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

University of Hertfordshire UH

UNIVERSITY OF LEEDS

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The University of Manchester

Tim Burnett, David Chau, James Elliott, Robert Hammond, Victoria Hutter, Darragh Murnane, Robert Price, Kevin Roberts, Philip Withers

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Health and Wellbeing

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nanopharm

3M Drug Delivery Systems Division

AstraZeneca

gsk

Intertek

Melbourn Scientific

team. medical design and development

neutec

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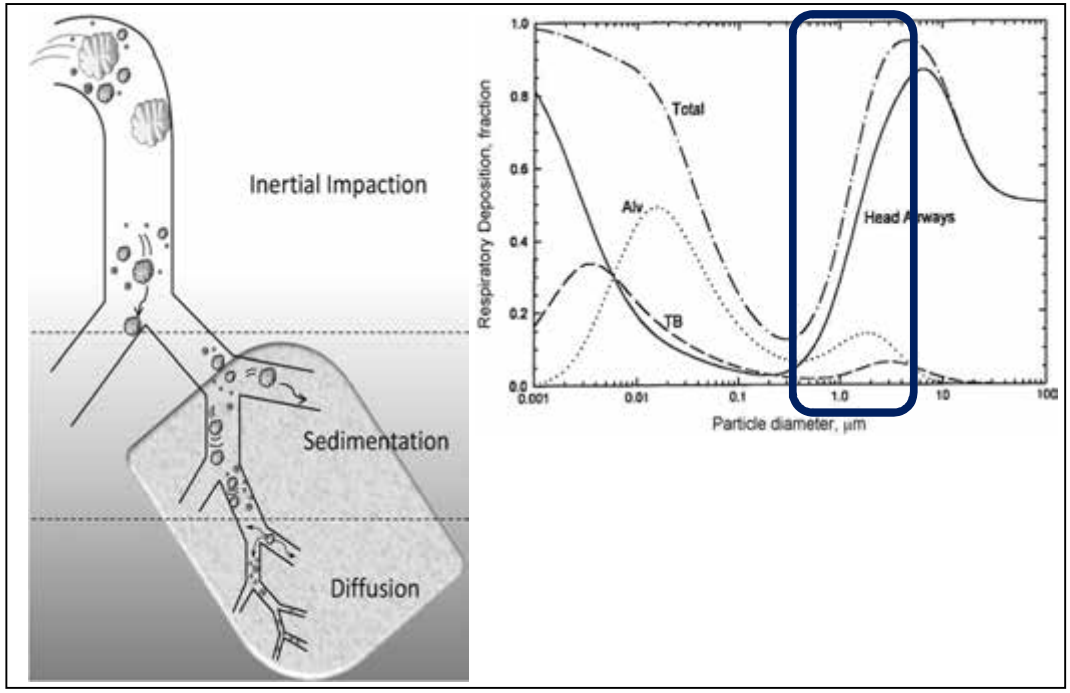
Pulmonary drug delivery

Challenges and barriers to effective therapy

The performance requirement:
Inhale ~0.5-3.0 µm aerosol slowly for systemic and small airways delivery
Inhale ~0.5-6.0 µm aerosol for targeting conducting airways



Pulmonary drug delivery
Challenges and barriers to effective therapy

So – what's the problem?

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Pulmonary drug delivery
Challenges and barriers to effective therapy

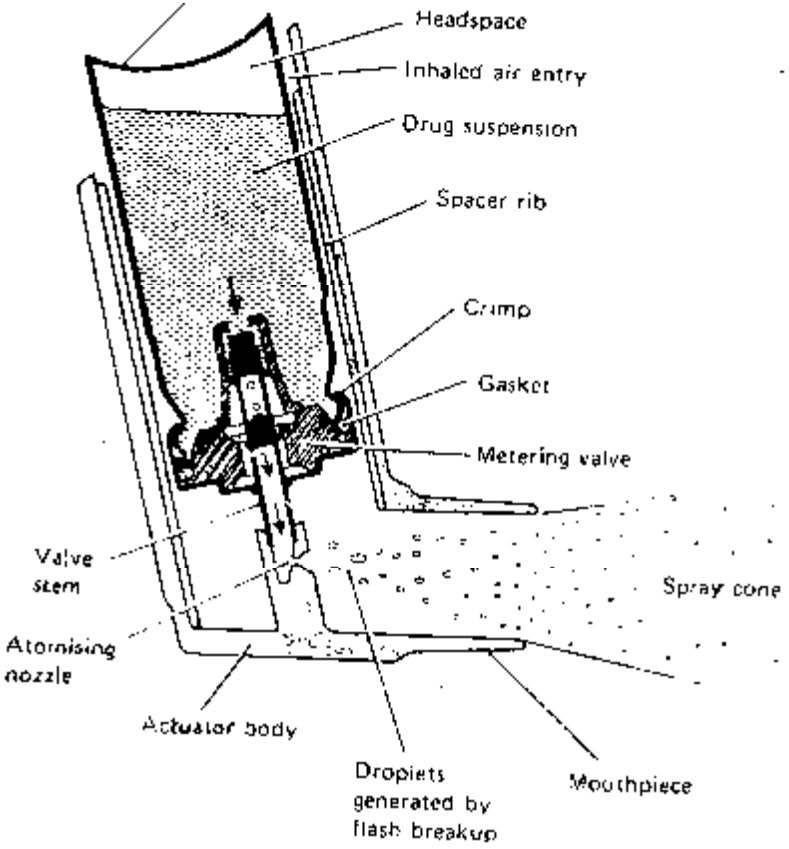
So – what's the problem?

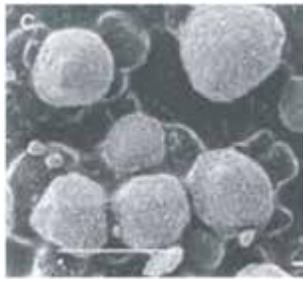
Require a portable, easy-to-use product
Must be able to densify the aerosol phase
Must be able to regenerate the aerosol phase on demand
That regenerated aerosol has a tight specification

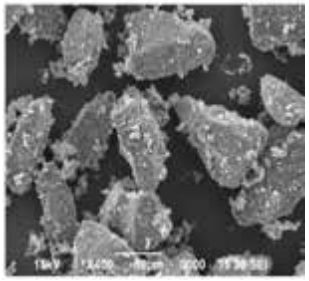
We don't have a lot of excipient options to work with!

Portable inhalation therapies

Pressurized metered dose inhalers and dry powder inhalers







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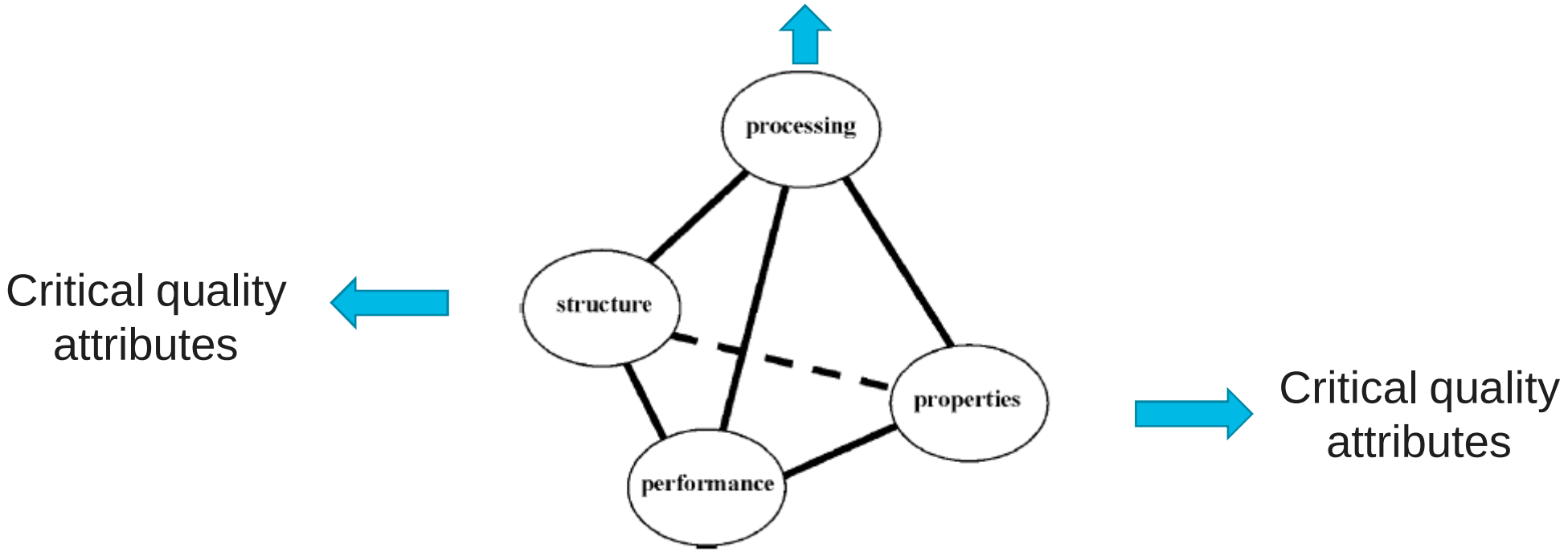
Key formulation challenges

Quality by design framework for pharmaceutical manufacture

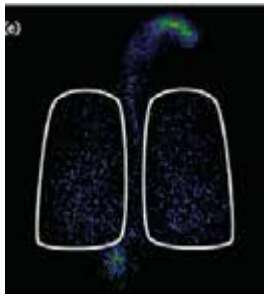
The materials science tetrahedron establishes the principle of linking the measurement of input material properties, through manufacturing parameters to product performance.

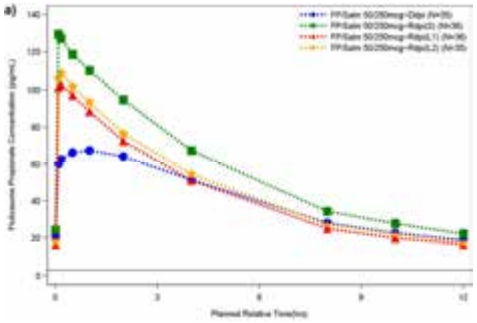
Critical Process Parameters or Critical Manufacturing Attributes



CC Sun's "Materials Science Tetrahedron" J. Pharm. Sci. 2009, 98(5) 1671-1687

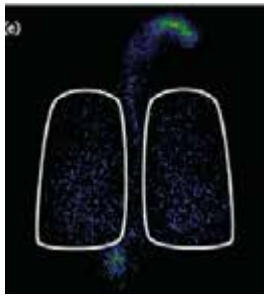
What are the typical performance criteria for inhalers?

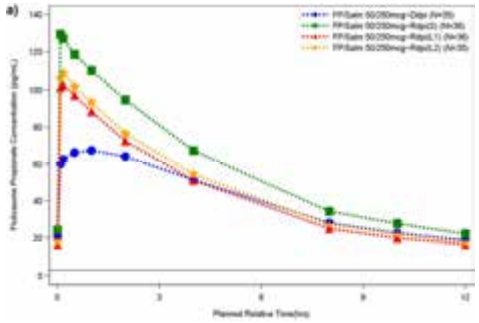




What are the typical performance criteria for inhalers?

Impaction analysis provides an indication of the particle size mass distribution which would be inhaled by a patient





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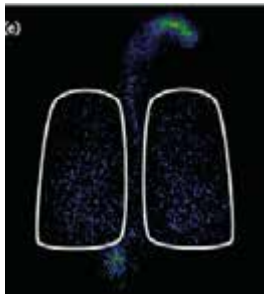
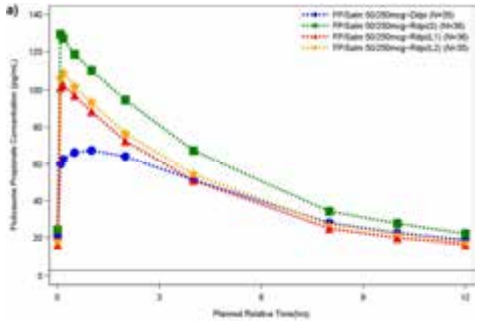
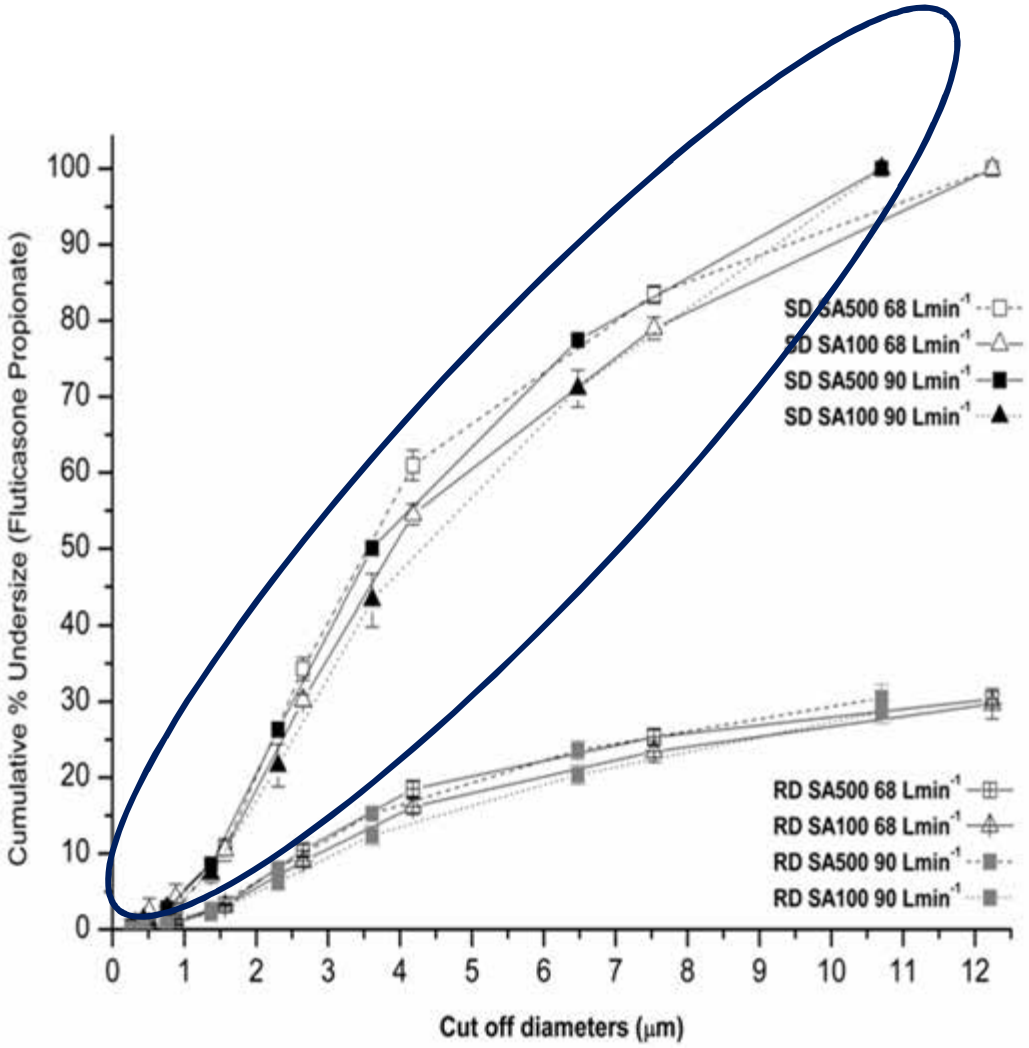




Very high variability is allowable for inhaled products (± 15 % in many instances) according to regulatory standards.

Formulation performance of a dry powder

Impaction analysis is the key performance test



- Determine median aerodynamic diameter from the sizeable particle dose
- Consider the fine particle dose
- The *true* aerodynamic size distribution not sizeable fraction
- **Why is so much depositing on the non-sizeable stages?**

Unpublished data

Formulation performance of a dry powder
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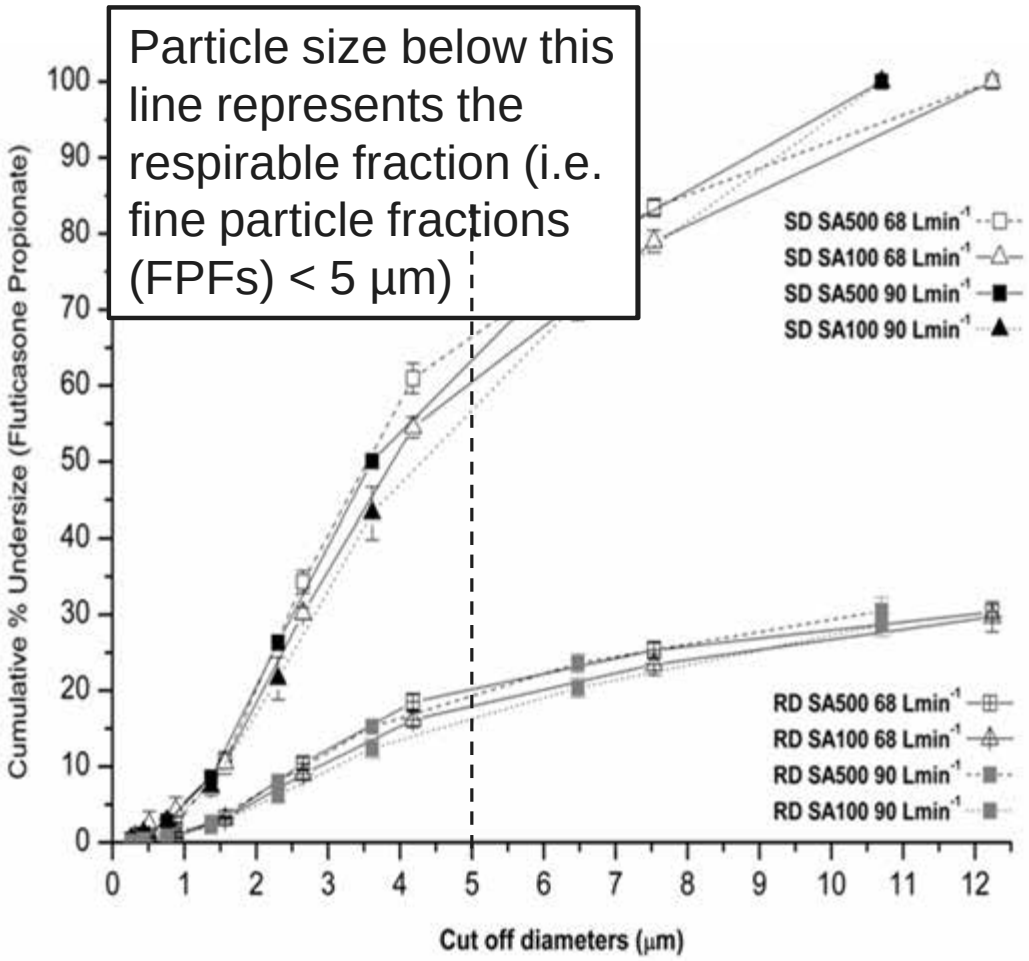

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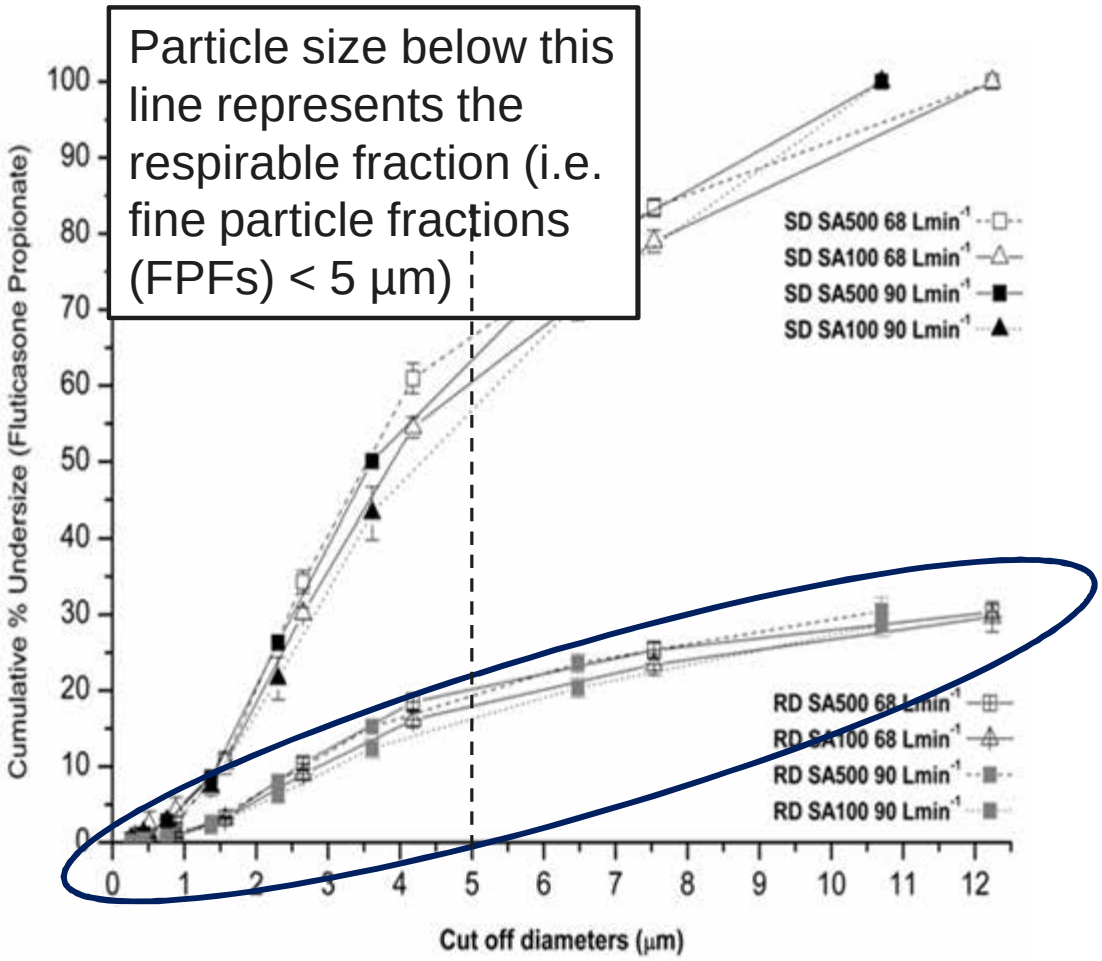

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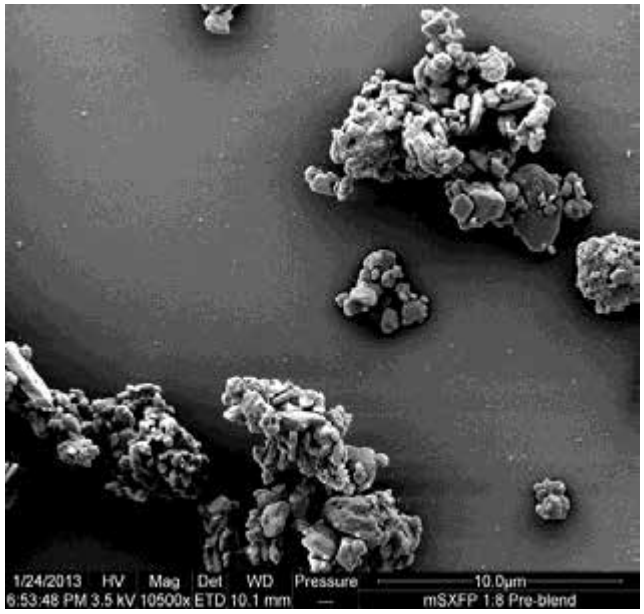
Key formulation challenges

Aggregation is a fundamental behaviour of inhalable particles

- Particle size < 10 µm
- Small particles have high specific surface area
- High surface area = high surface free energy!



Micronized SX and FP scanning electron microscopy (X10500), unpublished

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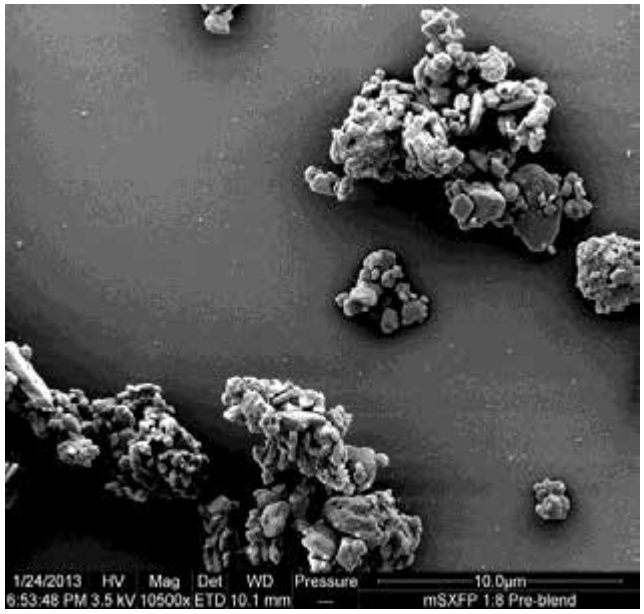
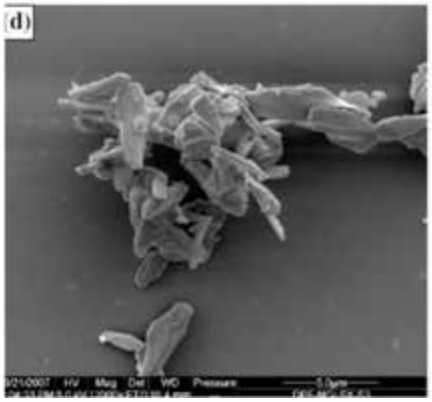


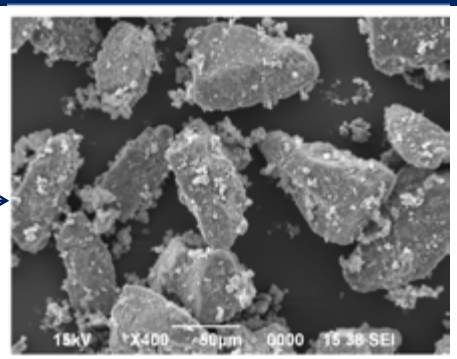
Micronized SX and FP scanning electron microscopy (X10500), unpublished

What factors determine the propensity to aggregate & how is this affected by formulation & manufacture?

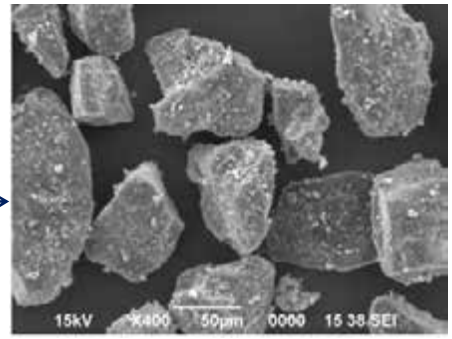
Considering agglomerated microparticles as the fundamental unit: Can we predict how materials will behave during manufacture?



Images from Parisini et al. AJPS (2015) 10: 501-512



Cohesion

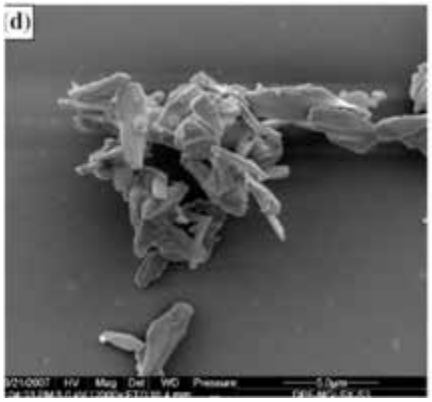


Adhesion

Secondary processing steps:

- Are agglomerates dispersed through blend?
- Do particles agglomerate in propellant?
- How does blending energy determine agglomerate behaviour?

Considering agglomerated microparticles as the fundamental unit: Can we predict how materials will behave during manufacture?



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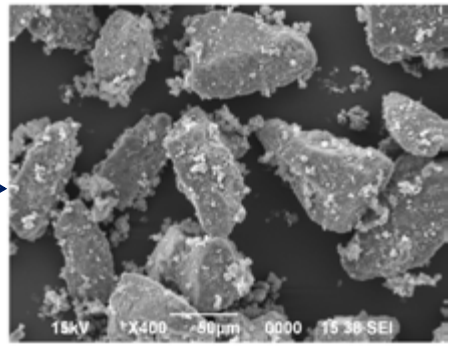

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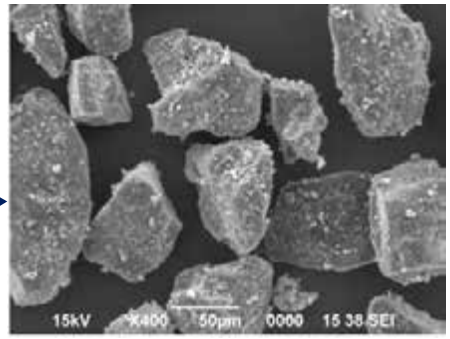


Adhesion

Blending step:

- Are agglomerates dispersed through blend?
- Do particles agglomerate in propellant?
- How does blending energy determine agglomerate behaviour?

Aerosolization step:

- Do agglomerates stick to excipients?
- Do individual drugs stick to excipients?
- How do agglomerates respond to emission and evaporation processes?

Metered dose inhaler formulations

Drug particles also agglomerate in propellants

	$D_{(v, 0.5)}$ (µm)	% < 6.4 µm (calc.)	% < 6.4 µm (meas.)
mSX (raw)	1.13 ± 0.12	97.7 ± 0.5	-
mSX (in HFA)	7.03 ± 0.95	39.8 ± 6.7	45.7 ± 2.3

- What are the kinetics of agglomeration?
- What is the mechanical strength of agglomerates?

Murnane et al. Pharm. Res (2008) 25: 2283-2291

The state of play for future formulation of inhaled therapies?

Inhaled delivery of advanced therapeutics is technologically difficult with high development costs, poor success, and challenging consistency of product efficiency.

Physical interactions between active pharmaceutical ingredients (API) and excipients dominate performance, but are difficult to detect experimentally.

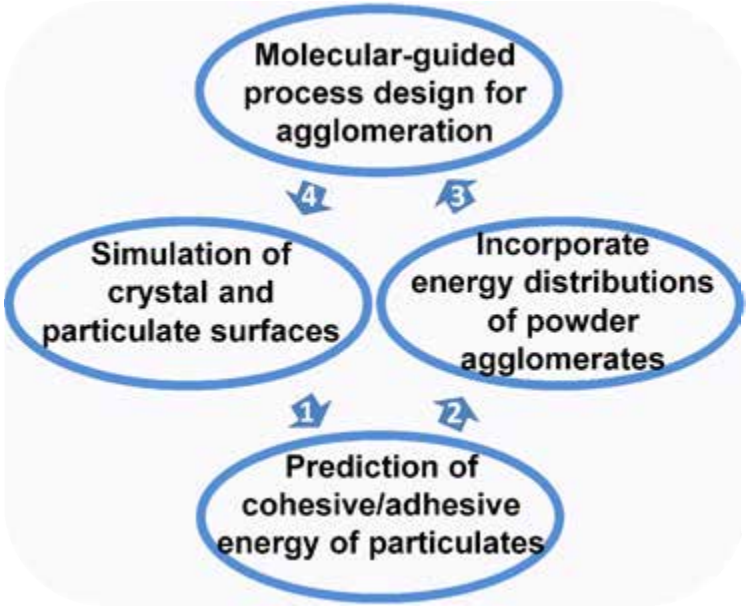
Key research challenges for the INFORM 2020 Programme

INFORM 2020 aims to meet the challenges of formulating (bio)pharmaceutical nano- and microparticles into inhaled products.

Computational pharmaceutics approach

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



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Computational pharmaceutics approach

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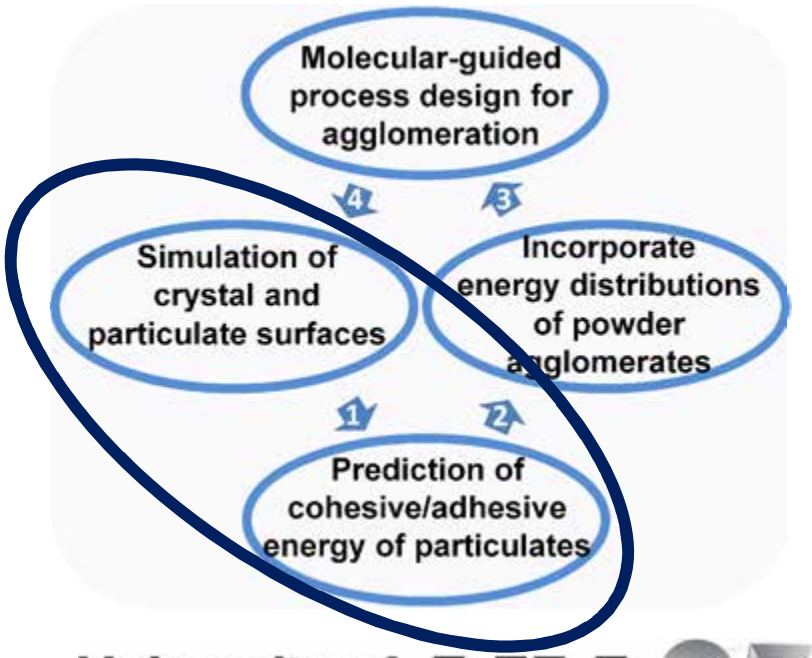

Examine raw materials first

(1) Particle surfaces of selected compounds will be simulated *in silico* based on single crystal data using VisualHabit.

(2) VisualHabit and in-house SystematicSearch software will be used with molecular dynamics simulations to predict surface energy and adhesion/cohesion propensity.

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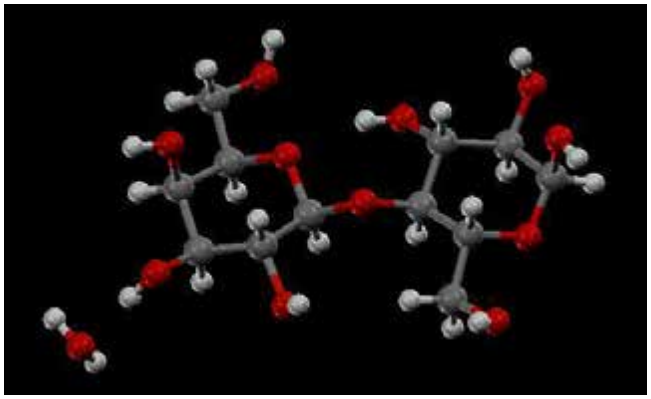
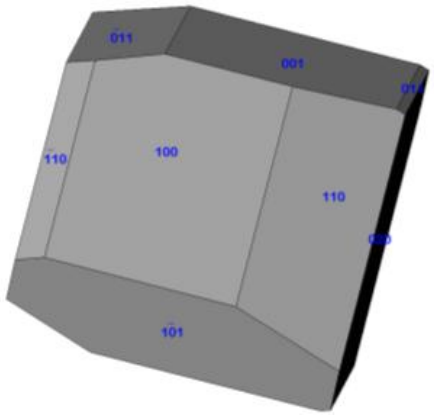
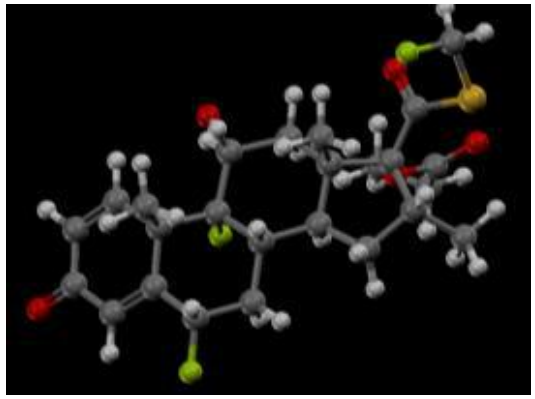
WS1 approach using synthonic engineering design

R Hammond, K Roberts, I Rosbottom, TBC

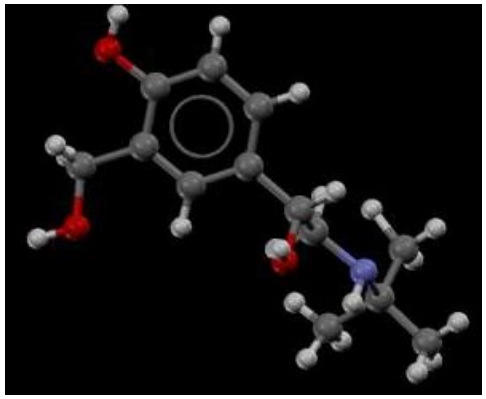




α-Lactose monohydrate and predicted crystal



Fluticasone propionate



Salbutamol

Step 1: Examine properties of the crystal structure and habit
Step 2: Computational measurement of adhesive/cohesive forces

Ramachandran, et al. *Mol. Pharm*. (2015) 12:18-33

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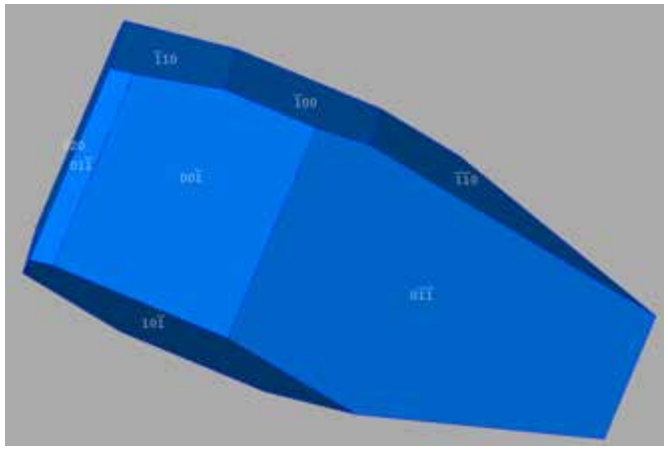
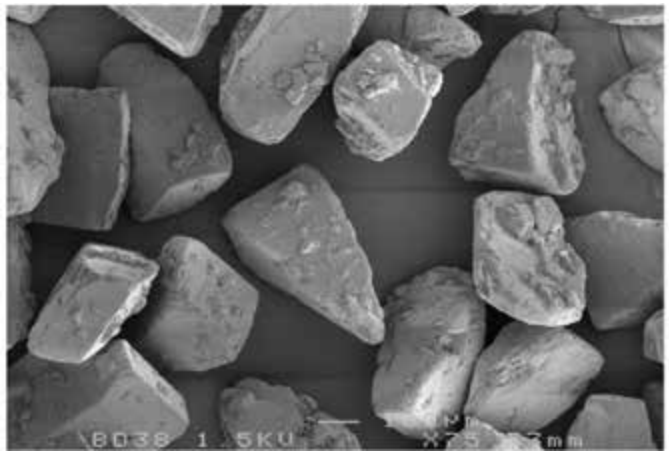
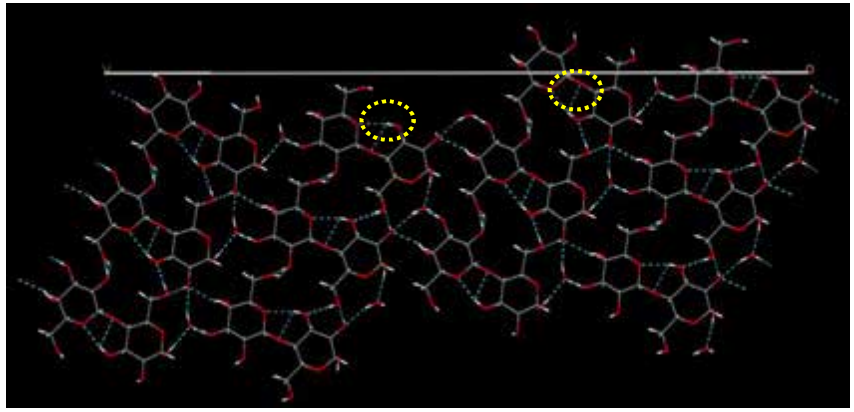
Extrinsic synthons from single crystal or computed crystal structures

Interactions arising from unsaturation at the interface



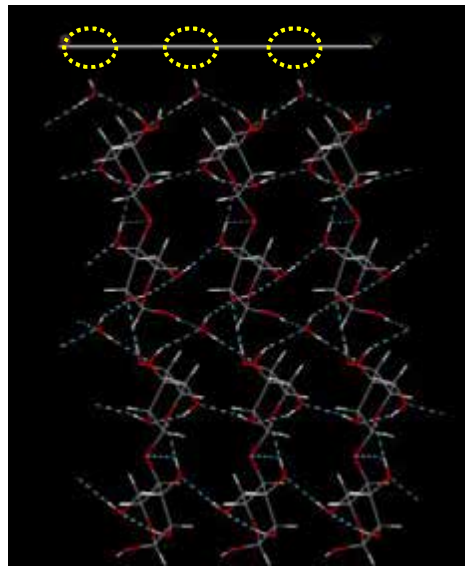


(0 1 1) surface of LMH



Dense net of H-bonds between Lac molecules below the crystal surface

(0 2 0) surface of LMH



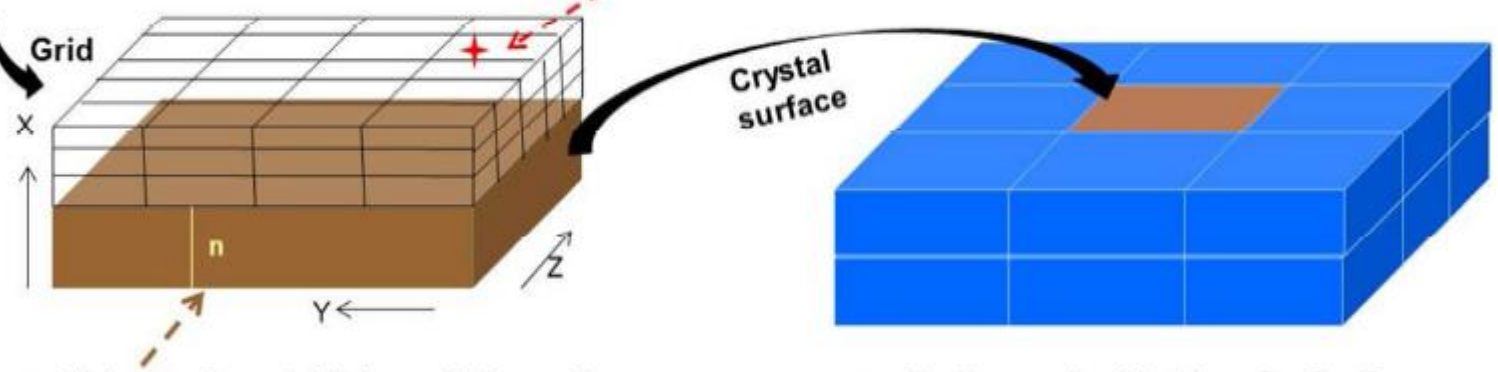
Water molecules close to the surface Lac molecules zig-zag perpendicular to the surface

Ramachandran et al. *Mol. Pharm*. (2015) 12:18-33
Dickhoff et al, Intl. J. Pharm. 327 (2006) 17-25

Employ systematic grid-based search for possible interaction energies of extrinsic synthon interactions at the interface

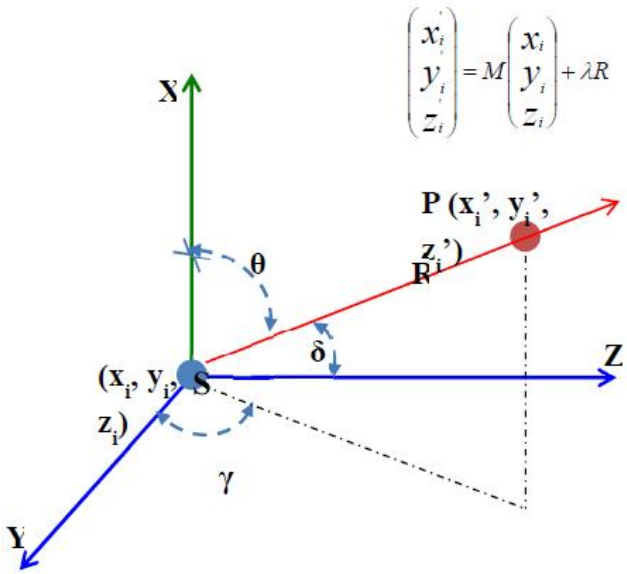
- 3 dimensional grid near surface under study
- Typical number of steps in X, Y and Z directions are: 8 x 8 x 8
- One probe molecule explores every grid point on a reticular area

- Probe molecule (shown as red star) visits every grid point
- It is oriented in three degrees of rotation (θ, γ, δ)
- For every set of X, Y, Z, θ, γ, δ, interaction energy of probe molecule is calculated

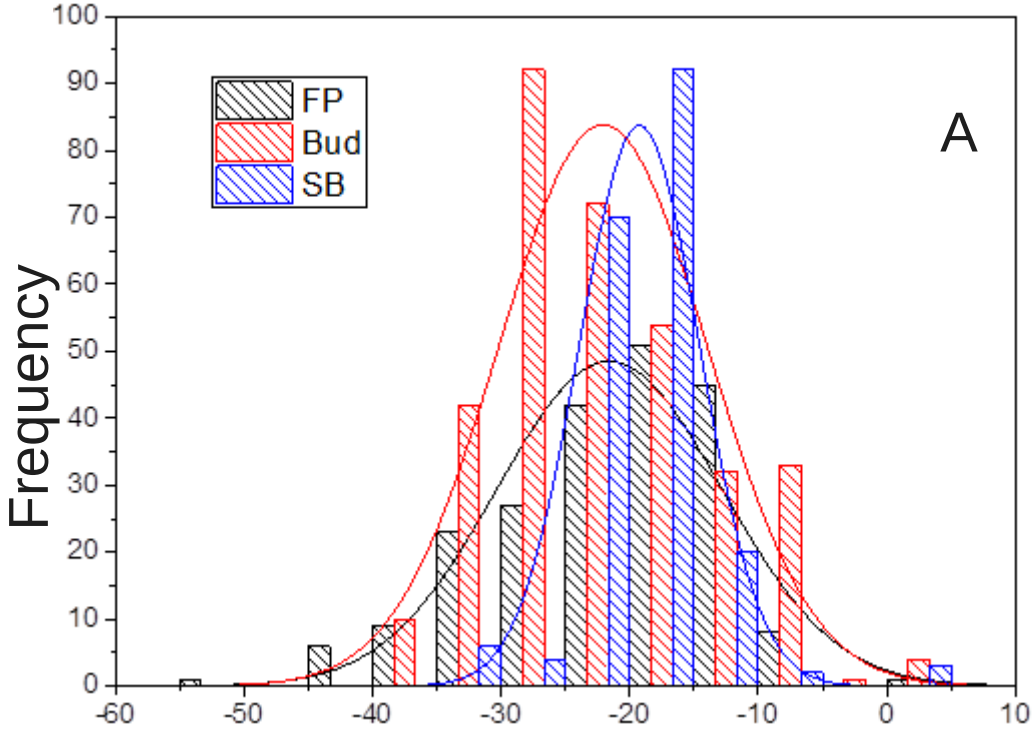


- Volume of crystal (shown in brown) considered for simulation is defined in input
- Slice thickness (n) is multiple of d_{hkl}

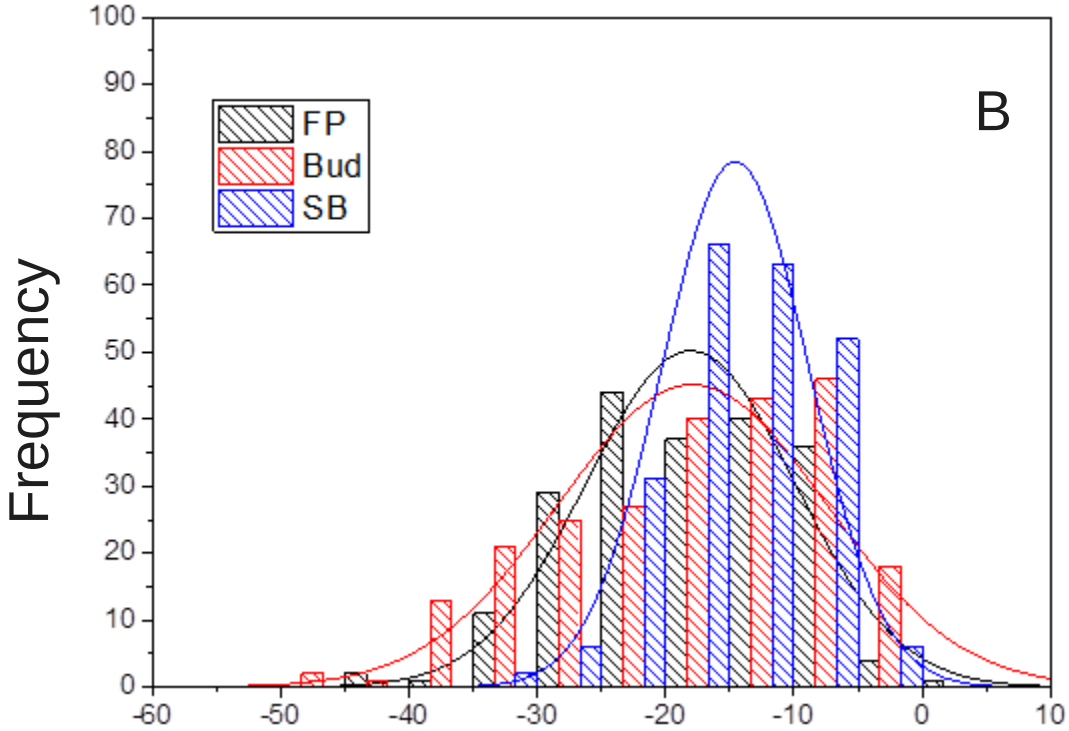
- Surface embedded in a 3 x 3 x 2 matrix to overcome edge effects on simulation



We can calculate the drug-drug cohesive forces at crystal surfaces



Intermolecular cohesive binding force ($kJmol^{-1}$) on smallest surfaces



Intermolecular cohesive binding force ($kJmol^{-1}$) on dominant surfaces

Data altered and adapted from Ramachandran et al. *Mol. Pharm*. (2015) 12:18-33

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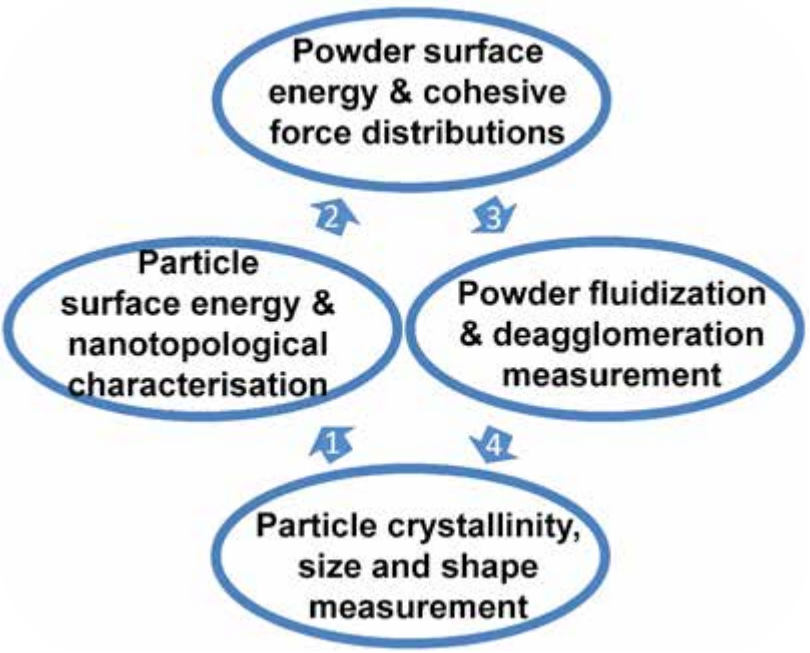
We can calculate the drug-drug cohesive forces at crystal surfaces

Do these calculations have any physical meaning or relevance?

Mechanistic understanding of inhaled powder performance

Hypothesis 2

Integrated assessment of particle and agglomerate bulk and surface properties is required to understand agglomeration behaviour.



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Experimental evidence of molecular models of particle cohesive forces

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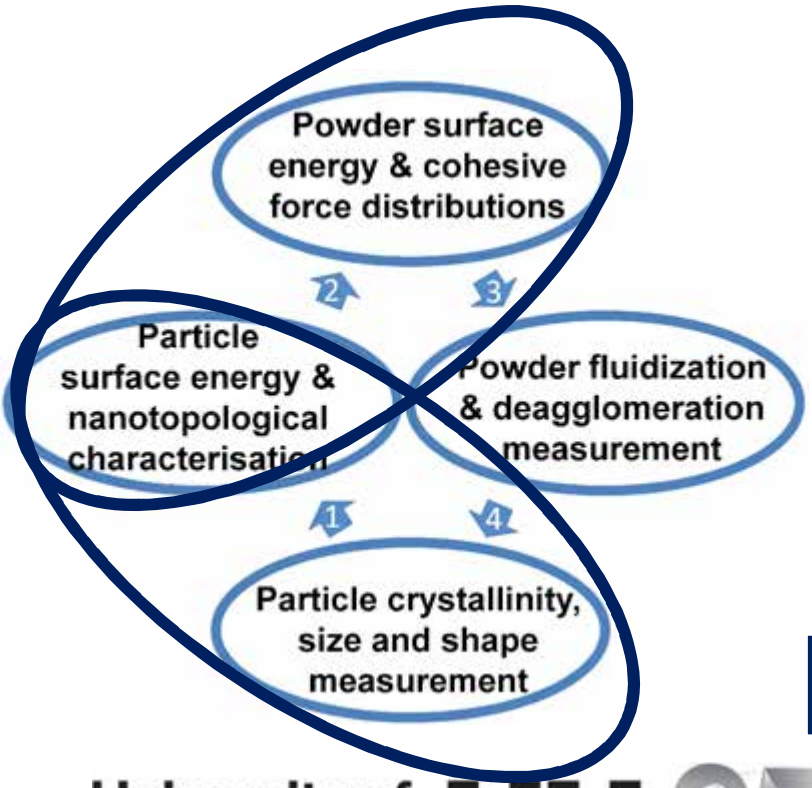

(1) Raw materials will be characterized for surface, bulk and micromeritic properties (e.g. energy, charge, crystallinity) to identify CMAs that indicate agglomerative potential.
(2) Powder deagglomeration by aerodynamic shear will study degree of powder cohesion

Validation of computational predictions

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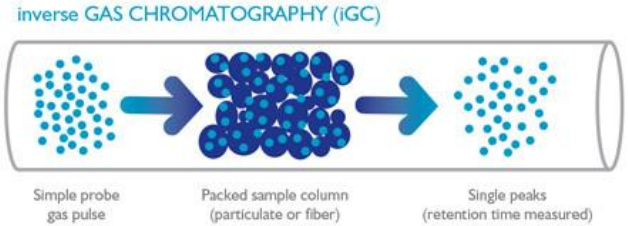
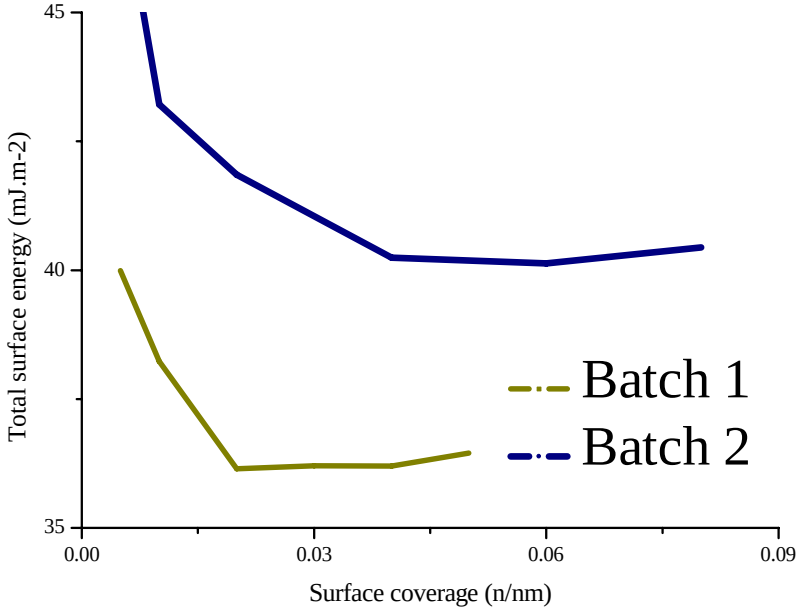
WS4 Validation of intra- & inter-agglomerate force prediction

W Ganley, D Murnane, R Price, ID Styliari

Critical primary pressure = CPP





Jaffari et al. Int. J. Pharm. 447 (2013) 124-131;
Jaffari et al. Pharm. Res. (2014) 31: 3251-3264
Images: Sympatec, SMS UK Ltd.

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WS4 Validation of interparticulate force prediction

Measuring intra-agglomerate cohesive forces

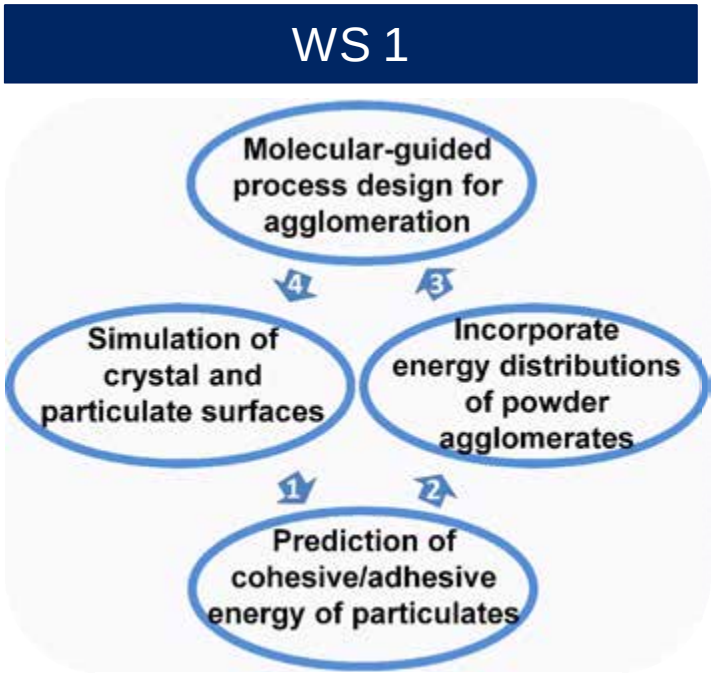
Sample	CPP (Bar)	Mean Cohesion ($kJmol^{-1}$)	Max Cohesion ($kJmol^{-1}$)
Salbutamol base	1.0	-32.5	-35.0
Budesonide	2.0	-41.7	-46.5
Fluticasone propionate	3.5	-48.2	-54.3

1. FP most cohesive API overall
2. SB least cohesive overall and Bud was intermediate
3. This rank order was similar to the computational predictions

Jaffari et al. Int. J. Pharm. 447 (2013) 124-131; Jaffari et al. Pharm. Res. (2014) 31: 3251-3264; Ramachandran, et al. *Mol. Pharm*. (2015) 12:18-33

WS1 Computational prediction of adhesion/cohesion
Challenges to be addressed

1. **Validate synthonic modelling of salts & hydrates**
2. **Computation of adhesion/cohesion in presence of capillary liquids**



WS1 Computational prediction of adhesion/cohesion
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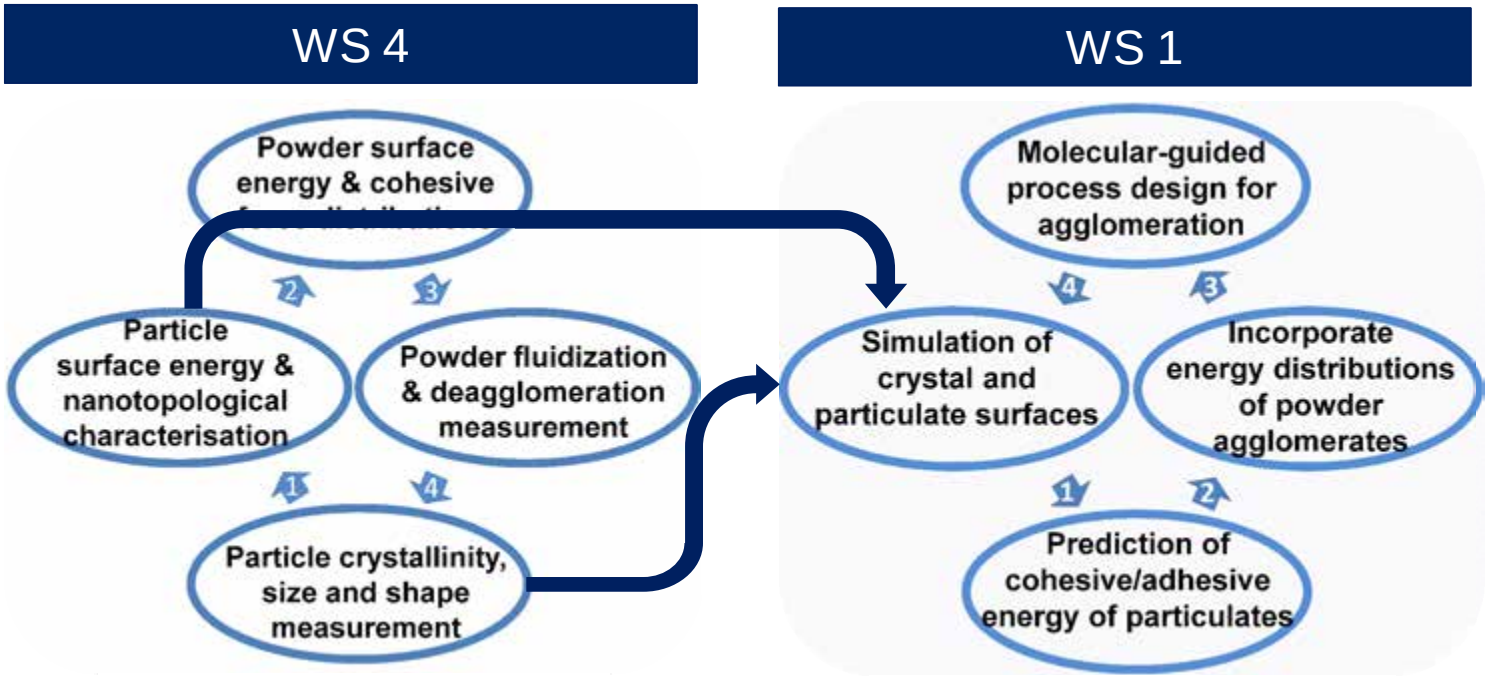
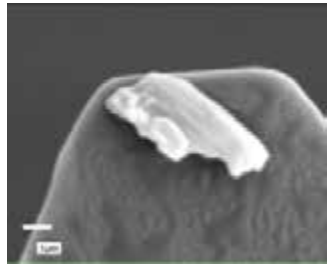
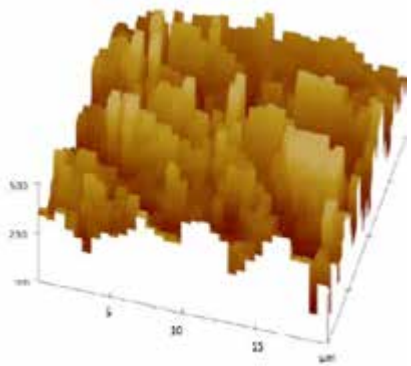
3. **Crystal models require realistic surface nanotopography (e.g. roughness)**

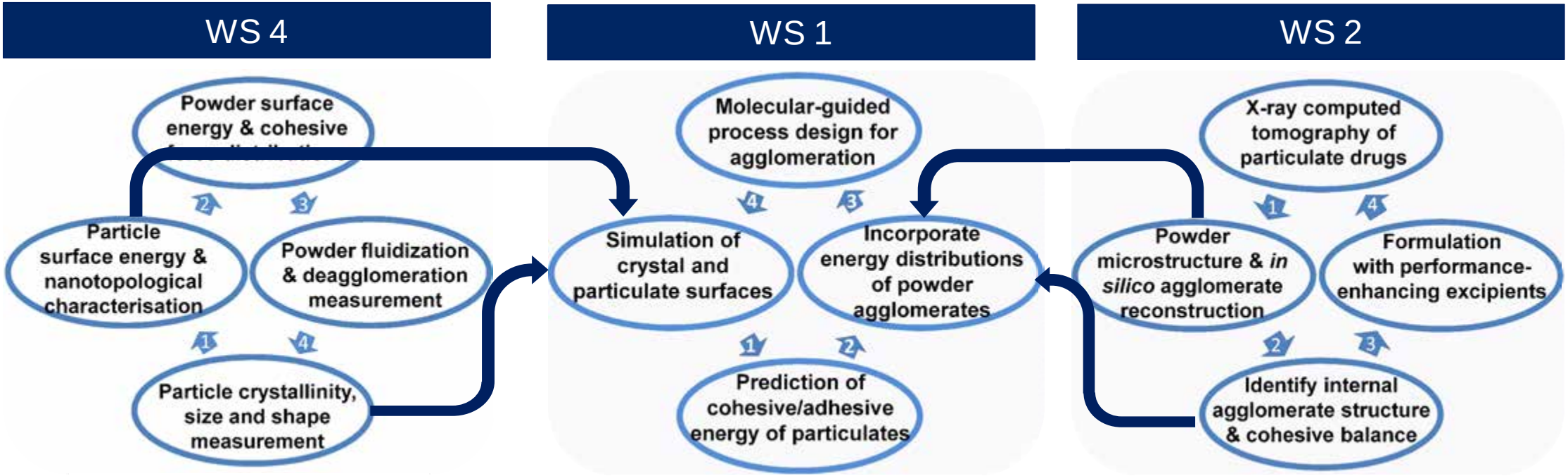






WS1 Computational prediction of adhesion/cohesion
Challenges to be addressed

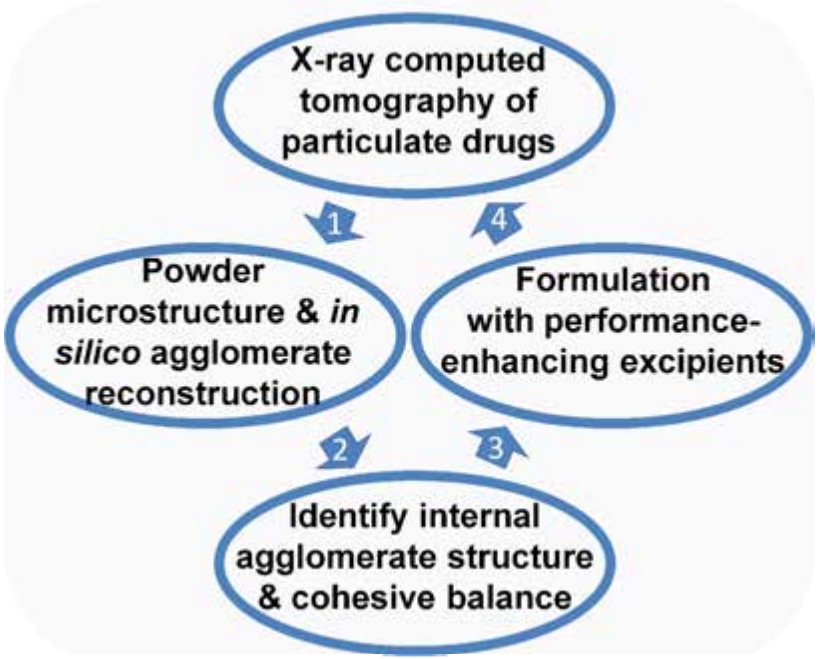
1. **Validate synthonic modelling of salts & hydrates**
2. **Computation of adhesion/cohesion in presence of capillary liquids**
3. **Crystal models require realistic surface nanotopography (e.g. roughness)**
4. **Computation of inter-particulate adhesive/cohesive forces within powders requires relative surface area contact of individual crystal faces**



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



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Enhanced Mechanistic Understanding of Inhaled Formulations

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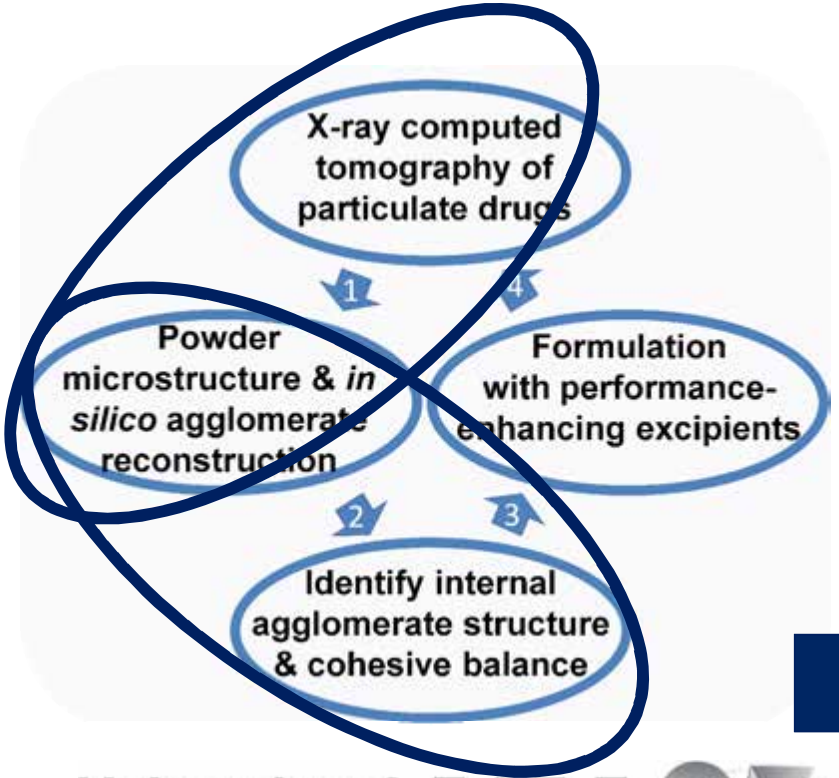

(1) Employ imaging techniques to generate nano-, micro- and meso-scale resolution of inhalation powder structure.
(2) X-ray microCT to generate powder structures with single-particle resolution
(3) Single particle microscopy to identify shape and topographical factors for WS1

Validation of computational predictions

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Health and Wellbeing

WS2 Nano-, micro- and meso-scale imaging of inhalation powders

T Burnett, P Gajjar, D Murnane, ID Styliari, P Withers

Correlative Tomography

Henry Moseley X-ray Imaging Facility, School of Materials, The University of Manchester, Manchester, UK

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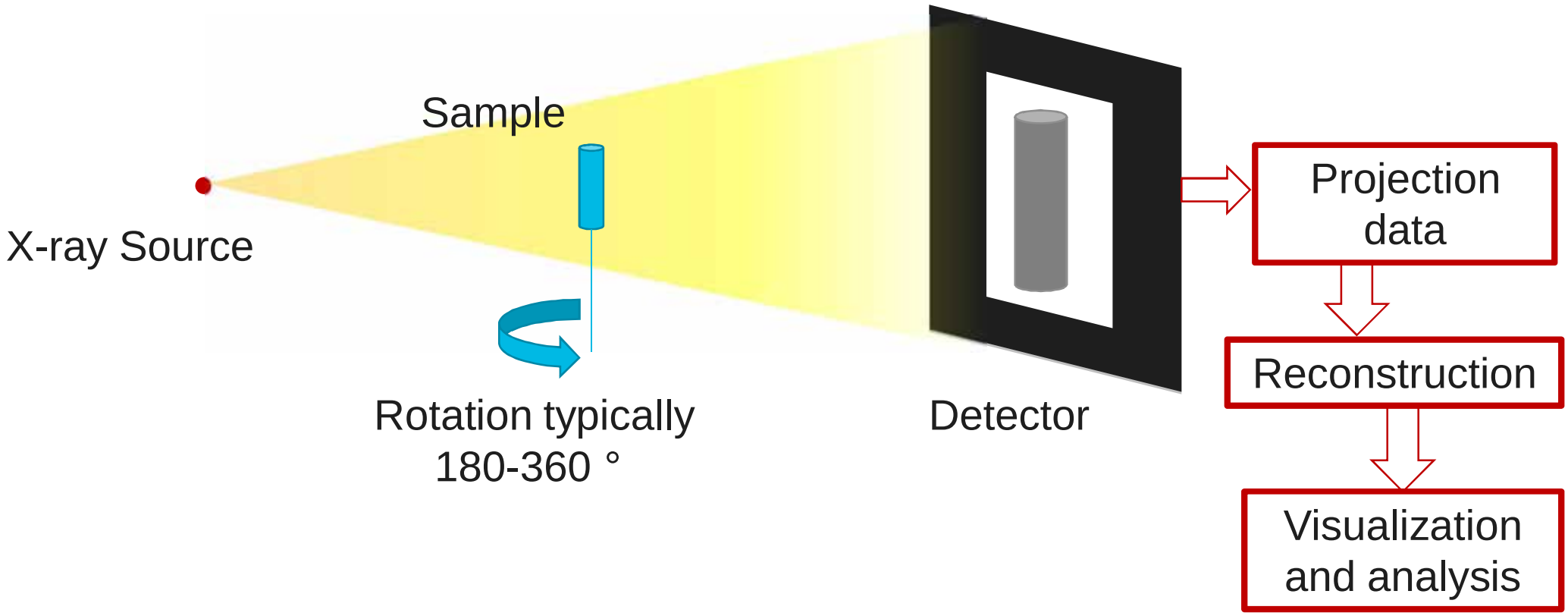
Health and Wellbeing

WS2 Nano-, micro- and meso-scale imaging of inhalation powders
Bulk powder assessment by x-ray microCT



Particles presented as bulk, rather than individual particles

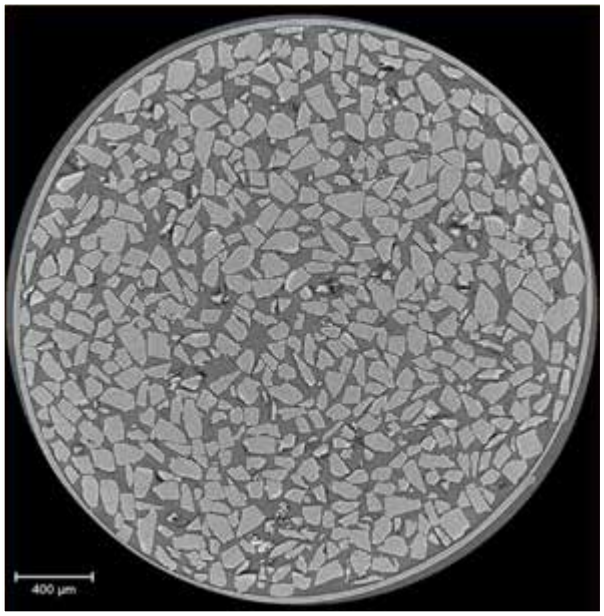
Provides enhanced assessment of the inter-particle contacts

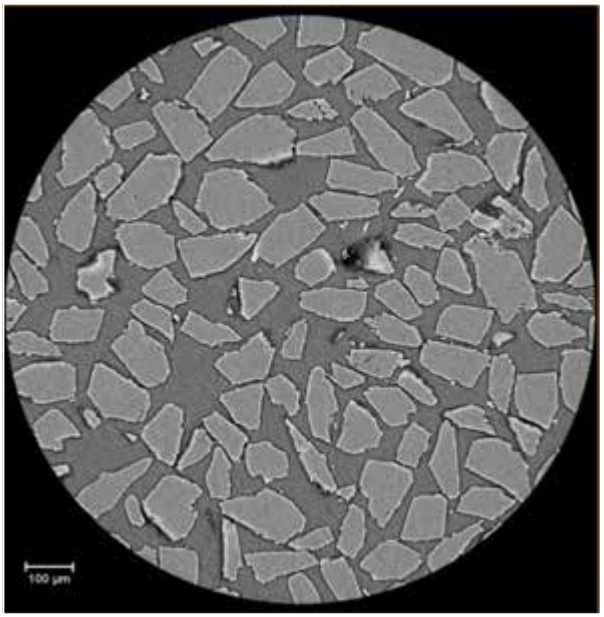
Zeiss Xradia Versa 520 with DCT

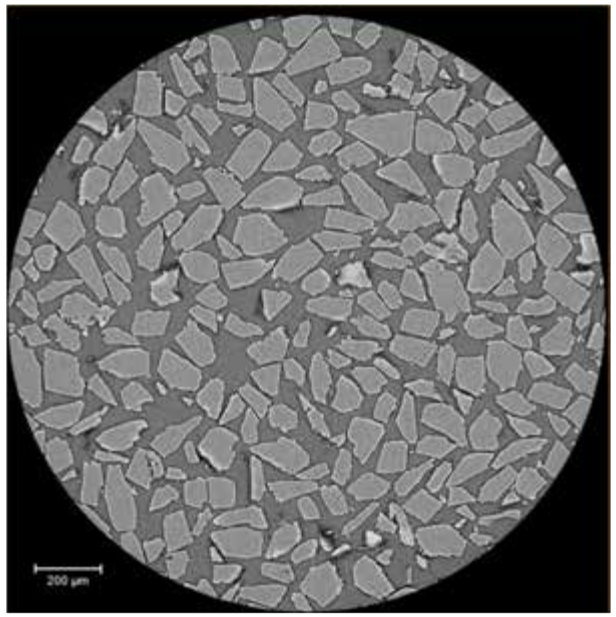
Samples mounted in Kapton tubes

Micro-CT provides rapid scanning approach in 3D

Image analysis in each slice identifying micromeritics properties



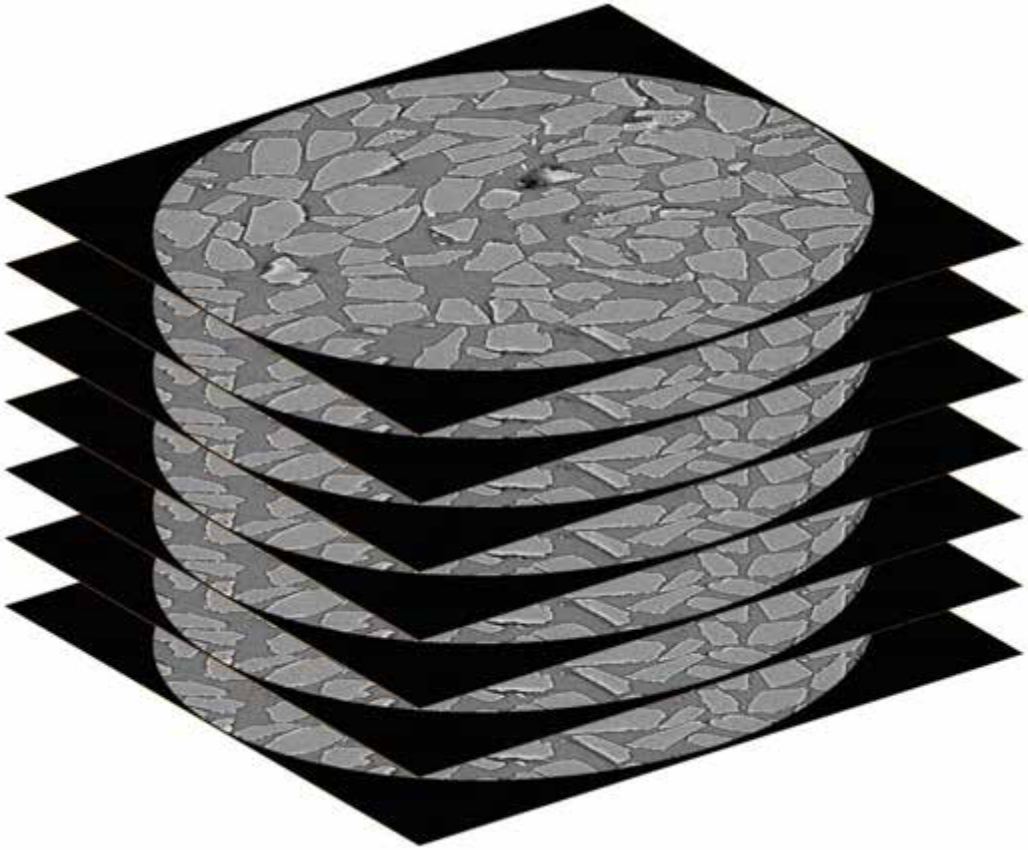


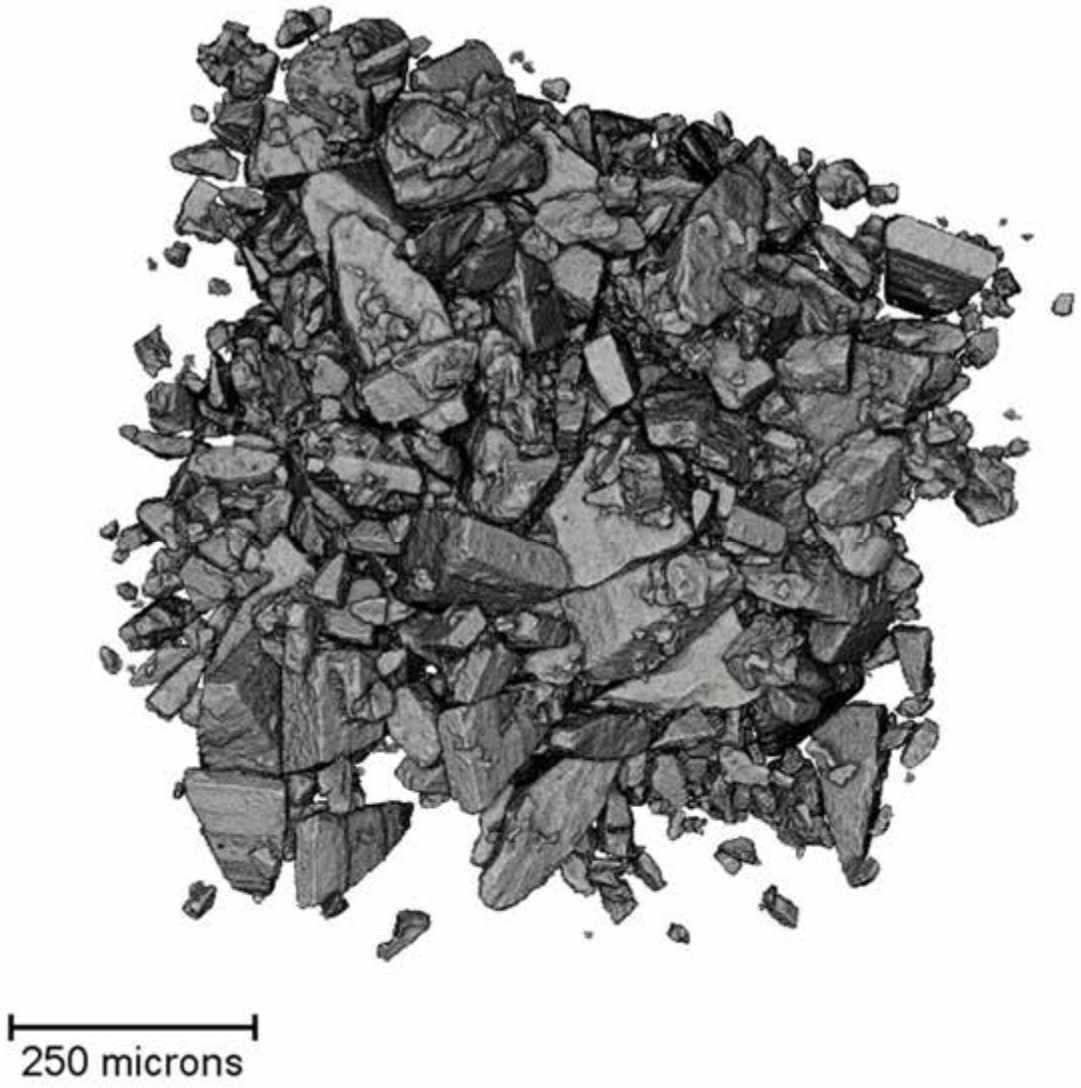


Voltage	80kV	80kV	80kV
Current	88uA	87uA	87uA
Source Distance	12mm	12mm	25mm
Detector Distance	14mm	14mm	12mm
Pixel Size	1.5593 um	0.6370 um	0.9322 um
Lens	4x	10x	10
Exposure time	1 sec	3.5 sec	10 sec
Projections	3201	3201	3201

Micro-CT provides rapid scanning approach in 3D
Slices are reconstructed providing microstructural information

3D volume created from stack of virtual slices





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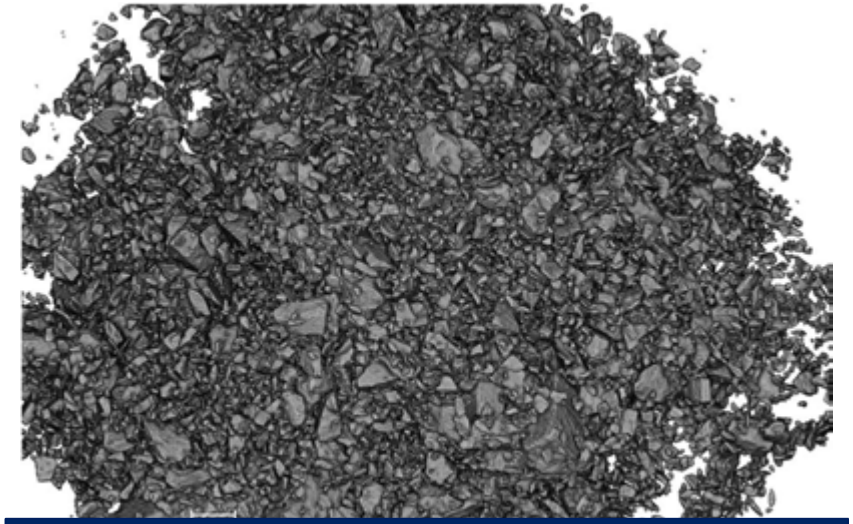
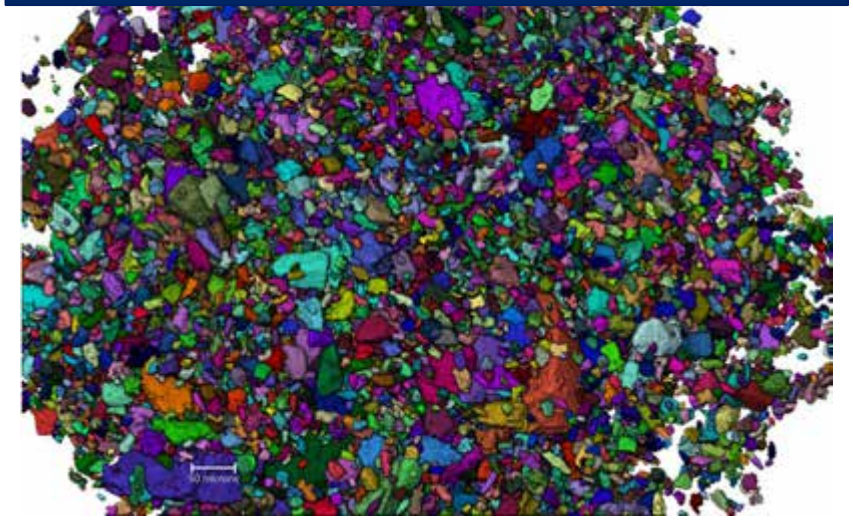
Health and Wellbeing

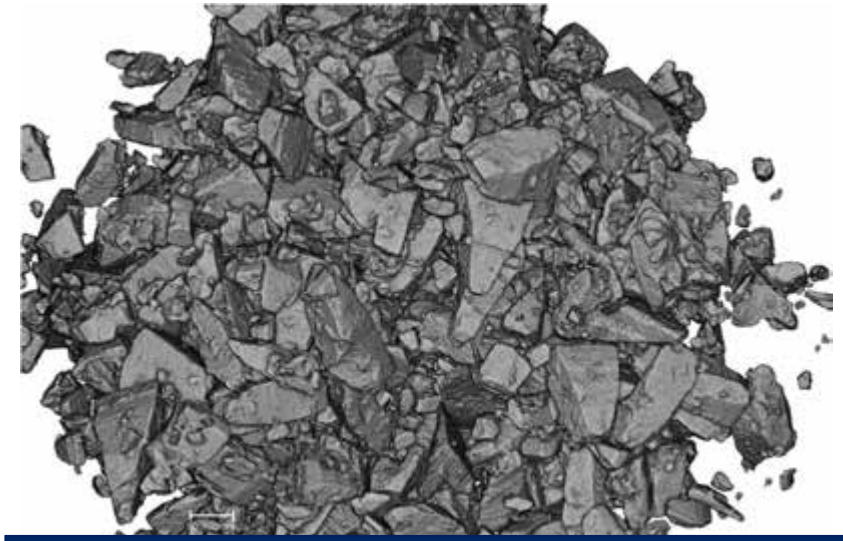
Enhanced mechanistic understanding of inhaled formulations

Information to be gained from microstructural powder studies

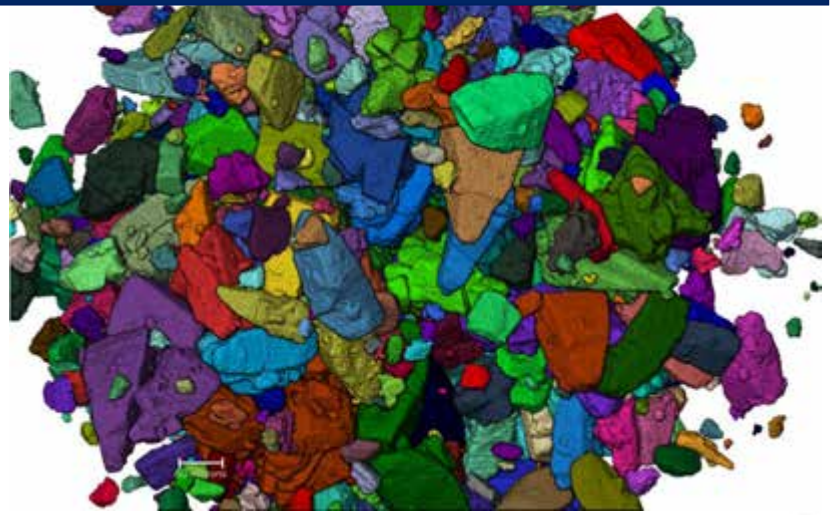


Milled lactose monohydrate





Sieved lactose monohydrate



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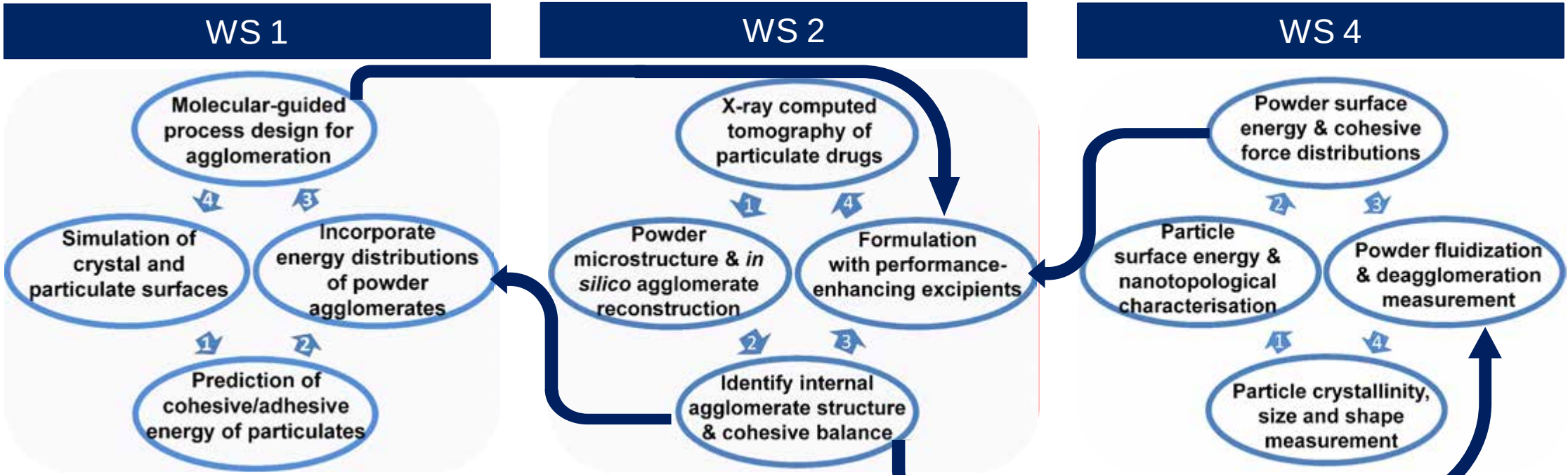
Health and Wellbeing

WS1,2,4 Rational design of formulations for inhalation particles

Computational and surface interaction approaches

Hypothesis 3

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



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Health and Wellbeing

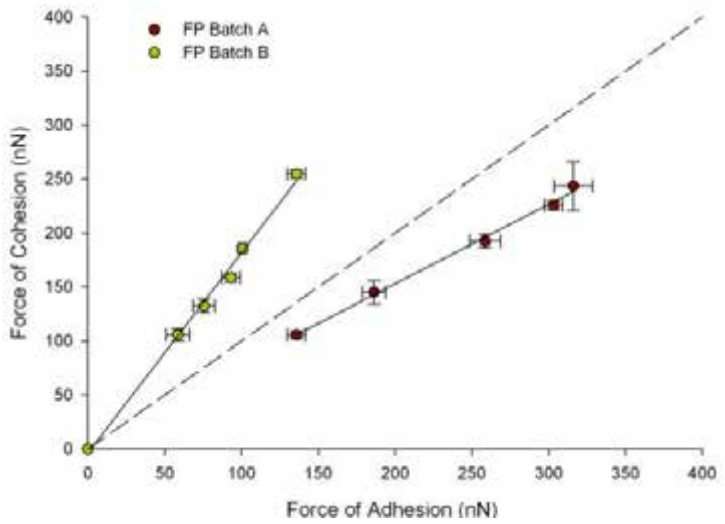
WS1,2,4 Rational design of formulations for inhalation particles
Computational and surface interaction approaches

What are the benefits of taking this approach?

WS1,2, 4 Validation of inter-particle and inter-agglomerate forces

Enhanced mechanistic understanding of inhaled formulations

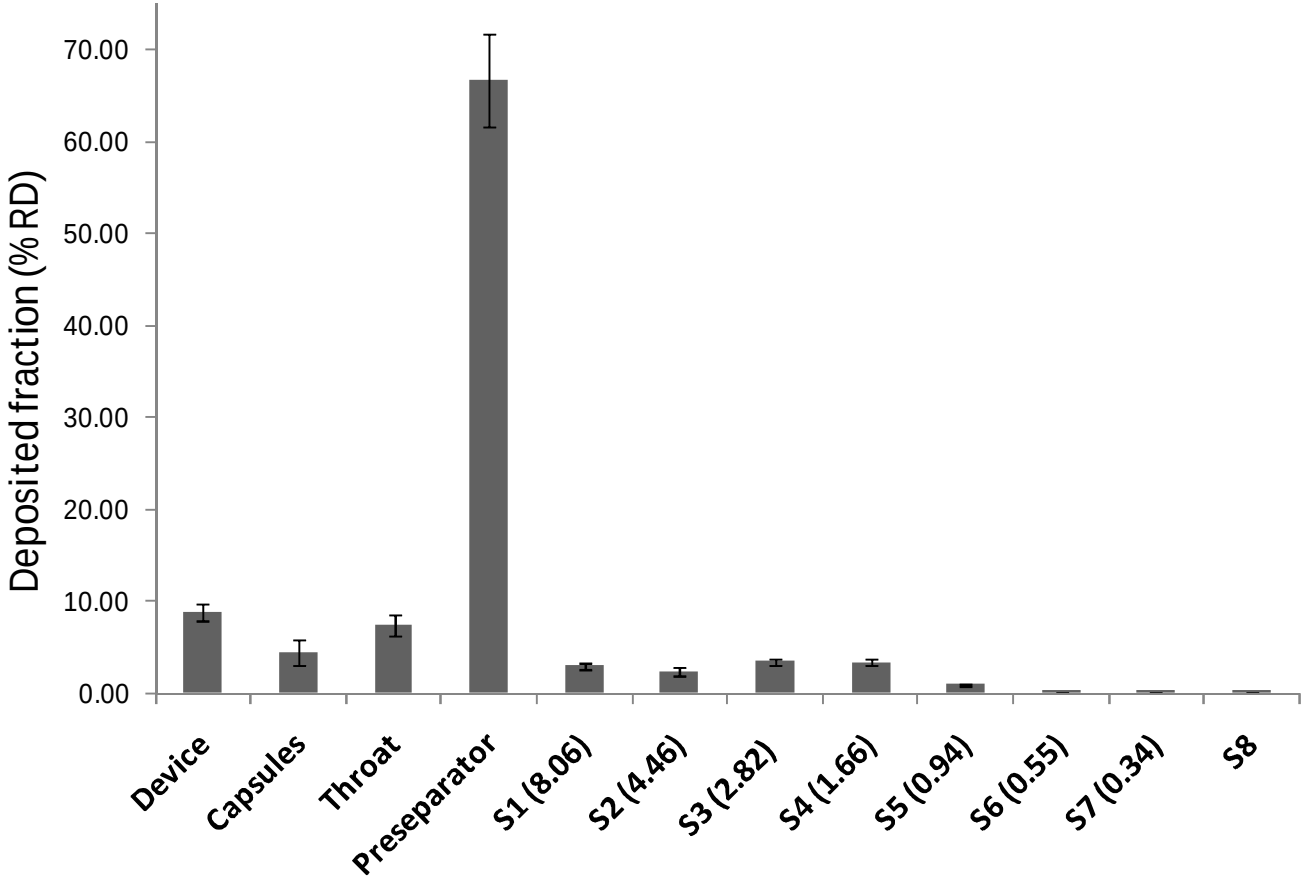
Sample	Max Interaction energy kJmol^{-1}	Mean Interaction energy kJmol^{-1}
FP2-FP2	-55.4	-48.2
LH200-FP2	-55.8	-48.9



1. Computational predictions of an adhesive balance for FP
2. This can be confirmed from surface energy (not shown) and single particle AFM measurements

Jaffari et al. Int. J. Pharm. 447 (2013) 124-131; Jaffari et al. Pharm. Res. (2014) 31: 3251-3264; Ramachandran, et al. *Mol. Pharm*. (2015) 12:18-33

Formulation performance testing



Content Uniformity: < 6% RSD
FPF: 7.95 ± 0.65
MMAD: 4.22 ± 0.07 µm

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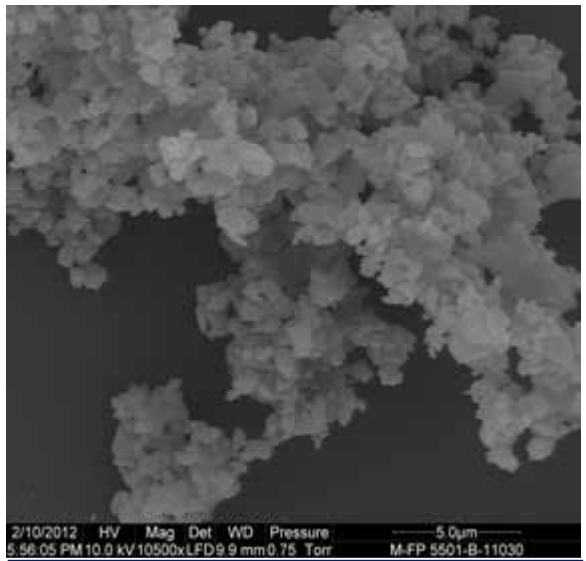
Enhanced mechanistic understanding of inhaled formulations

Information to be gained from microstructural powder studies

FP-LH200 blend



FP agglomerates

- Some FP particles adhere to lactose surface but much remained as agglomerates
- Microstructural imaging would reveal agglomeration behaviour to better inform understanding of cohesion before blending

WS1,2,4 Rational formulation design of inhaled products

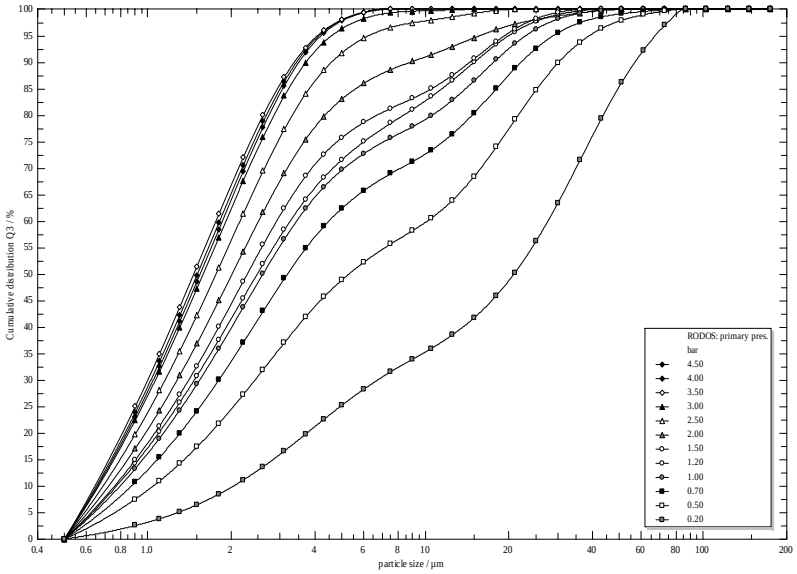
Challenges to be addressed

1. **Quantify the powder microstructure to measure density and understand particle-particle interaction geometry (e.g. which crystal face)**
2. **Serious challenges to couple nano- and microCT of 10^{-9}-10^{-3} m powders**
3. **Formulations are mixed particle systems, will need Raman chemical image to confirm agglomerate composition**

WS1,2,4 Rational formulation design of inhaled products

Challenges to be addressed

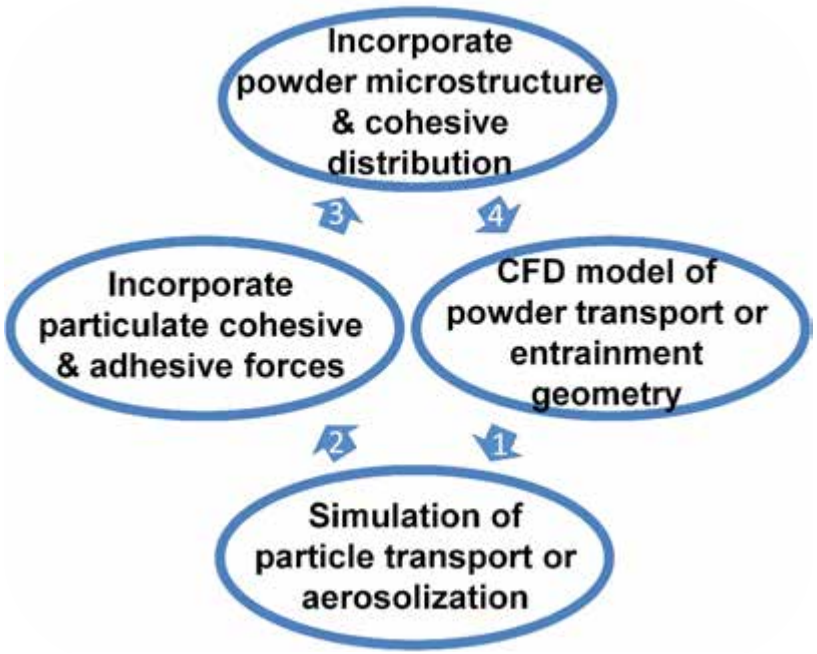
4. **Inter-particulate forces govern agglomerate strength, but we formulate powders, so we need to understand agglomerate-agglomerate contact**
5. **Computation of powder not particle-particle adhesive/cohesive forces**
6. **Development of deagglomeration rig and nano-indentation approaches to validate intra- and inter-agglomerate cohesion forces**



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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Computational pharmaceutical engineering approach

Hypothesis 4

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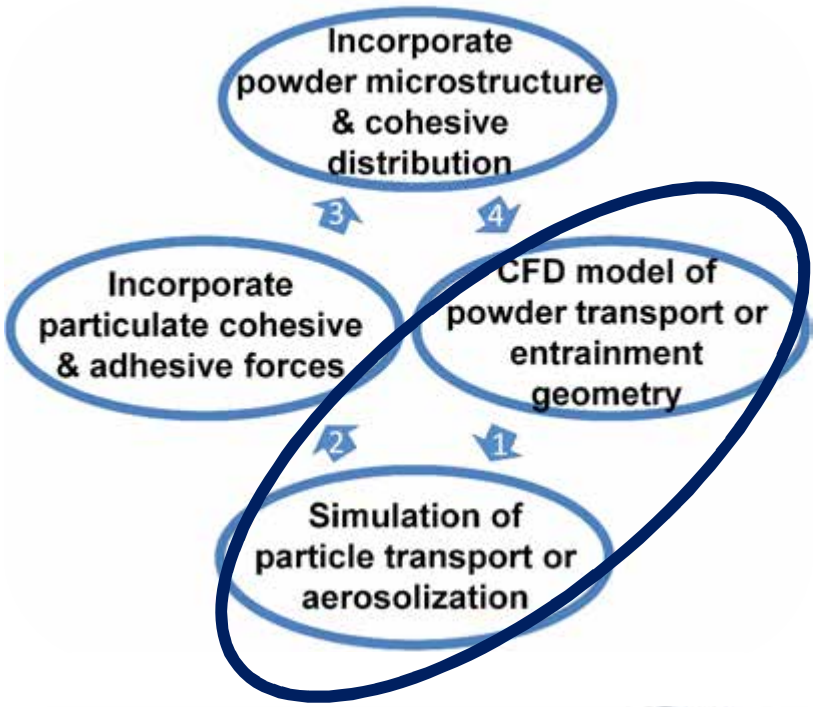

(1) Eulerian/Eulerian CFD with mass coupling between air, agglomerate and particle phases for efficient models of powder dispersal in inhalers.
(2) Eulerian/Lagrangian CFD for high fidelity models of aerodynamic shear and impact forces.
(3) Discrete element modelling (DEM) to assess agglomerate break-up during manufacturing.

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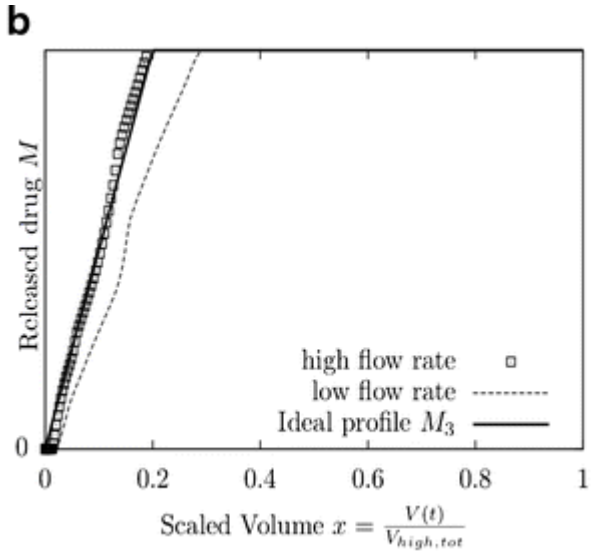
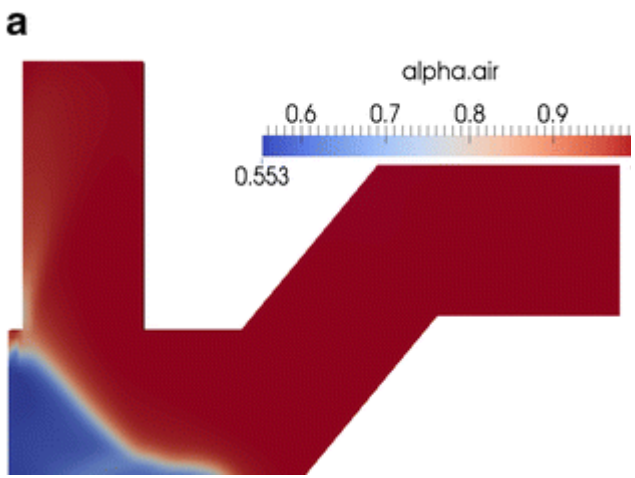
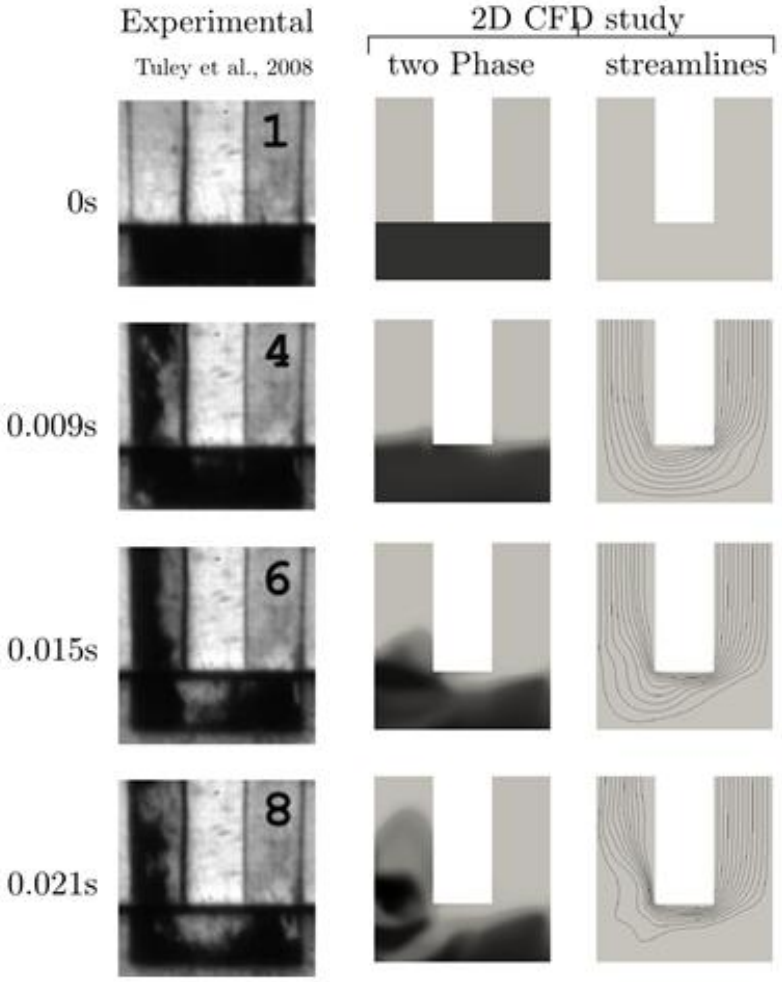
WS3 Engineering fluidization & de-agglomeration behaviour

James Elliott

Have developed an approach of scaling inhalation profiles and designed entrainment geometry that delivers drug to same lung depth in patients with different lung functions







Kopsch et al. (2016) Pharm Res 33 (11):2668–2679

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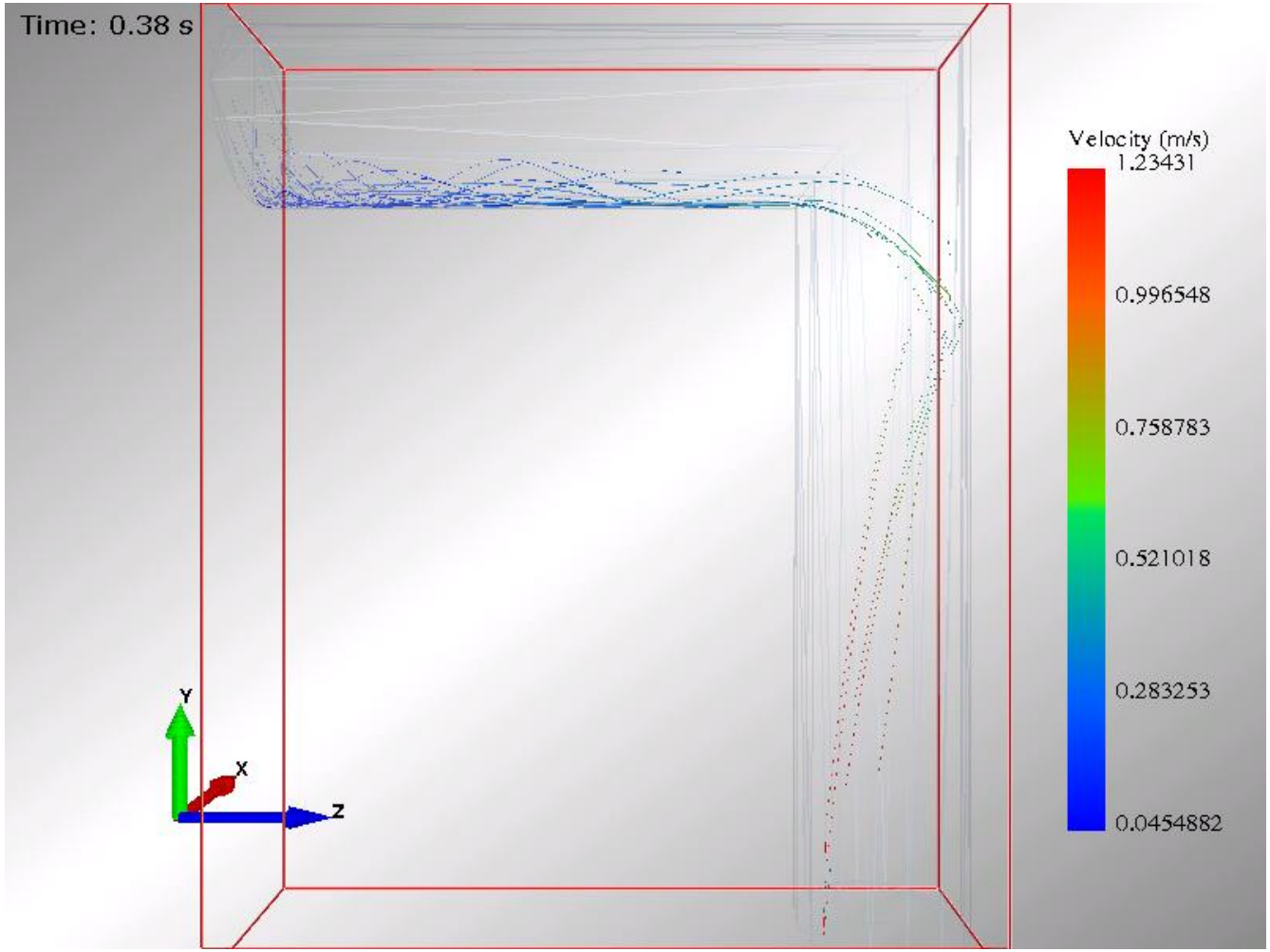
WS3 Engineering fluidization & de-agglomeration behaviour

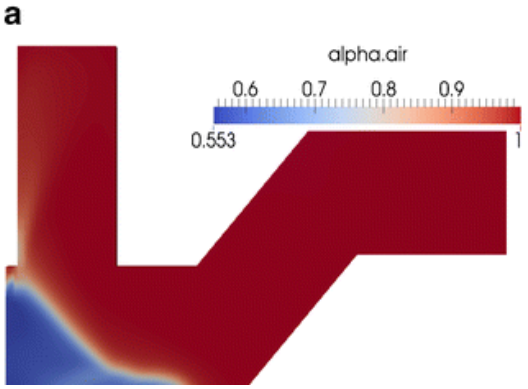
Tracking particle dispersion following fluidization

CFD/DEM simulation of particle flow in throat

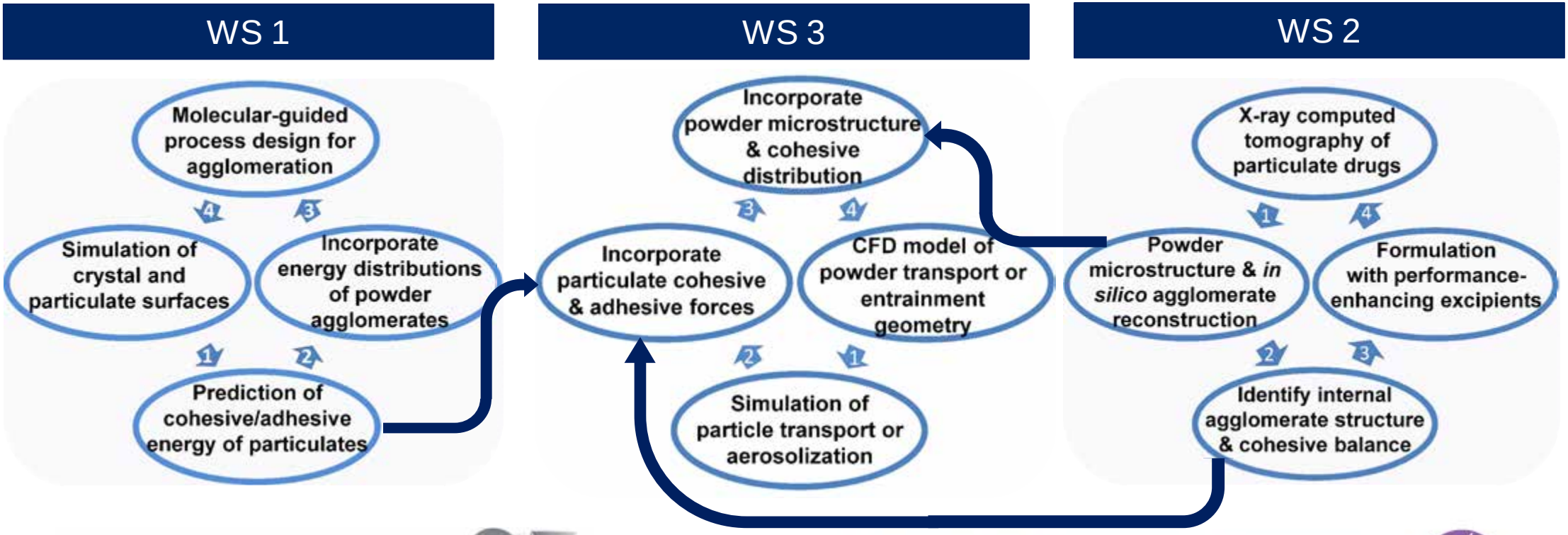


Computational pharmaceutical engineering approach

Challenges to be addressed



1. **Incorporation of powder microstructure**
2. **Incorporation of powder and agglomerate cohesion forces**
3. **Discrete element analysis of powder unit processes**



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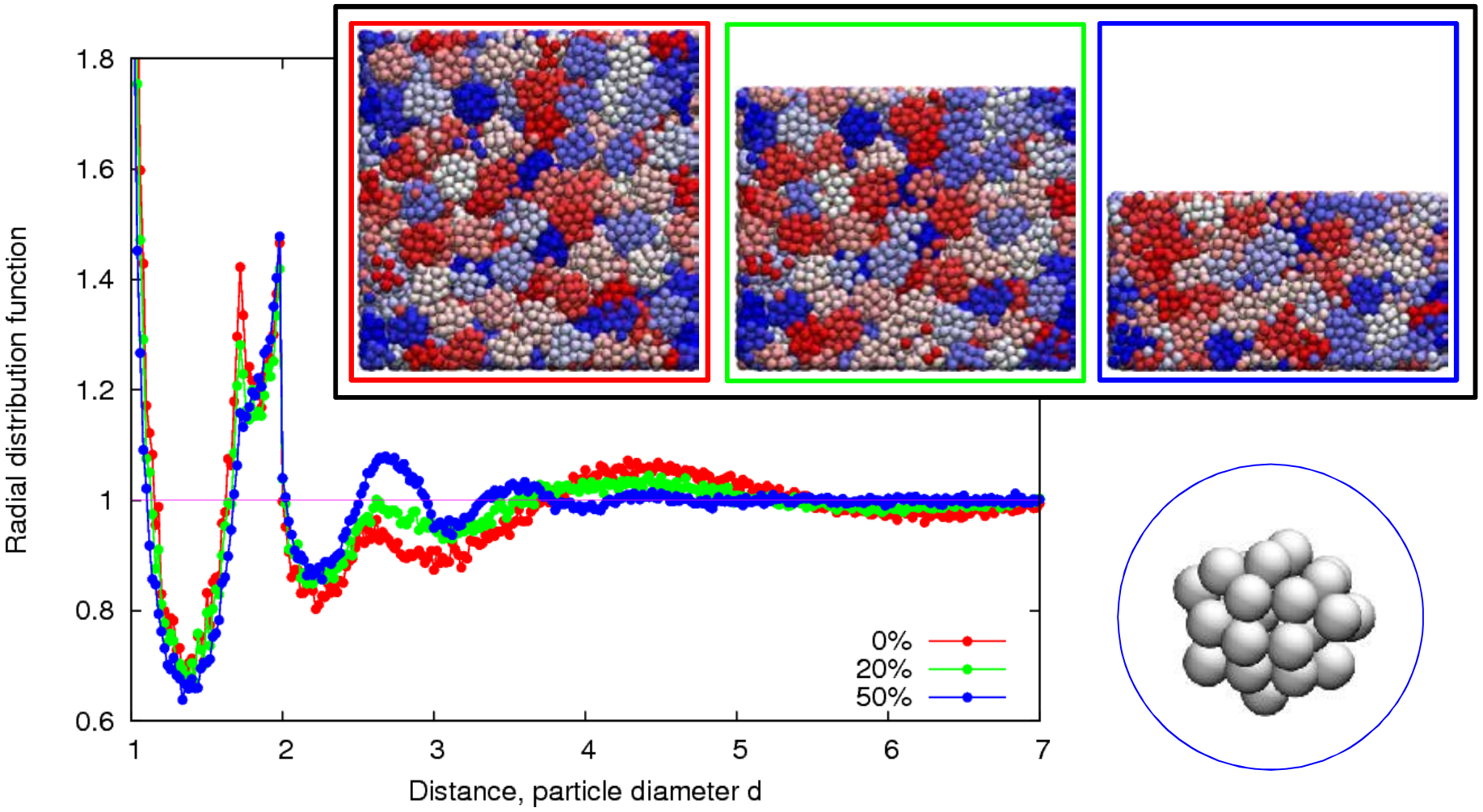
WS3 – Can we engineer the deagglomeration during mixing with compatible excipients?



Agglomerate structure during compaction

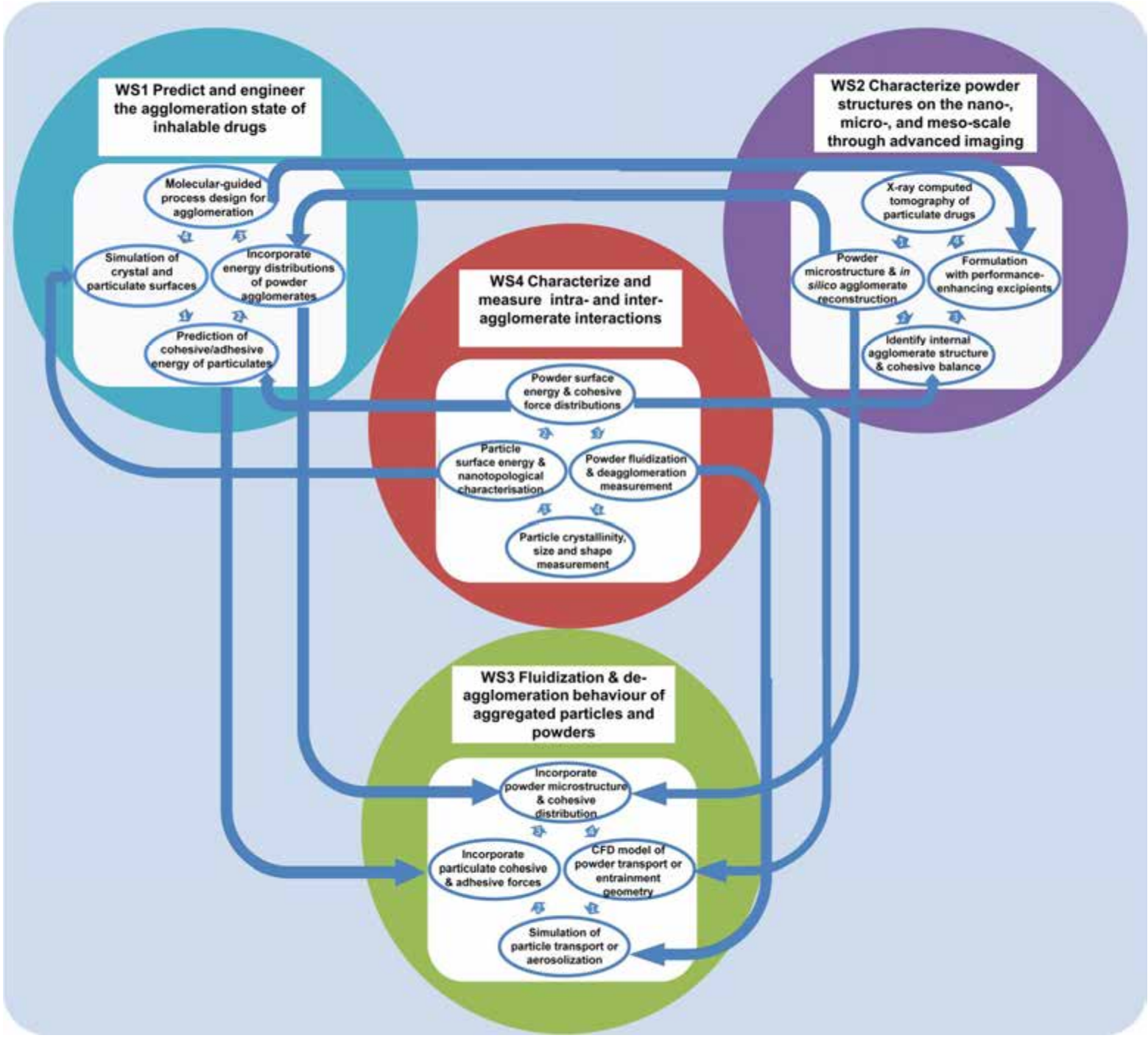
Computation pharmaceutics approach to inhaled formulation

WS5 Digitally-engineering manufacture of agglomerative products

Hypothesis 5

Computational pharmaceutics and digital design of formulations can be used to engineer function, manufacturability and performance into products

1. **Use synthonic model to direct a nano-into-microparticle manufacturing method**
2. **Employ agglomeration/deagglomeration engineering to differentiate aerosol performance**
3. **Inhalation/dissolution simulation assessment**


WS1 Predict and engineer the agglomeration state of inhalable drugs
Molecular-guided process design for agglomeration
Simulation of crystal and particulate surfaces
Incorporate energy distributions of powder agglomerates
Prediction of cohesive/adhesive energy of particulates
WS2 Characterize powder structures on the nano-, micro-, and meso-scale through advanced imaging
X-ray computed tomography of particulate drugs
Powder microstructure & in silico agglomerate reconstruction
Formulation with performance-enhancing excipients
Identify internal agglomerate structure & cohesive balance
WS4 Characterize and measure intra- and inter-agglomerate interactions
Powder surface energy & cohesive force distributions
Particle surface energy & nanotopological characterisation
Powder fluidization & deagglomeration measurement
Particle crystallinity, size and shape measurement
WS3 Fluidization & de-agglomeration behaviour of aggregated particles and powders
Incorporate powder microstructure & cohesive distribution
Incorporate particulate cohesive & adhesive forces
CFD model of powder transport or entrainment geometry
Simulation of particle transport or aerosolization

Expanded collaborative opportunities associated with the programme:

Hertfordshire Science Partnership

Single Local Growth Fund £2.5M
ERDF £2.5M

20 4-year Knowledge Exchange Industrial PhD Partnerships

Universities of Leeds & Cambridge

ADDOPT
ADVANCED DIGITAL DESIGN OF PHARMACEUTICAL THERAPEUTICS

Department for Business Innovation & Skills

Part-funded under the Advanced Manufacturing Supply Chain Initiative

University of Leeds CP^3

EPSRC Doctoral Training Centre in Complex Particulate Products & Processes

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Thank you for attention!

All investigators would like to acknowledge our funding:
Industrial sponsors and partners
EPSRC for funding the award EP/N025075/1

Other associated funding:
At Leeds: EP/L015285/1
At Manchester: EP/M010619/1
At Hertfordshire: Hertfordshire Local Enterprise Partnership/Dept for BEIS/Dept for CLG

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