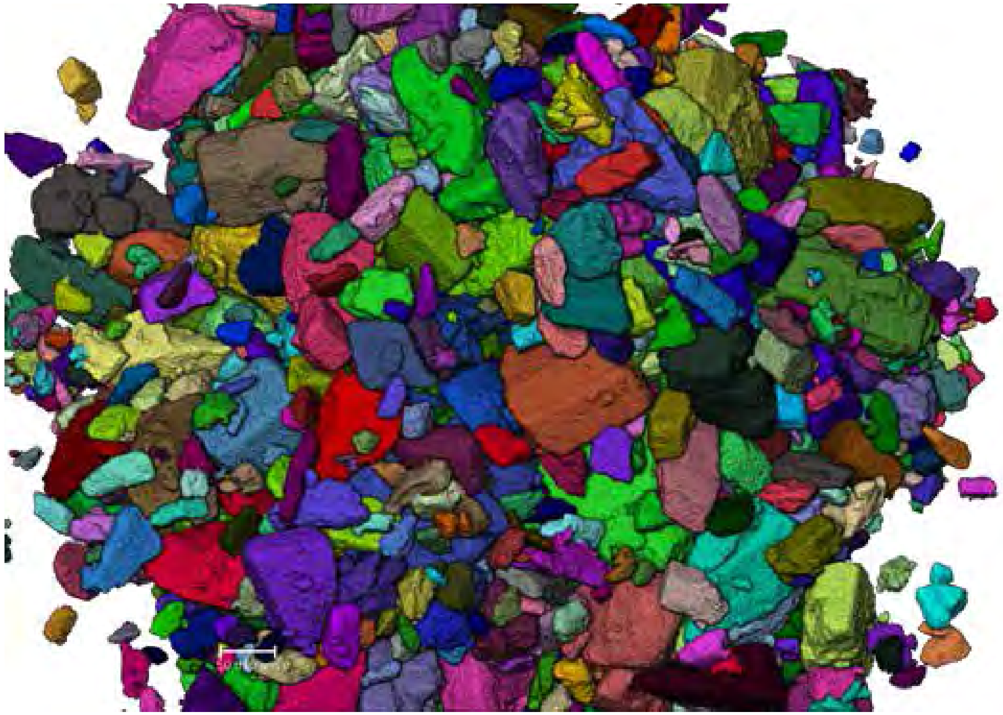
X-ray CT of Lactose Particles





LH200 – Ethanol decanted

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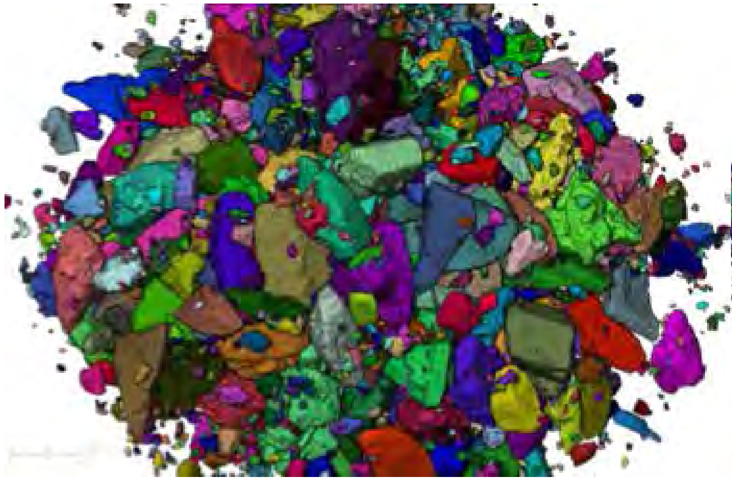
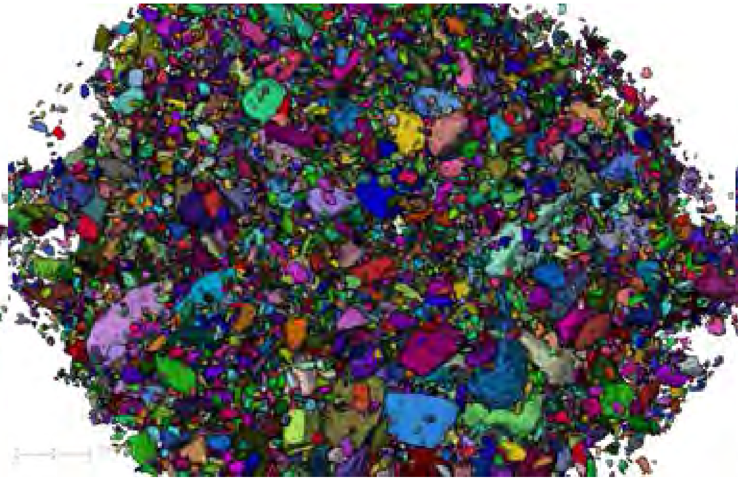
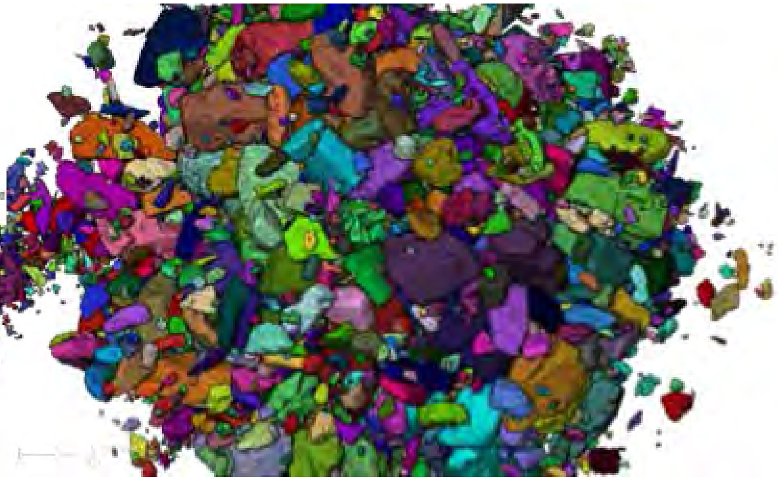
X-ray CT of Lactose Particles



LH100

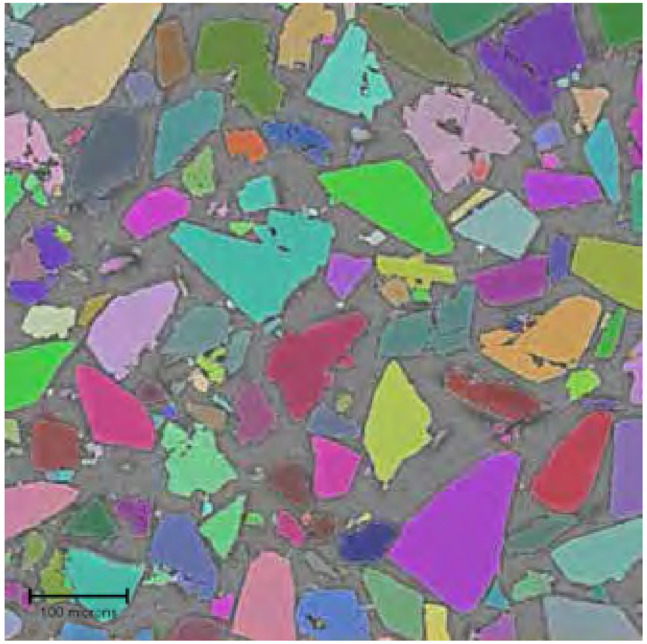


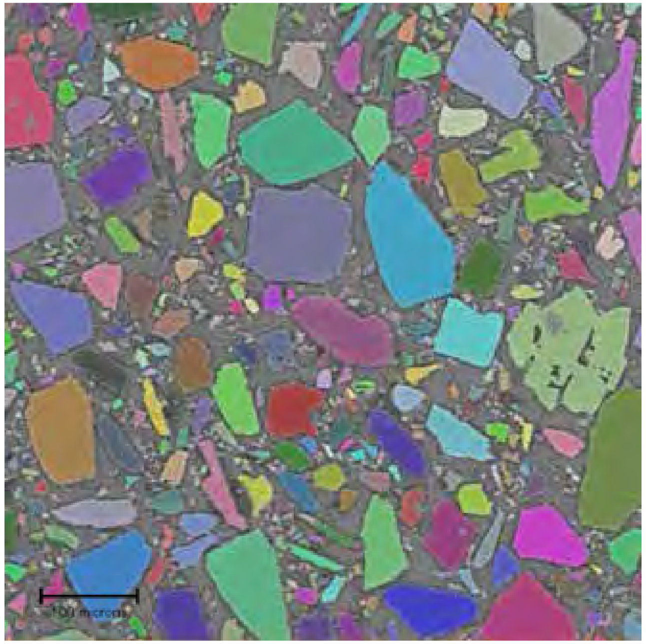
LH200

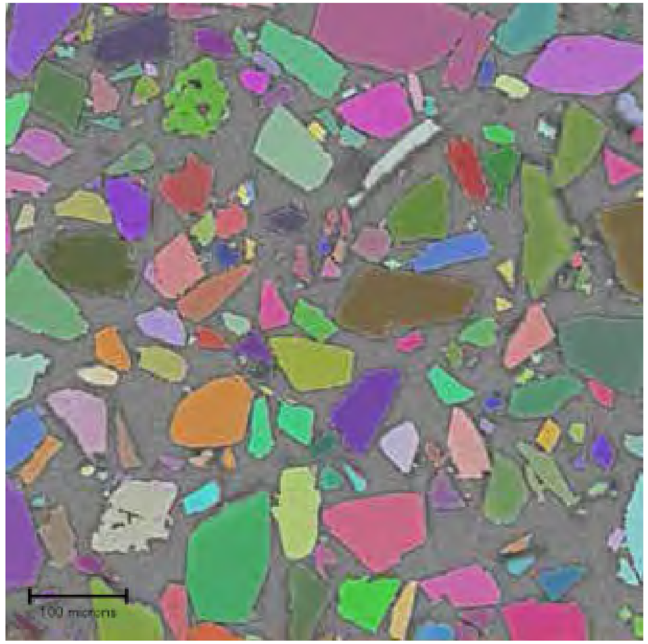


LH200 Ethanol Decanted

Generating particle sizing metrics from X-ray CT imaging







	LH100	LH200	LH200 Ethanol decanted
Total Particles	5824	37687	6248
Mean size (All)	13.47 um	8.73 um	16.47 um
Total S Particles	930	6832	873
Mean size (S)	2.36 um	2.89 um	2.41 um
Total L particles	4894	30855	5375
Mean size (L)	15.58 um	10.02 um	18.75 um

Analysed volume 0.75mm x 0.75mm x 0.75mm with a voxel size of 0.636989. Small particle defined as having 123 voxels.

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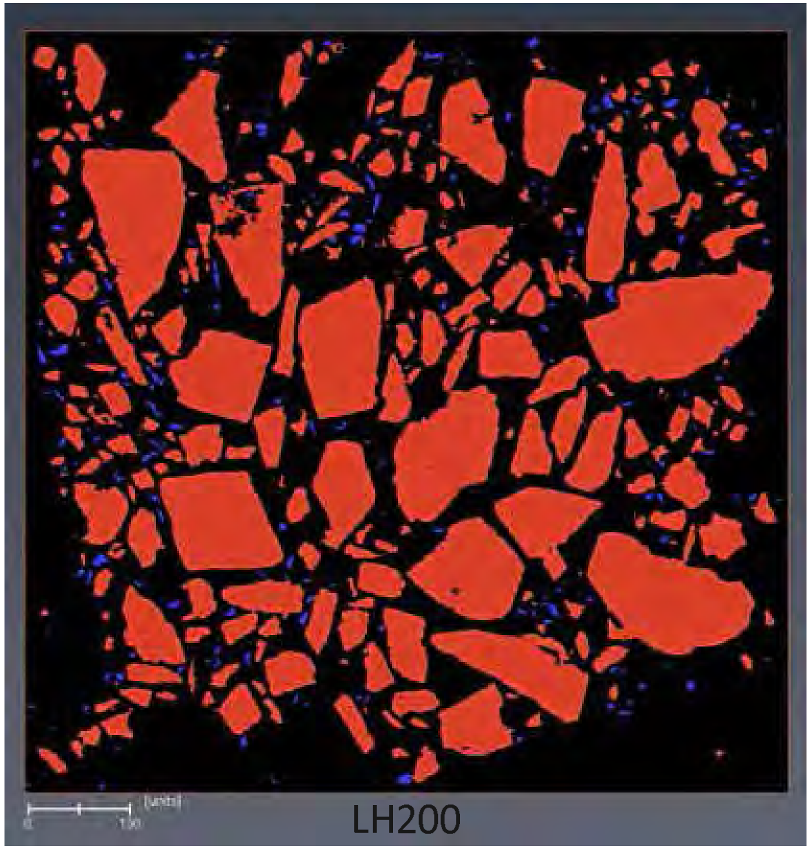
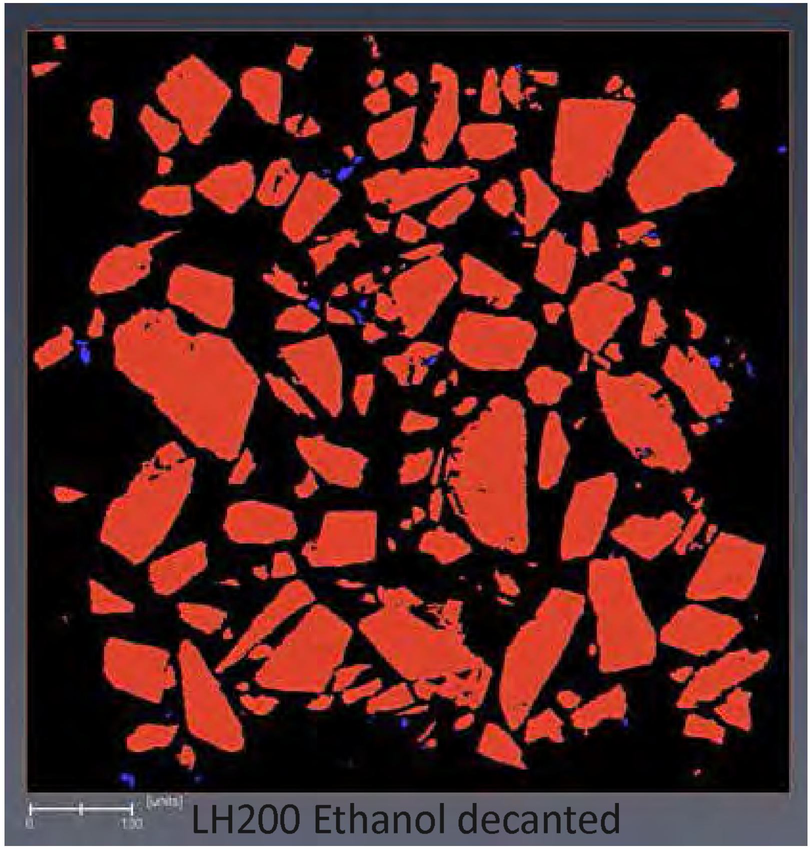
Examining the microstructure of powder blends



18316 micro particles in the analysis volume
Micro particle density of 43416 particles per cubic mm



2731 micro particles in the analysis volume
Micro particle density of 6473 particles per cubic mm

Comparing number and position of fines (<12 microns)

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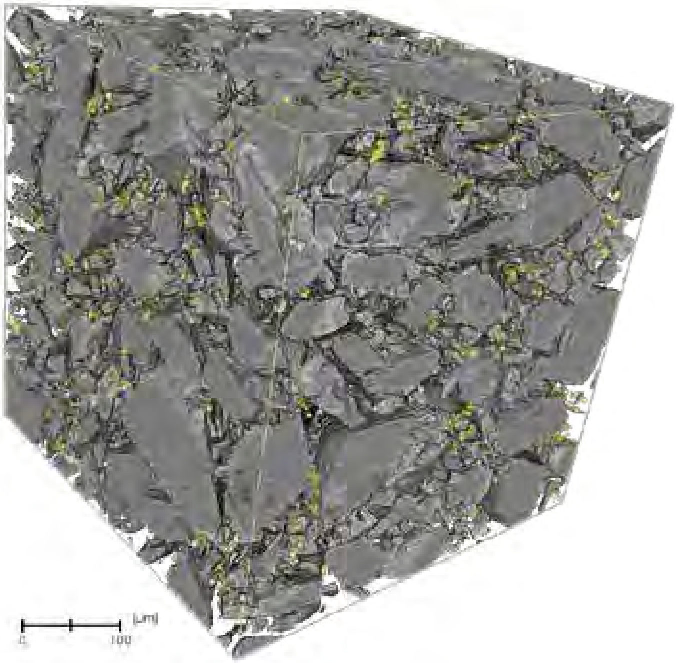
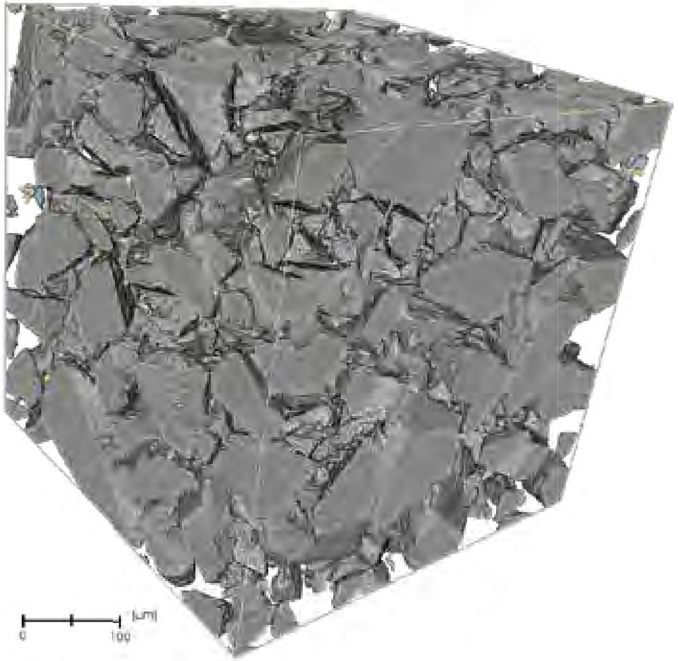
Examining the microstructure of powder blends



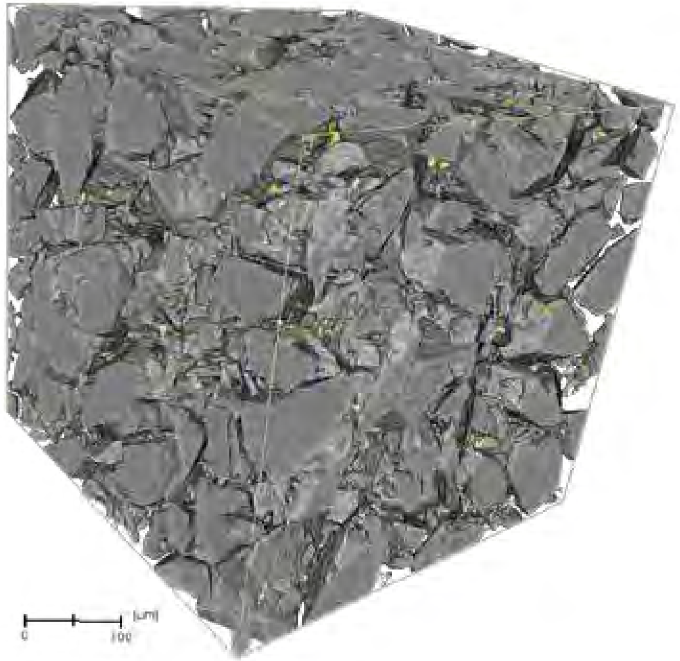
LH200

18316 micro particles in the analysis volume
Micro particle density of 43416 particles/mm^3



LH200 Ethanol decanted

2731 micro particles in the analysis volume
Micro particle density of 6473 particles/mm^3



LH200 IPA decanted

2995 micro particles in the analysis volume
Micro particle density of 7099 particles/mm^3

Comparing number and position of fines (<12 microns)

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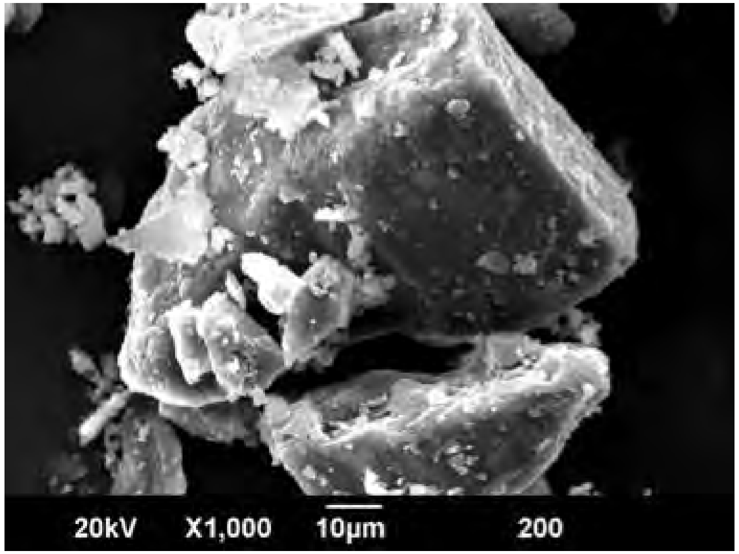
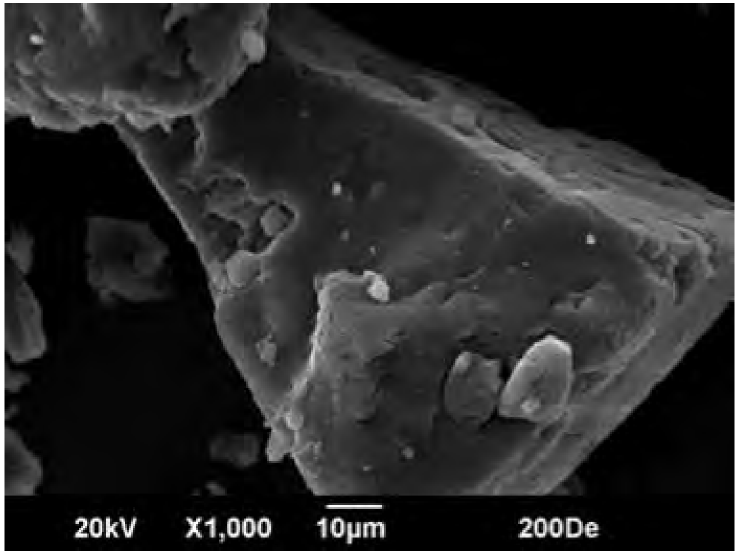
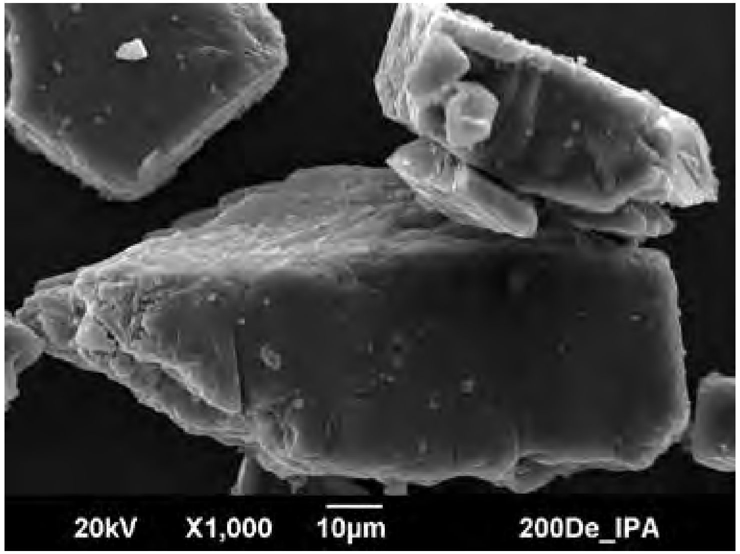
Electron microscopy of Lactose Particles



LH200



LH200 Ethanol decanted



LH200 IPA decanted

Comparing number and position of fines (<12 microns)

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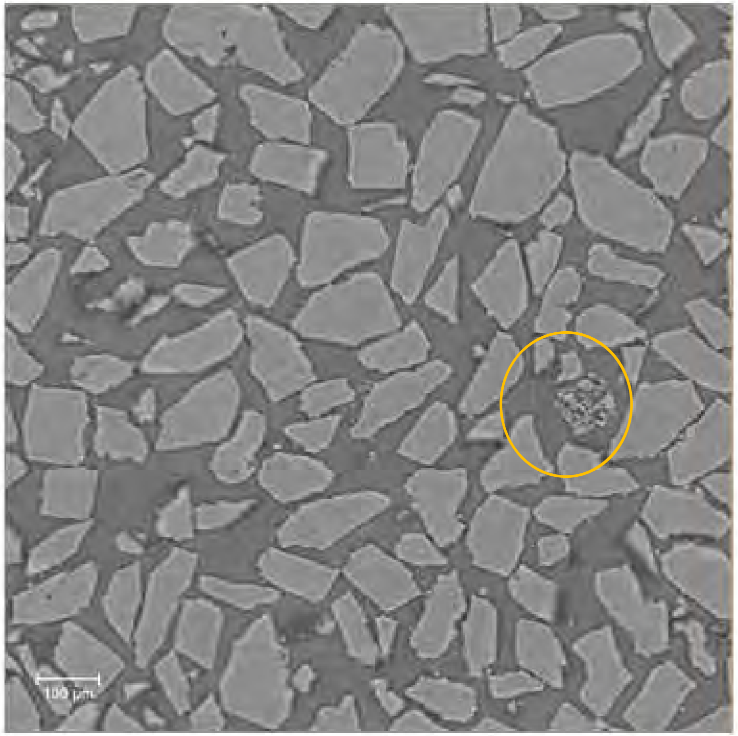
Assessing microstructural features through X-ray CT imaging



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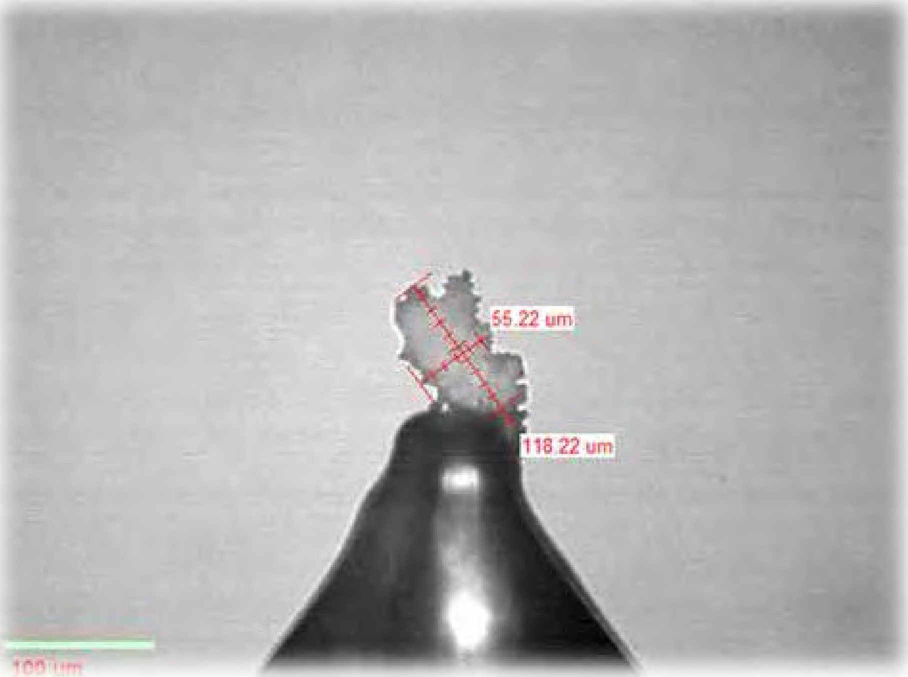
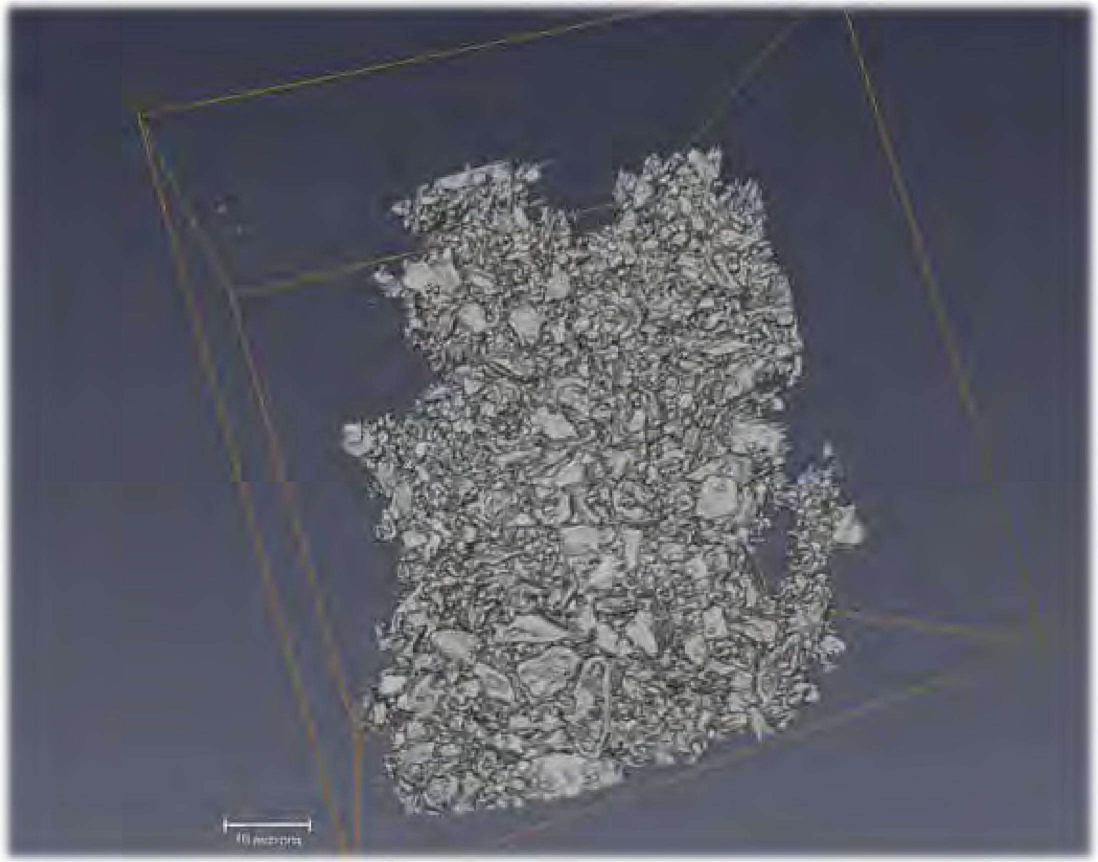
Nanoscale Analysis of micronised Lactose





Intra-agglomerate porosity: 0.358

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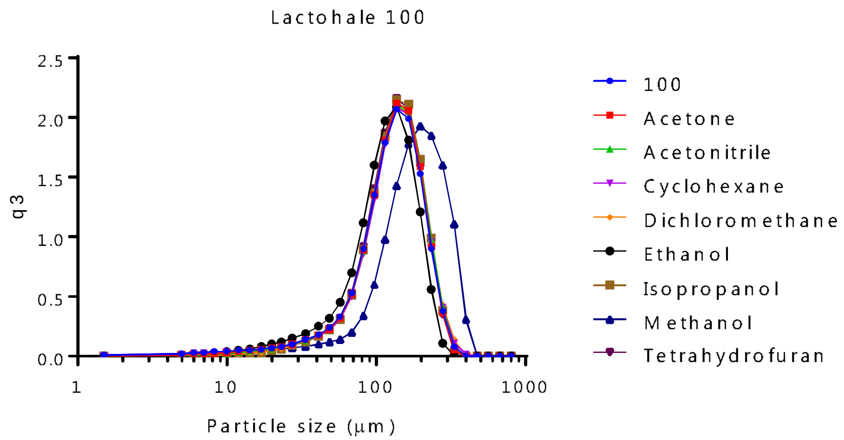
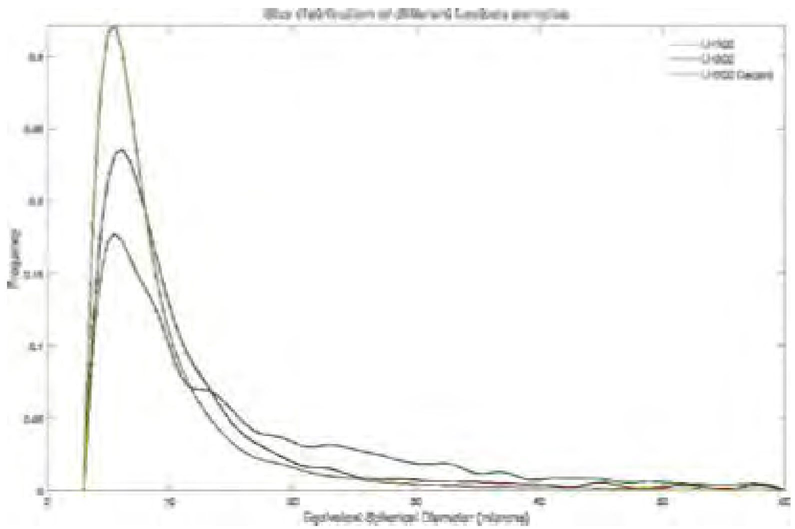
Future steps

Inter-technique translation

Laser Diffraction



XRCT



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Acknowledgements

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