ADVANCED DIGITAL DESIGN OF PHARMACEUTICAL THERAPEUTICS

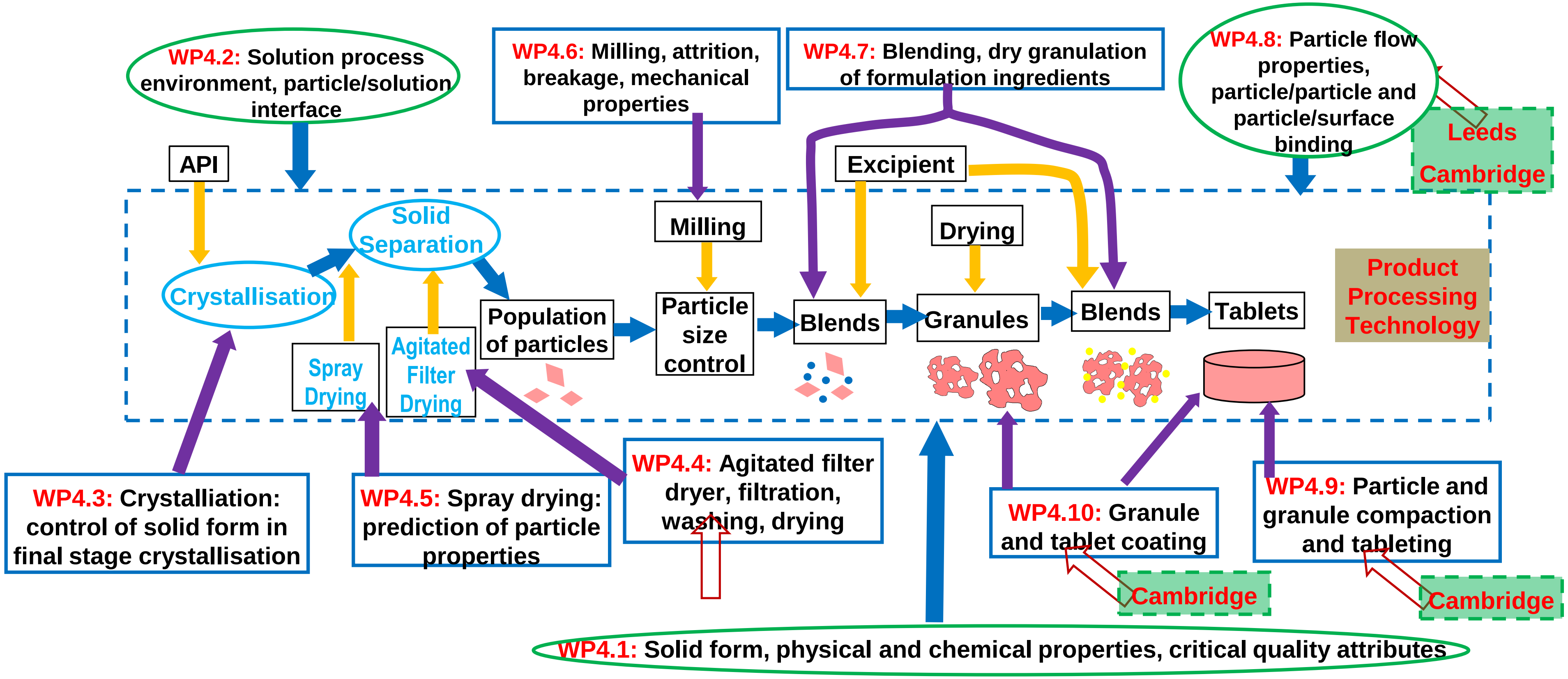
A Digital Design Approach to Prediction of Powder Flowability

James Elliott, Xizhong Chen (陈锡忠) and Chunlei Pei (裴春雷)

Macromolecular Materials Laboratory

University of Cambridge

ADDoPT Work Package 4



[see talk by Kevin Roberts (Leeds) for further details]

Overview of Work Flow in WP4.8a @ Cambridge

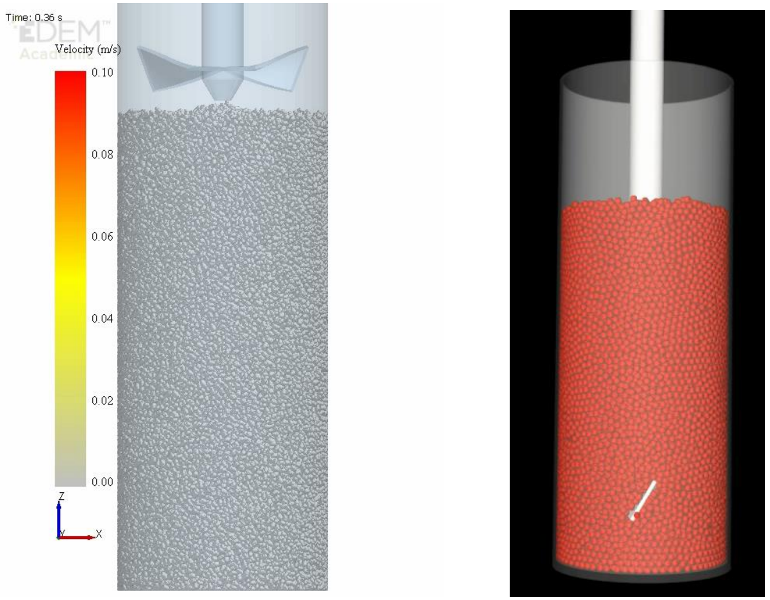
Particle properties
- Size and shape
- Elasticity/plasticity
- Cohesion/adhesion

Flowability test
- Angle of repose
- Ring shear cell
- FT 4

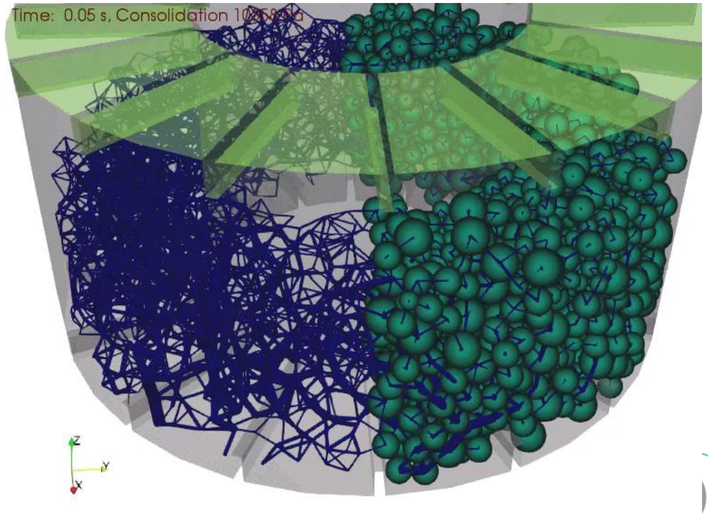
Design of Experiments (DoE)

Discrete Element Modelling (DEM) of particles with cohesion models

Predictive model and tools



[Umair Zafar (WP.8a Leeds)]

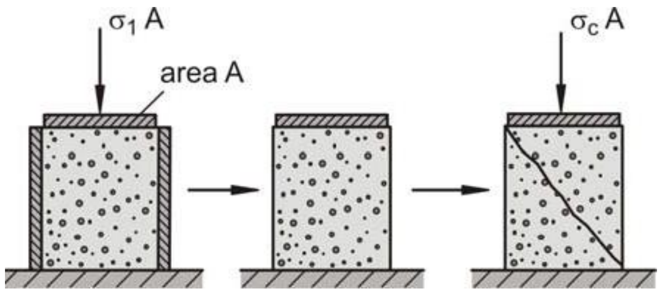


[Xizhong Chen (WP 4.8b Cambridge]

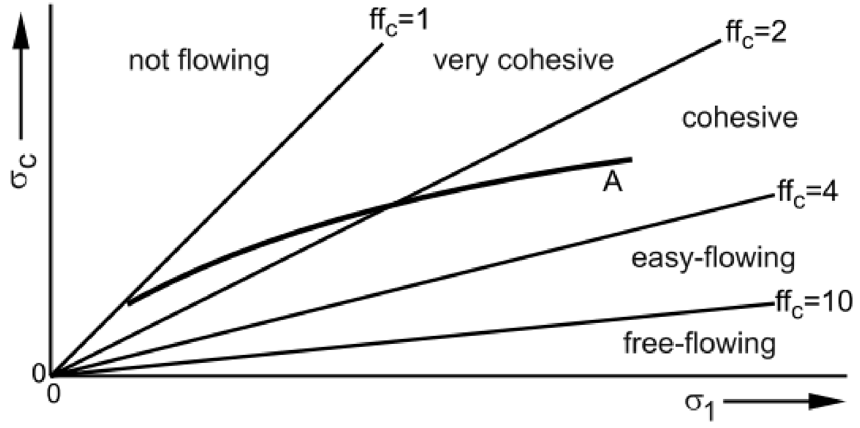
Powder Flow and Ring Shear Test

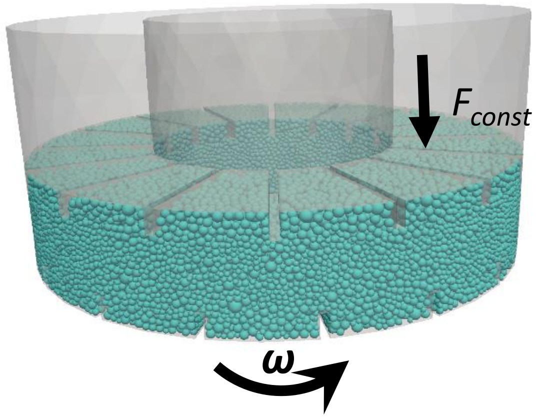
- Powder flowability can be characterised by a uniaxial compression test:

$$ff_c = \frac{\sigma_1}{\sigma_c}$$



- The ring shear test is commonly used to estimate the consolidation stress (σ_1) and unconfined yield stress (σ_c)





Schulze, Powder and Bulk Solid, 2008

Schulze Ring Shear Test

RST-XS Mr (standard)

Volume: ~ 30 ml

Cross-sectional (annular) area: 24.23 cm^2

Outer radius: 32 mm; inner radius: 16 mm

16 bars (3 mm in height) at top and bottom*

Rotational velocity

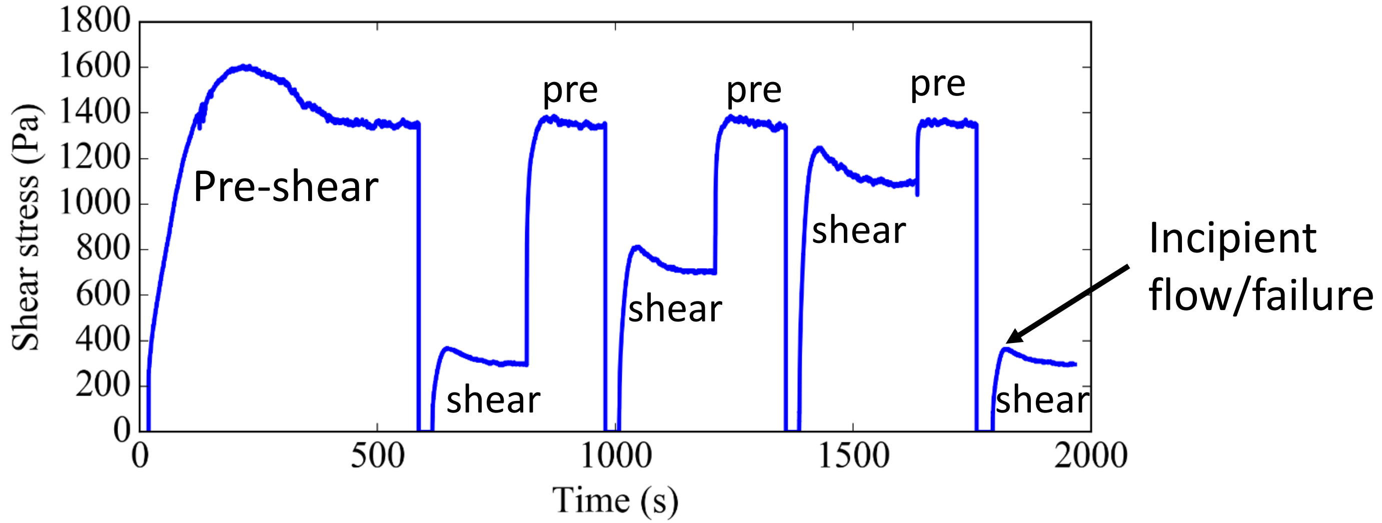
- 7.5 mm/min; 0.05 rpm (half of the max.) – 0.5 rpm (modelling)

Shear Stress Curves

Pre-stress: 2000 Pa; Normal stress: 400, 1000, 1600, 400 Pa

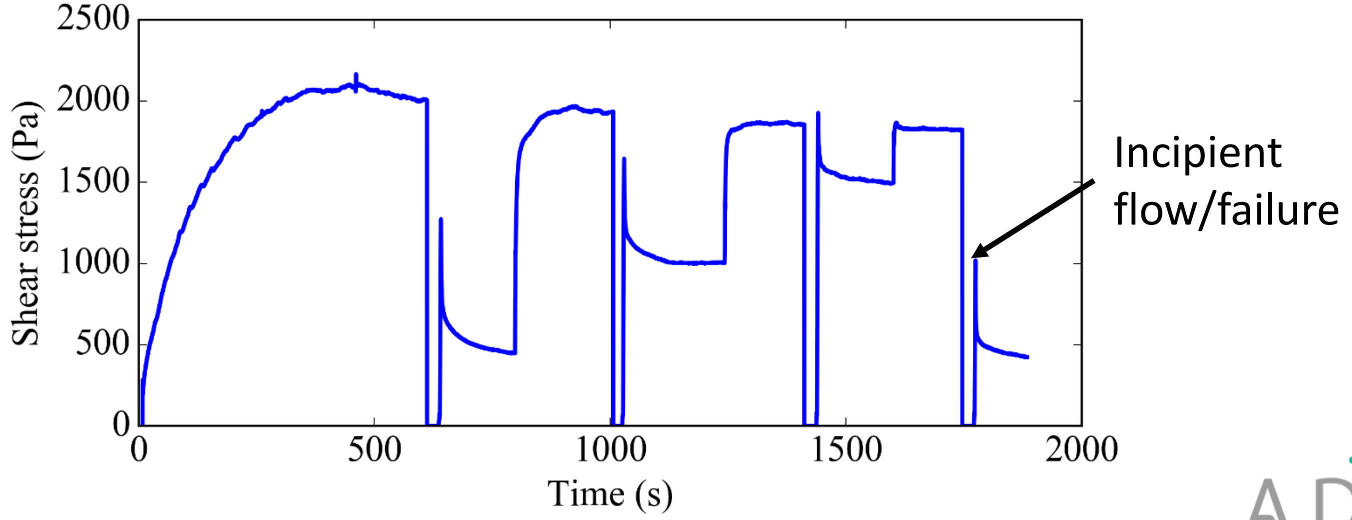
Tablettose 100
D_{50}: 150 µm
FFC: ~ 18

>10: free flow

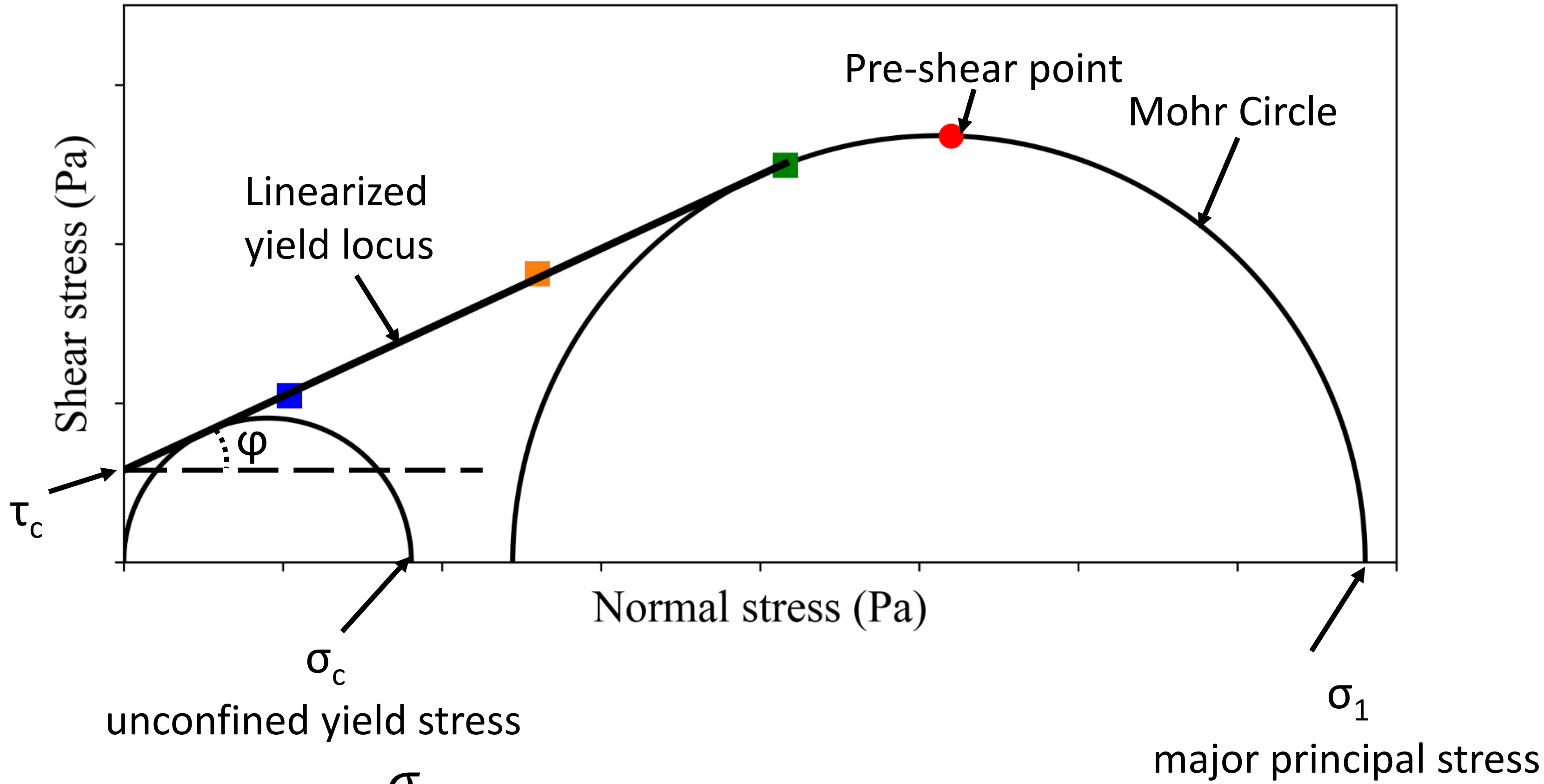


InHaLac 400
D_{50}: 7.7 µm
FFC: ~ 1.0-1.5

<2: very cohesive



Yield Curve



$$\mathrm{ff_c} = \frac{\sigma_1}{\sigma_c}$$ Flow function coefficient

τ_c Bulk cohesion

φ Angle of internal friction at yield locus

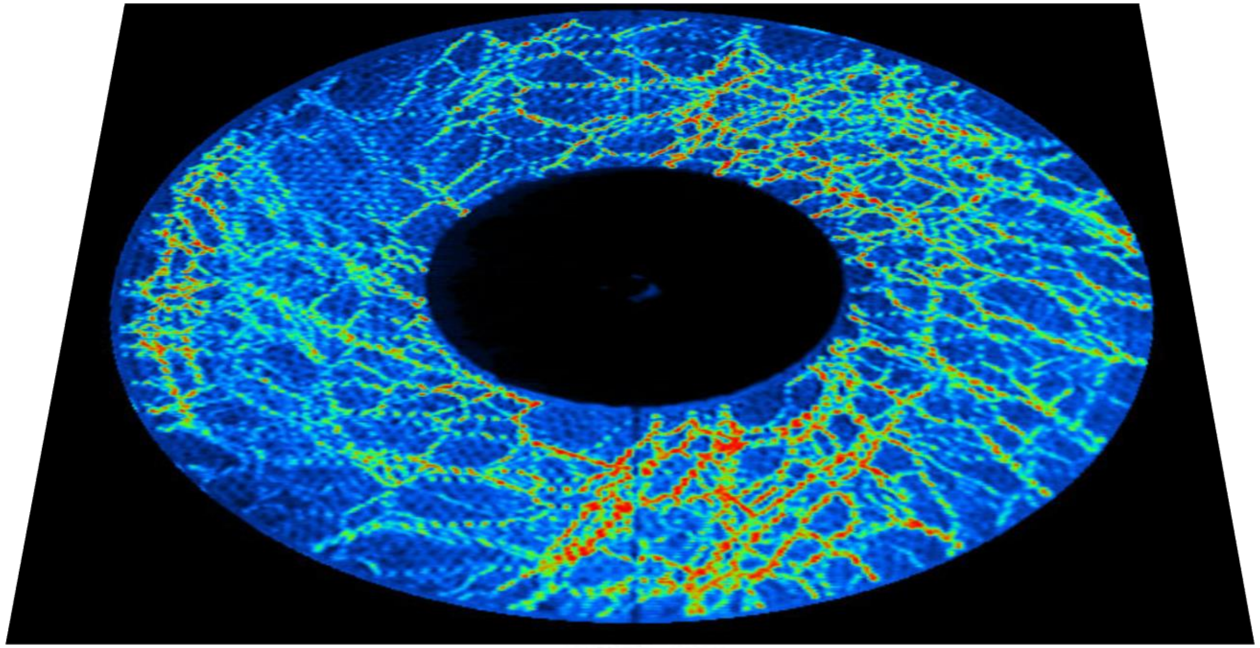
Ring Shear Test for Pharmaceutical Powders

ffc measured under pre-consolidation normal stresses: 2, 5, 10 kPa respectively

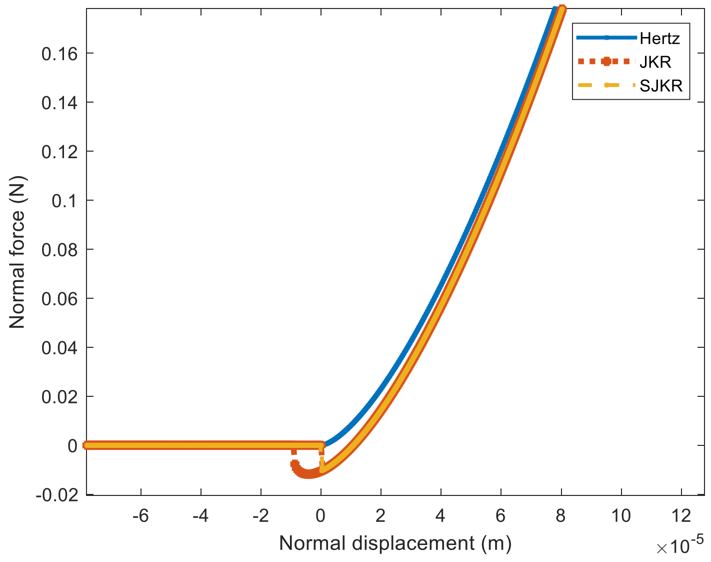
	FFC	Size （D_{50} µm）	
Tablettose 70	20, 29, 36	200	Lactose monohydrate
Tablettose 100	18, 19, 19	150	Lactose monohydrate
DuraLacH	4.9, 7.0, 8.6	150	Lactose Anhydrous
InHalac400	1.07, 1.18, 1.5	7.7	Lactose monohydrate
PH 102	5.9, 7.1, 7.4	100	MCC, Moisture 3.0-5.0%
PH 102 SCG	7.3, 7.7, 8.8	150	MCC, Moisture 3.0-5.0%
PH 101	4.6, 5.1, 5.4	50	MCC, Moisture 3.0-5.0%
PH 105	2.0, 2.3, 2.5	20	MCC, Moisture ~5.0%
PH DG	6.6, 7.8, 7.4	42	MCC & Calcium phosphate

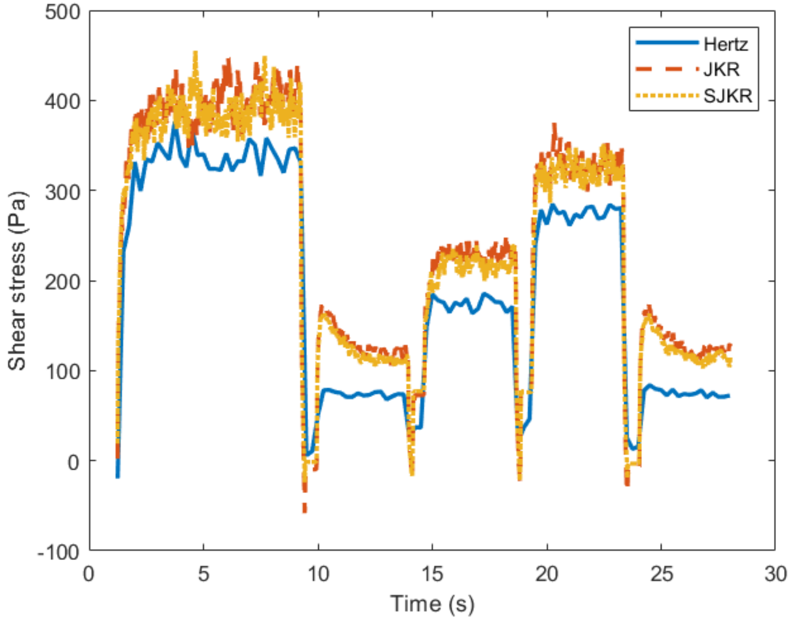
Cohesion Model in DEM

- JKR model
  - Surface energy (J/m^2)
  - Pull-off force
  - Loading history (incremental)
  - Work of adhesion



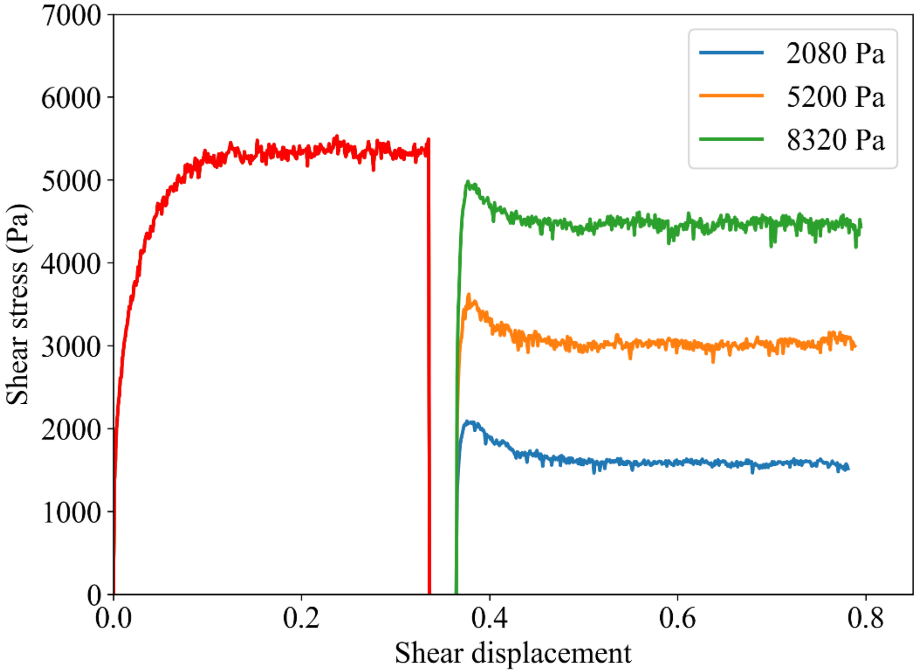
Particles are coloured by normal forces (Grayscale)
Contacts are coloured by normal forces (RGB)

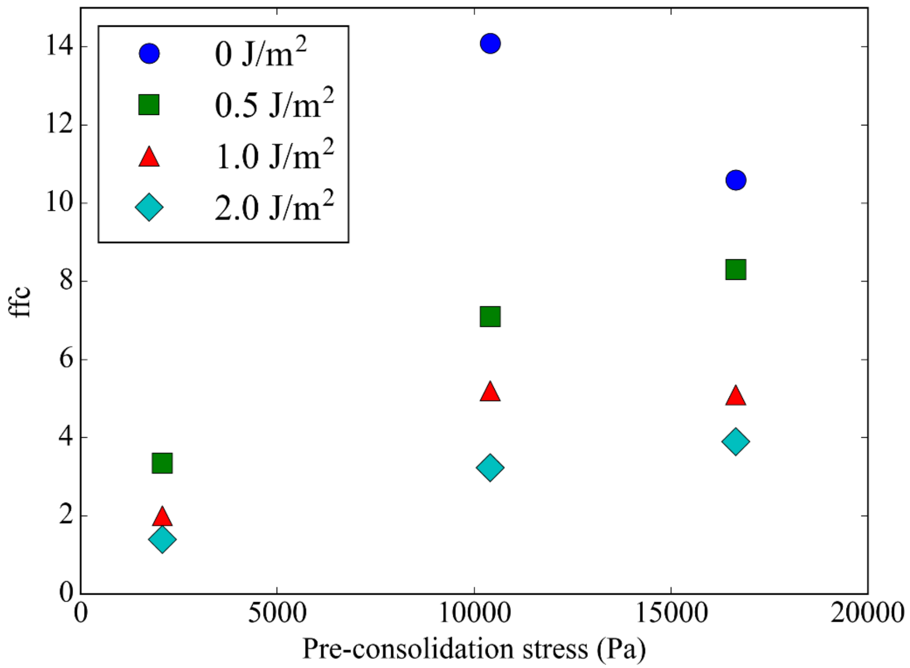




Flow Factor from DEM

Normal stress at pre-shear: 10 kPa
Surface energy : 2 J/m^2

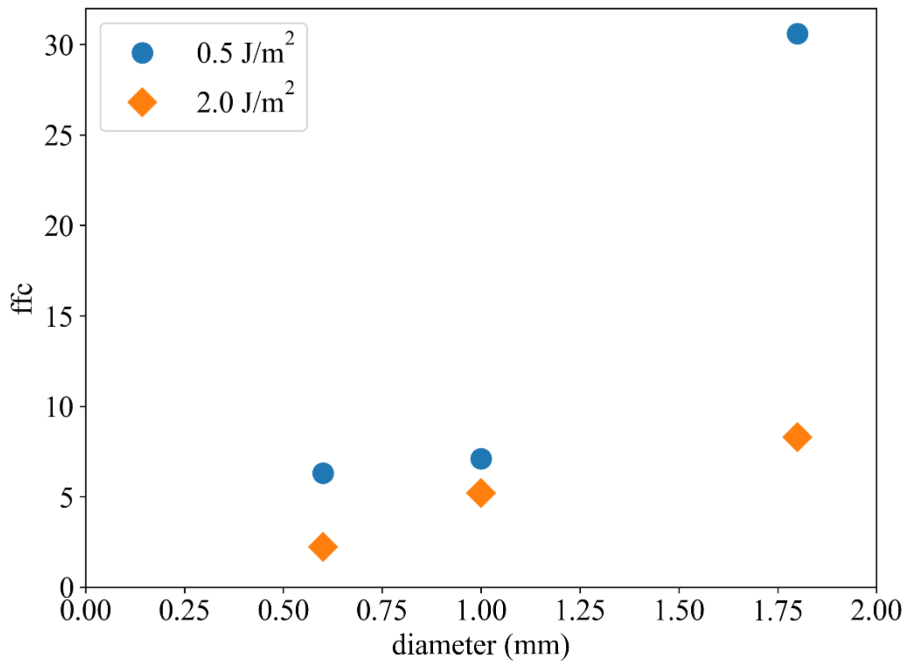




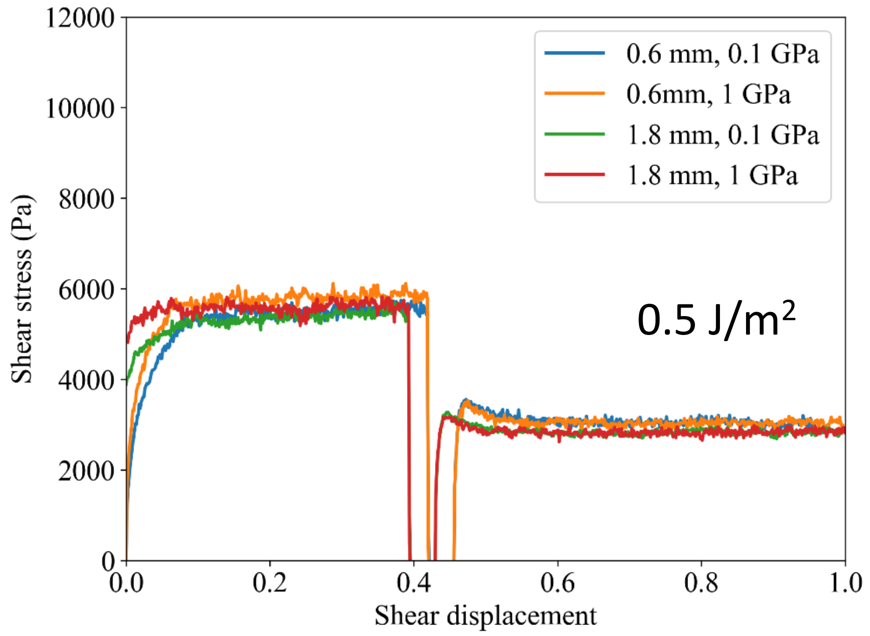
- The *shear stress increases* with the *increase of normal stress*
- *ffc increases* with the increase of *pre-consolidation stress* for cohesive powder

The Influence of Particle Properties

- The size of spheres



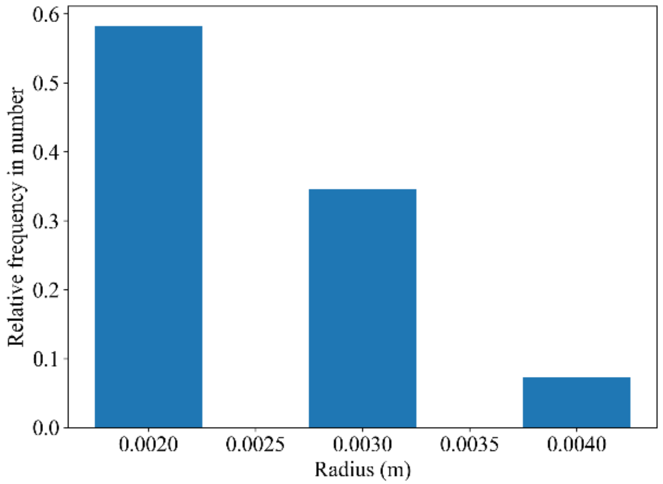
- Young's modulus



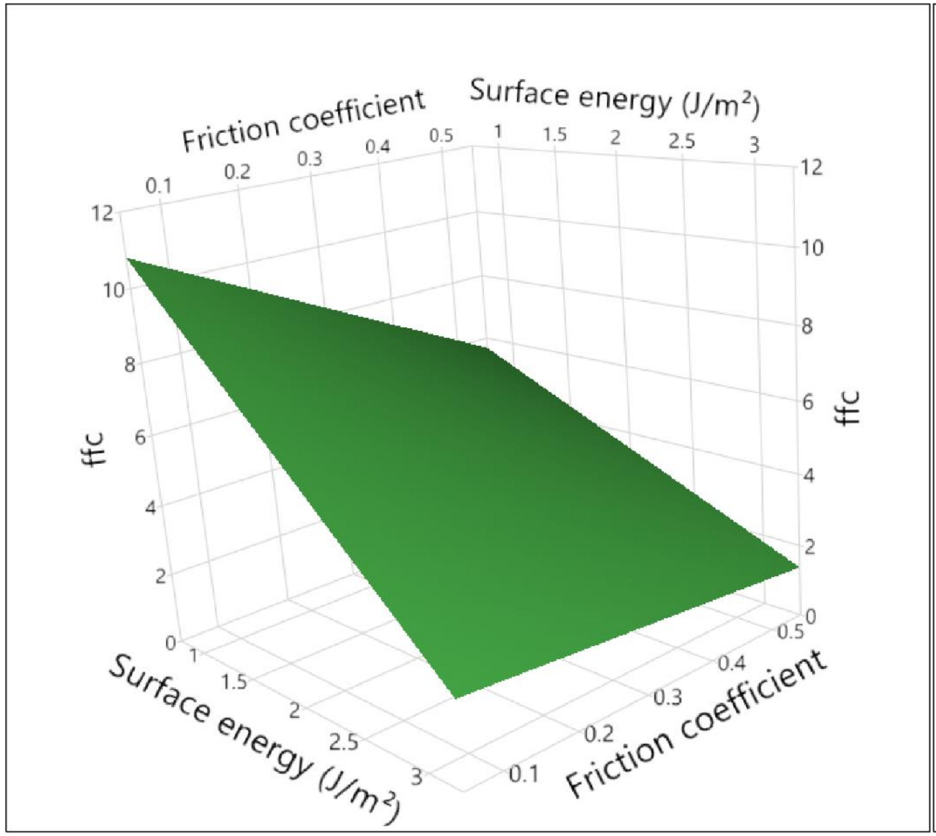
➢ ffc decreases with the decrease of particle size and increase of surface energy

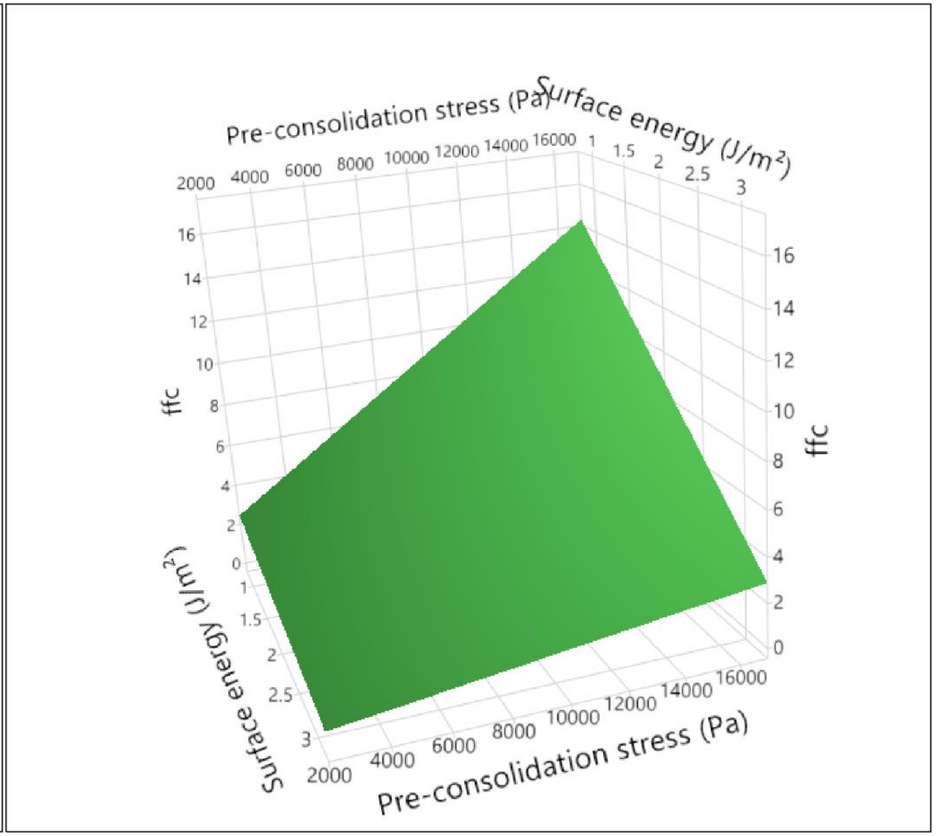
Design of Experiments (DoE) of Powder Flowability

- 200,000 particles
- Diameter: 400 – 800 um
- Spherical particles
- Influence factor (Input)
  - Surface energy: 1.0 – 3.0 J/m^2
  - Friction coefficient: 0.1 – 0.5
  - Pre-consolidation stress: 2 – 16 kPa
- Response (output)
  - Flow function coefficient (ffc)
  - Angle of internal friction at yield locus
  - Bulk cohesion



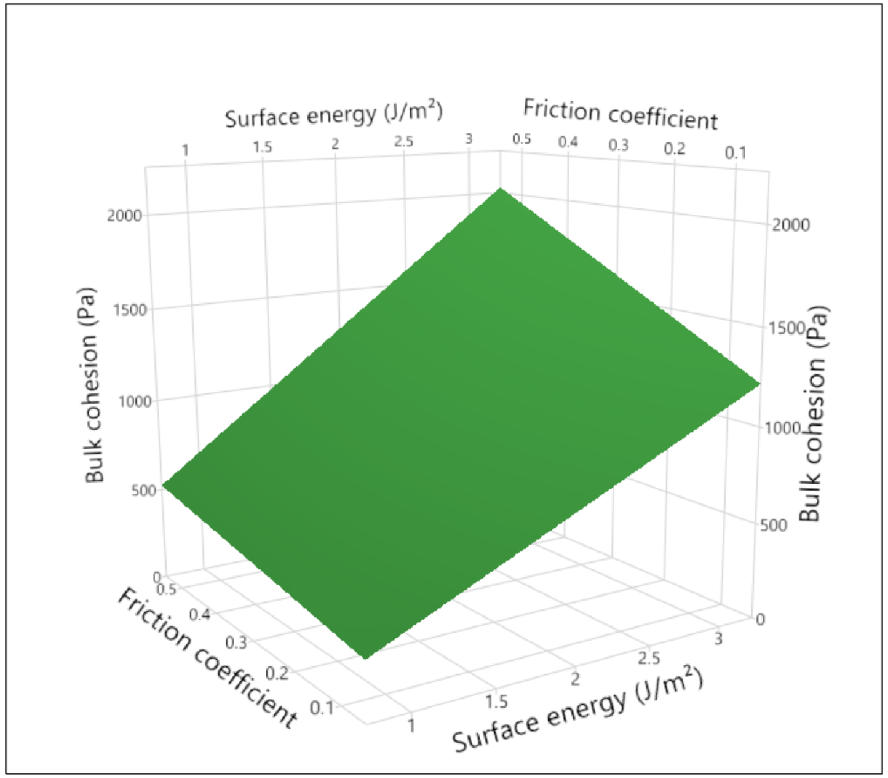
Flow Function Coefficient (ffc)

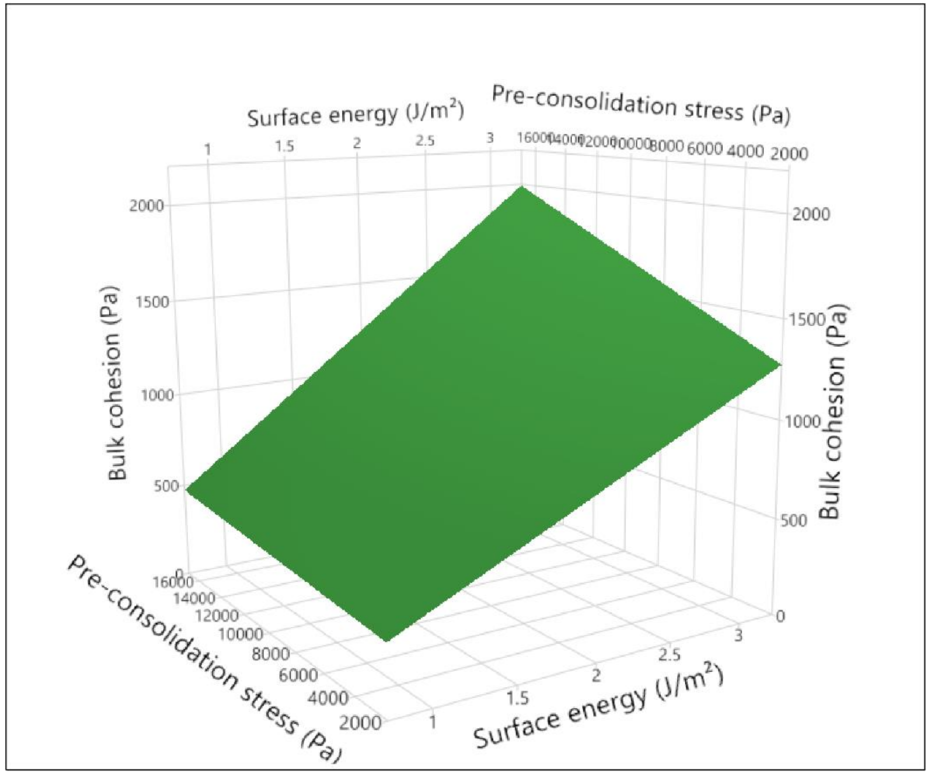




- ffc decreases with the increase of surface energy and friction and the decrease of the pre-consolidation stress
- The *pre-consolidation stress* and *surface energy* show the most significant influence

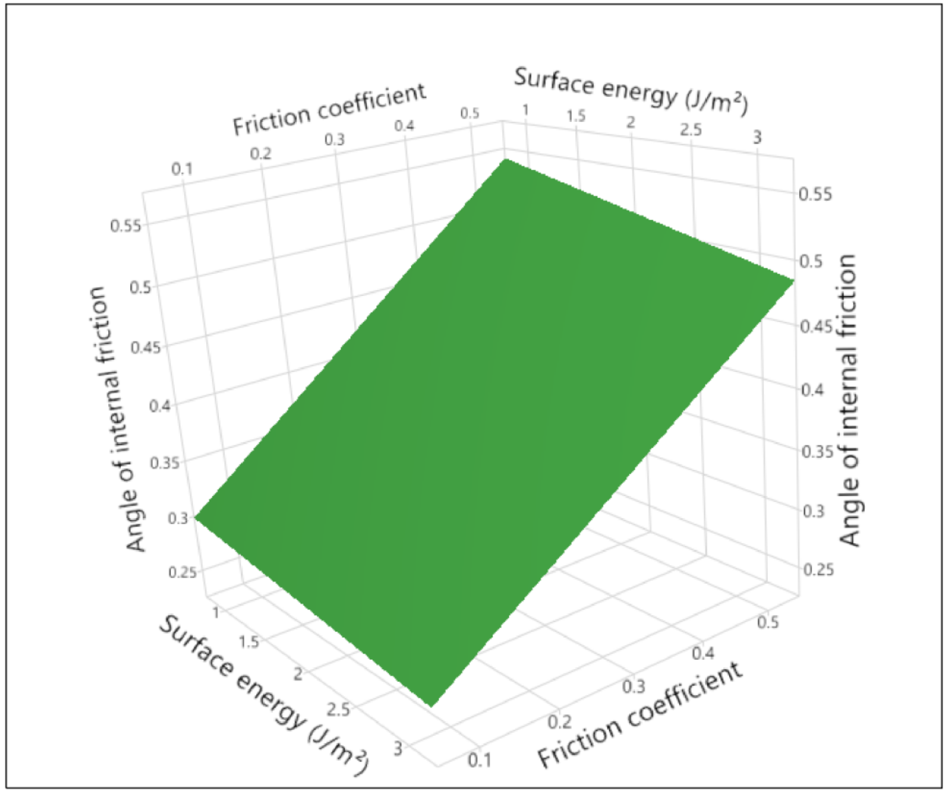
Bulk Cohesion

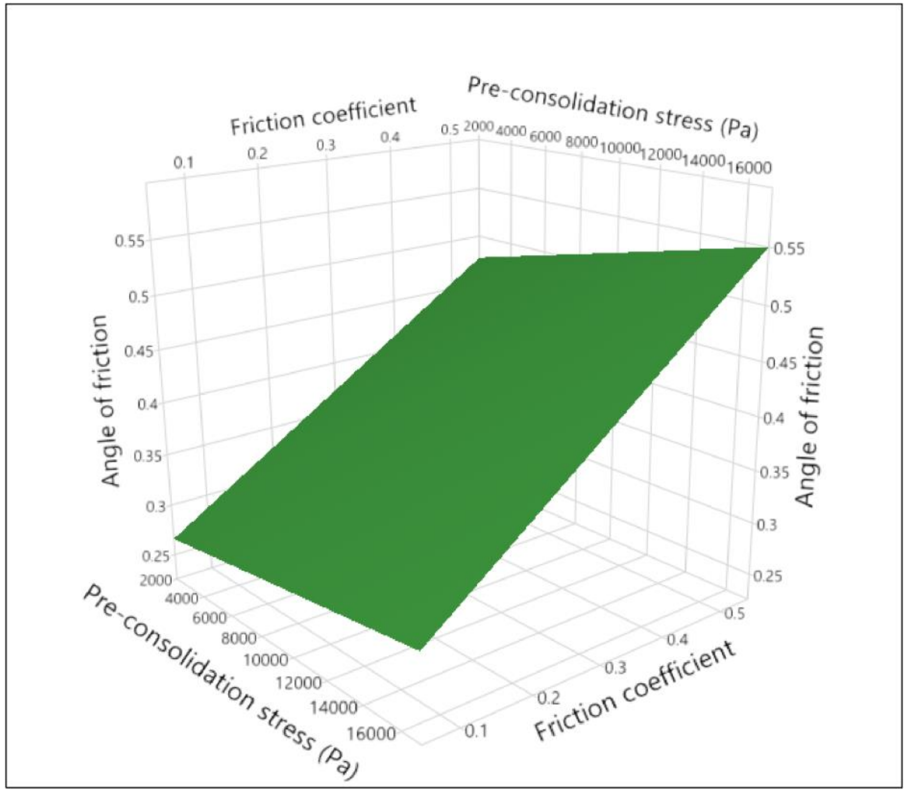




- ➢ *Bulk cohesion* primarily increases with the *increase of surface energy*

Angle of Internal Friction





- ➢ The *angle of internal friction* primarily increases with the *increase of friction coefficient*

Variable Importance

- The *variable importance* estimates how significant the factor influence the response in the selected range
- If the variation of the factor causes high variability in the response, the factor is relatively important to the model

	Surface energy	Friction	Pre-consolidation
ffc	**0.387**	**0.092**	**0.604**
Bulk cohesion	0.740	0.146	0.143
Angle of internal friction	0.035	0.868	0.081

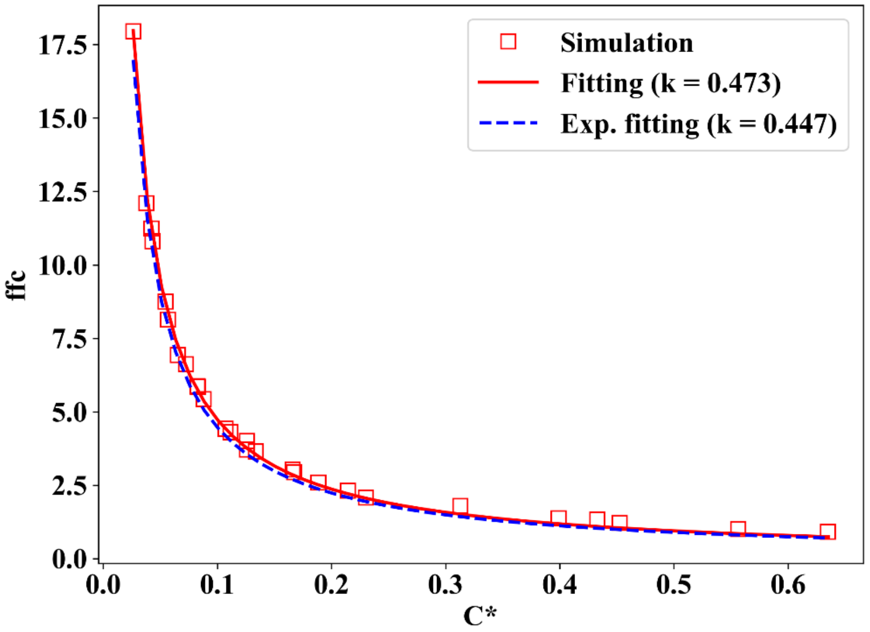
	Surface energy	Friction	Pre-consolidation
Overall response	0.387	0.276	0.604

Comparison with Experiments

- Glasser, Muzzio *et al.* (2015, 2016) conducted the ring shear test for 41 types of powders on 3 types of instruments (Schulze, FT4 and Brookfield PFT). The experimental results show that ffc is inversely proportional to the cohesion normalised by the pre-consolidation stress

$$ffc = {}^{k}/_{C^*} = {}^{k}\Big/_{\frac{\tau_c}{\sigma_{pre}}}$$

- τ_c is the bulk cohesion
- σ_{pre} is the pre-consolidation stress
- *k* is a constant coefficient related to internal friction (for various powders)

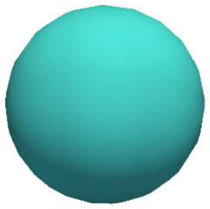


- The simulation results are consistent with experimental results, showing that flowability is well-captured by digital model

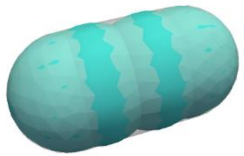
Wang, et al., Powder Technology, 2016, 294, 105-112
Koynov, et al., Powder Technology, 2015, 283, 103-112

Influence of Particle Shape

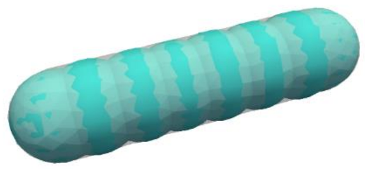
- Spherical vs Elongated
  - Equivalent volume diameter
  - JKR cohesion



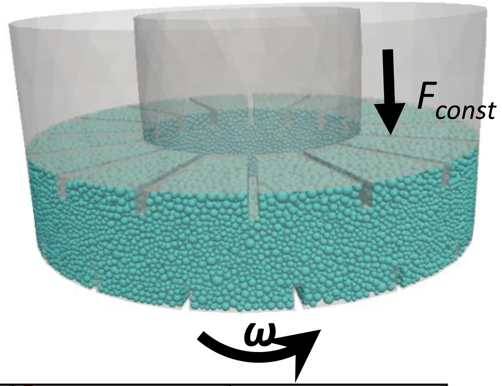
Sphere

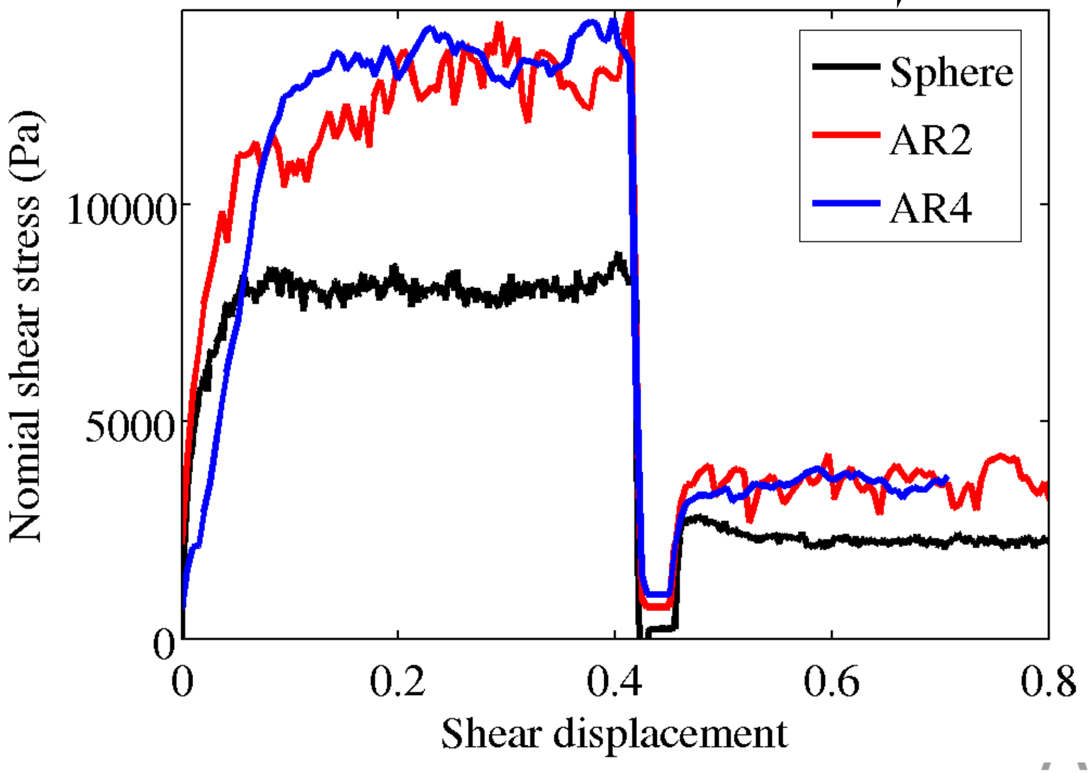


Aspect ratio = 2

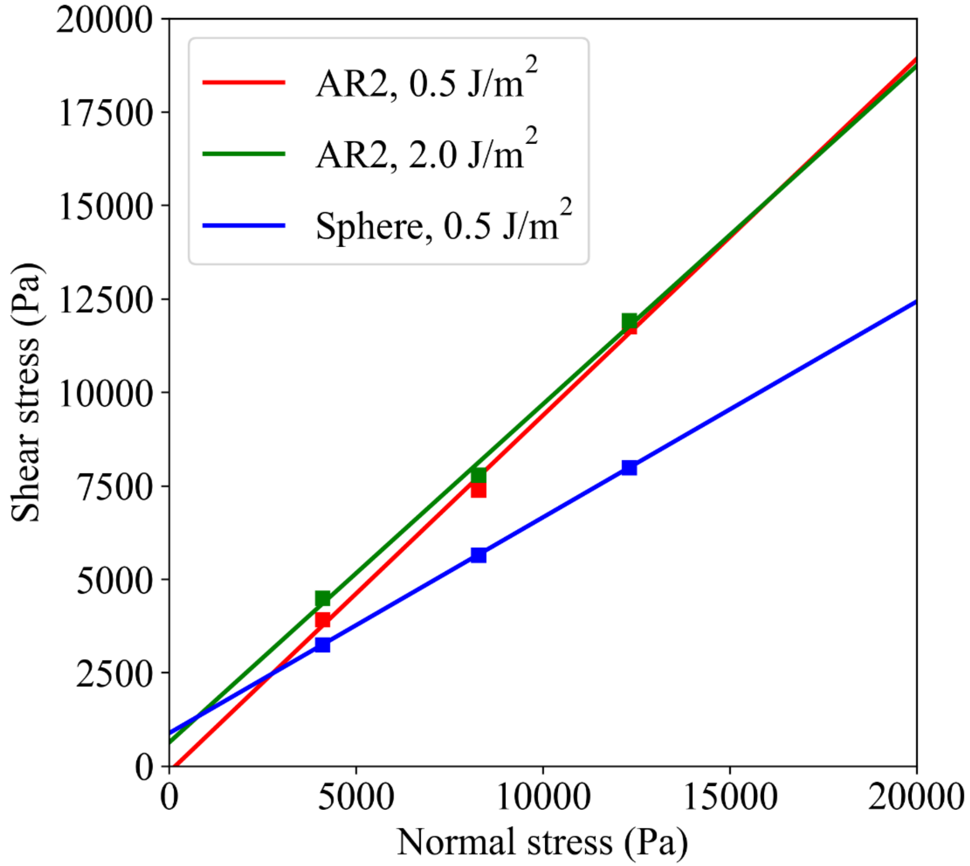


Aspect ratio = 4



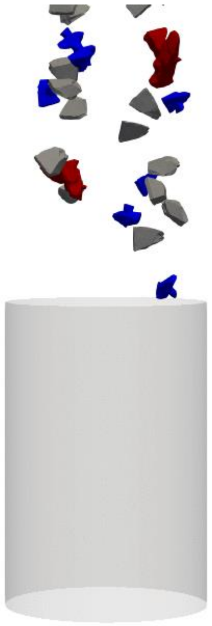


Influence of Particle Shape

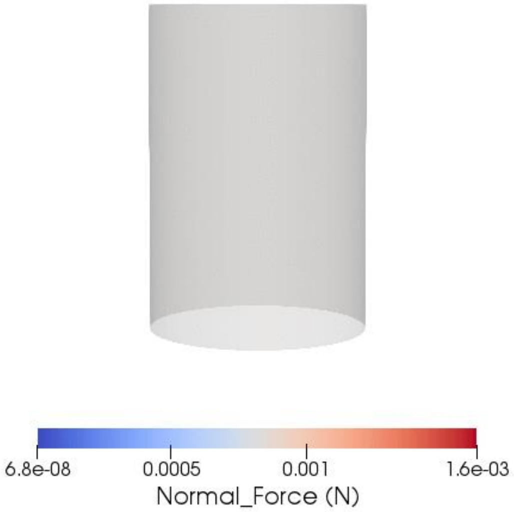


The particle shape plays a role in the angle of friction of failure which also varies the interception on the axis of shear stress.

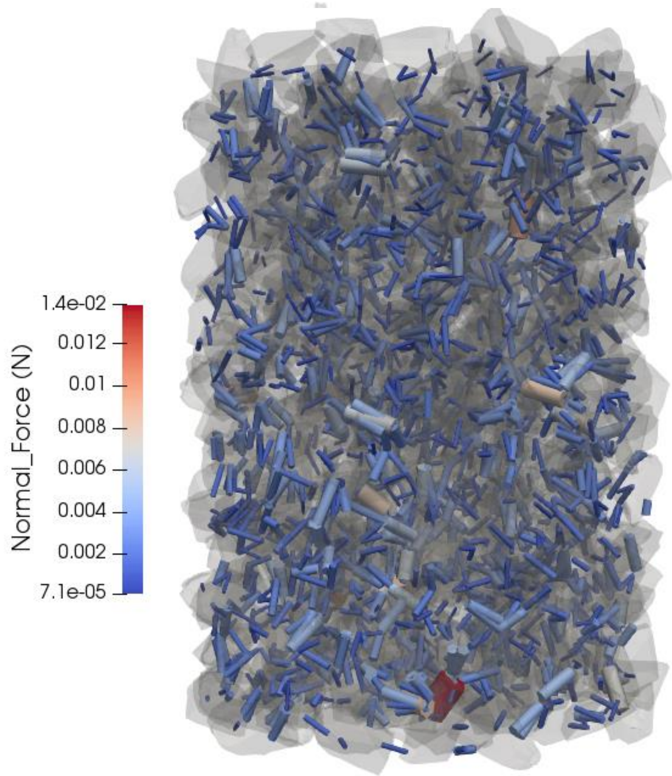
Particle Shape from X-ray CT (INFORM 2020)



Packing of three shapes



Force Network



Micro-structure

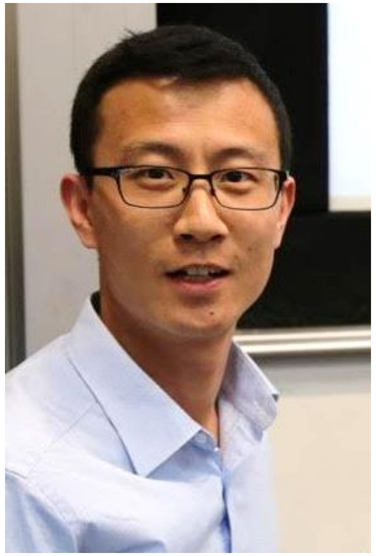
Concluding remarks

- A Design of Experiments approach based on Discrete Element Modelling was conducted to examine the influence (variable importance) of surface energy, friction and pre-consolidation stress on the powder flowability (ffc), internal friction angle and bulk cohesion.
- DEM can be employed to study the powder flowability in a ring shear cell and the influence of particle and process properties
- The surface energy and friction between particles contribute significantly to the bulk cohesion and internal friction angle, respectively
- Modification of the particle shape can significantly alter the powder flow properties
- These insights be applied in practice through a digital process design tool

Acknowledgements

ADDOPT

ADVANCED DIGITAL DESIGN OF PHARMACEUTICAL THERAPEUTICS



Dr Chunlei Pei (裴春雷)

Thank you

Dr Xizhong Chen (陈锡忠)

PSE | AstraZeneca | Bristol-Myers Squibb | Britest

UNIVERSITY OF CAMBRIDGE | The Cambridge Crystallographic Data Centre | gsk GlaxoSmithKline | UNIVERSITY OF LEEDS

PERCEPTIVE ENGINEERING LTD | Pfizer | Hartree Centre Science & Technology Facilities Council | University of Strathclyde Glasgow | ADDOPT