Digitalisation of Pharmaceutical Product Development with Physics-based Multiscale Models

Formulation 4.0: Put Digital into Formulation, London, UK, 26th July 2024

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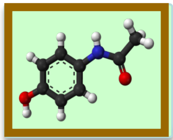
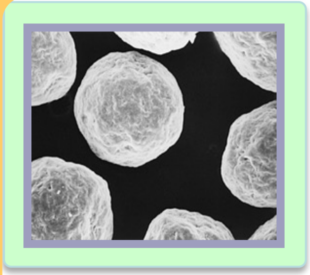
RSC INTEREST GROUP FORMULATION SCIENCE & TECHNOLOGY

Digital Formulation Engineering



Primary manufacturing

(synthesis, crystallization)



Secondary manufacturing

Formulation Engineering; Process Engineering

Digital Transform APIs to Products– Digital Product Engineering

An ambitious scientific question

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Can we develop a digital tool that can assess the performance, process-ability and product properties of identified drug molecules

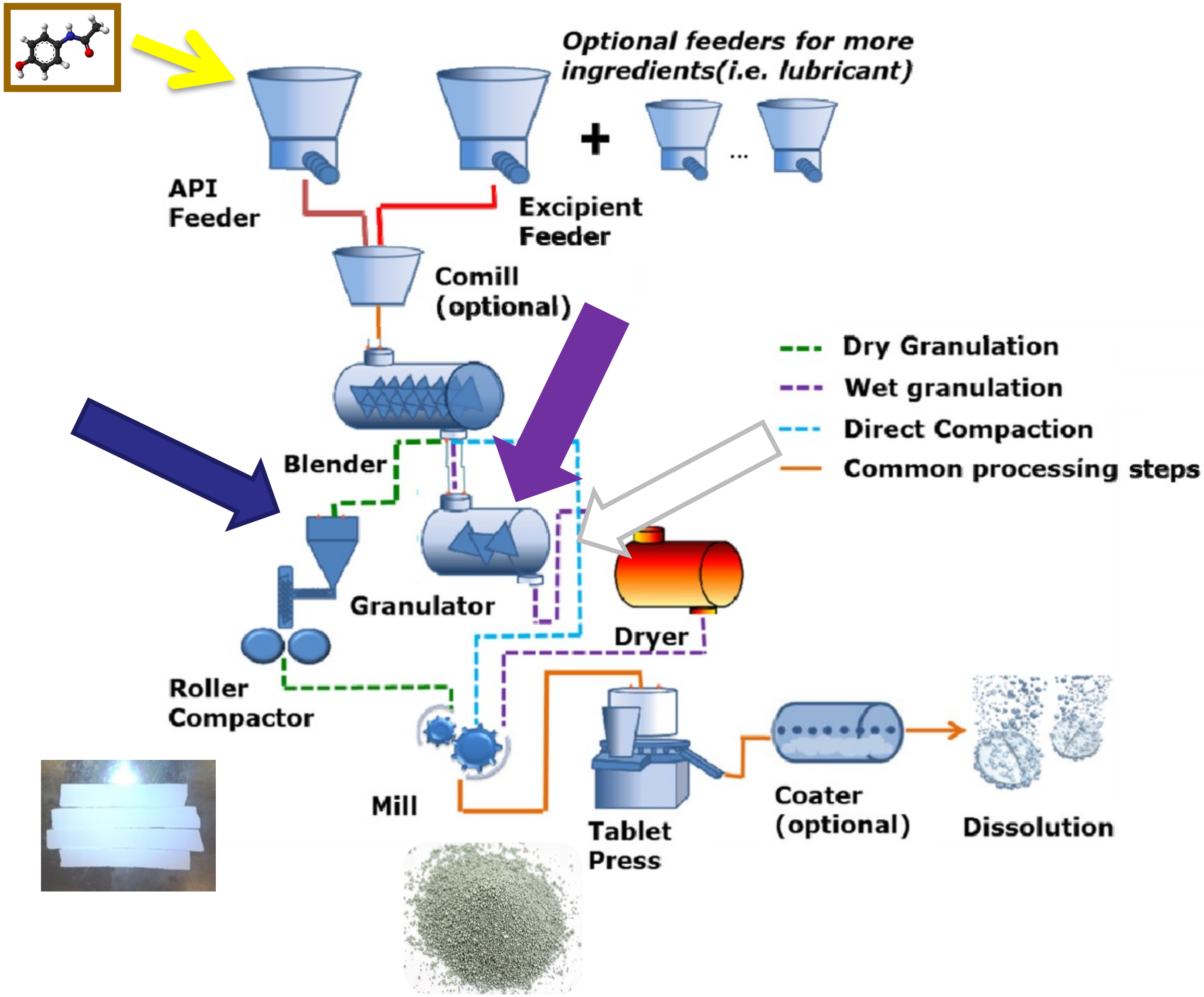
At a very early stage of drug development

Using only a very limited amount of materials

Based upon a small amount of experiments

so that optimal formulation and manufacturing processes can be designed and the duration and costs of drug development can be significantly shortened?

Pharmaceutical Manufacturing Processes



Formulation development challenge

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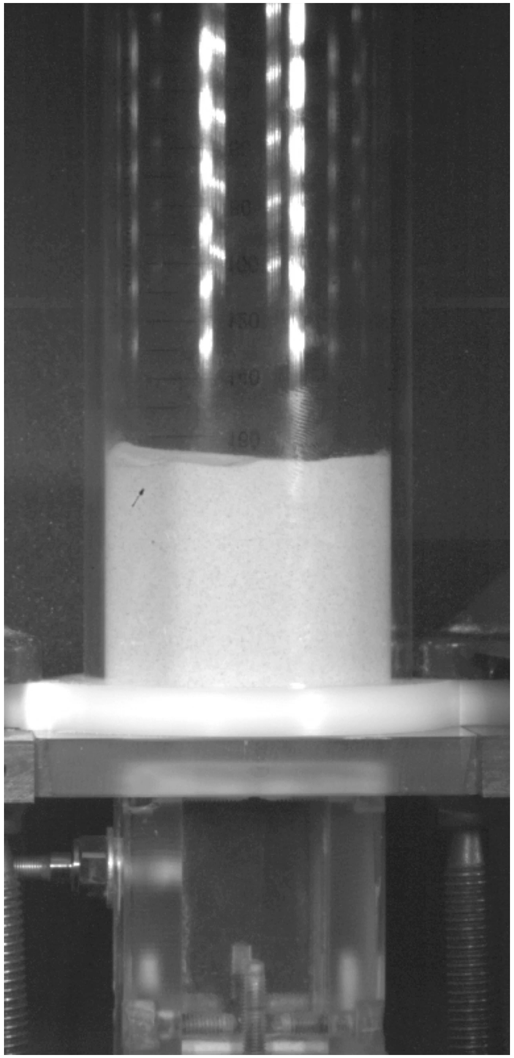
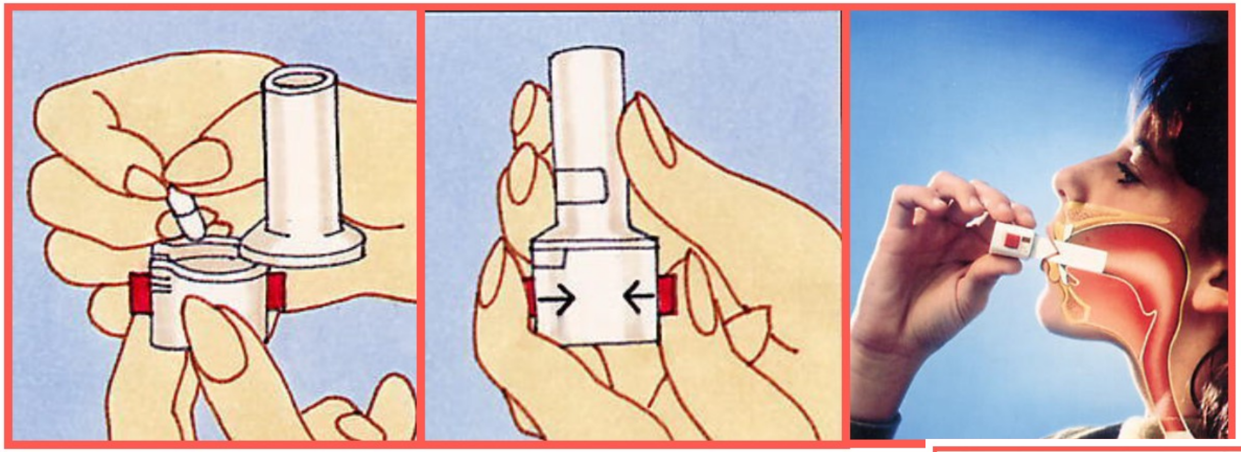
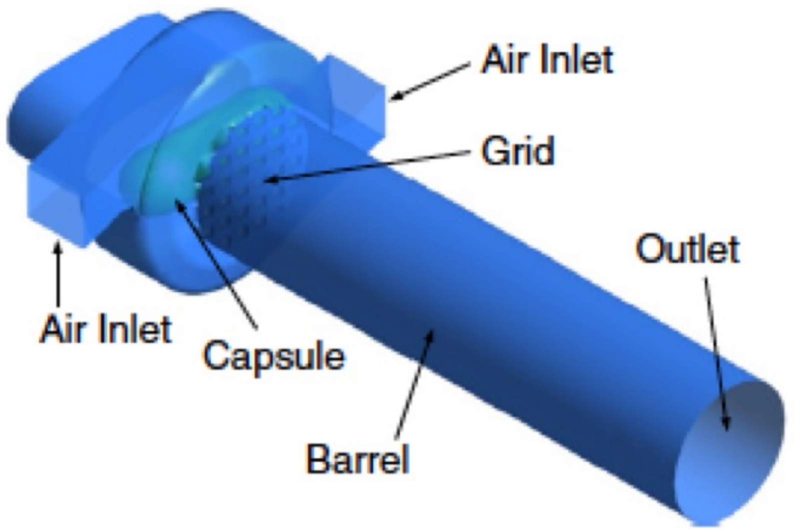
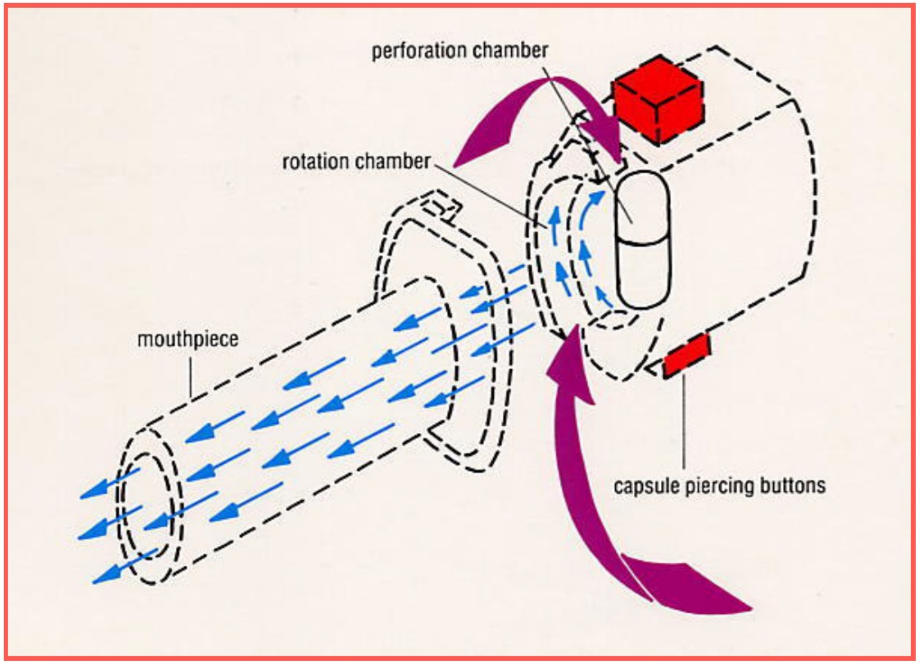
- With an identified API, formulation development and process design is not a trivial task.
- Need to ensure each unit operation is performed properly.
- Conventional trial-and-error approach is time consuming and costly.
- To some extent, pharmaceutical industry lags behind many other industries in exploiting innovative tools and technologies, such as digital technology and AI.
- Partly due to the distinctive materials attributes of powders from conventional solids, liquids and gases.
- For a typical manufacturing process, **powders can manifest themselves as fluids or solids in different unit operations**.
- Computational tools need to able to describe the diverse powder behaviours. It is challenging (not impossible) for one model to fit all requirements.



A system approach in product development







Key questions in pharmaceutical product development

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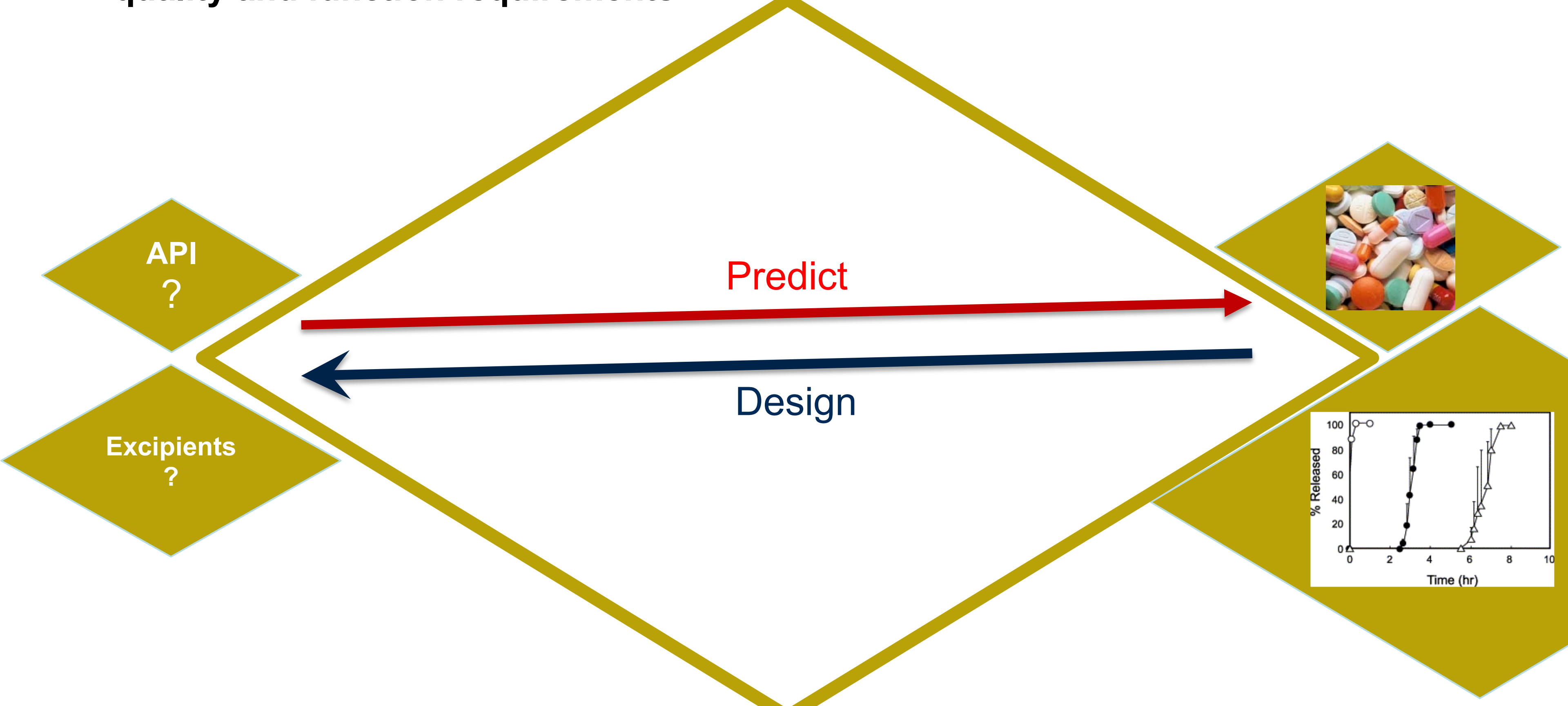
1) Can we predict the behaviour of API and excipients in formulation and manufacturing?
2) Can we use it to optimise the formulation and process conditions?
3) Can we design the formulation and manufacturing processes based upon the quality and function requirements.



Two computational approaches

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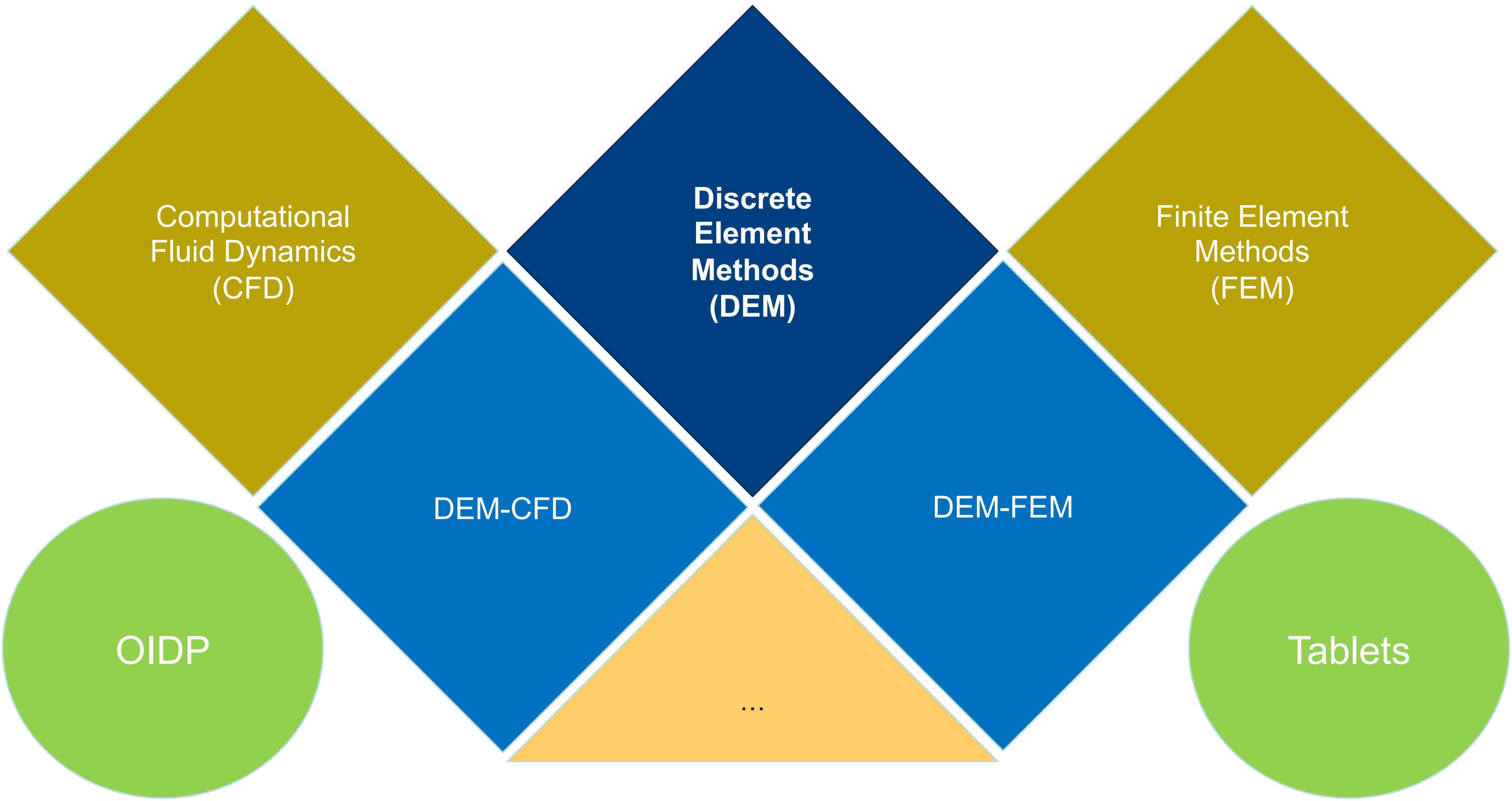
Mechanistic Modelling

- Based upon underlying physics, chemistry and biology
- Using mathematical tools (e.g. Differential equations, stochastic models) to describe the dynamic behaviour of the system
- Formulate mathematical/numerical models capturing the interplay between various parameters.
- Focus on unit operations, i.e. step by step (hopper flow, mixing/blending, milling, dry granulation, wet granulation, die filling, tableting roll compaction coating)

Machine Learning

- Enables computers to learn from data and make predictions without explicit considering the underlying physics, chemistry or biology.
- Using algorithms that allow computers to learn patterns and insights from large datasets, facilitating predictive analysis.
- Depend on data, not process.

Mechanistic Modelling Tools



Discrete element method (DEM)

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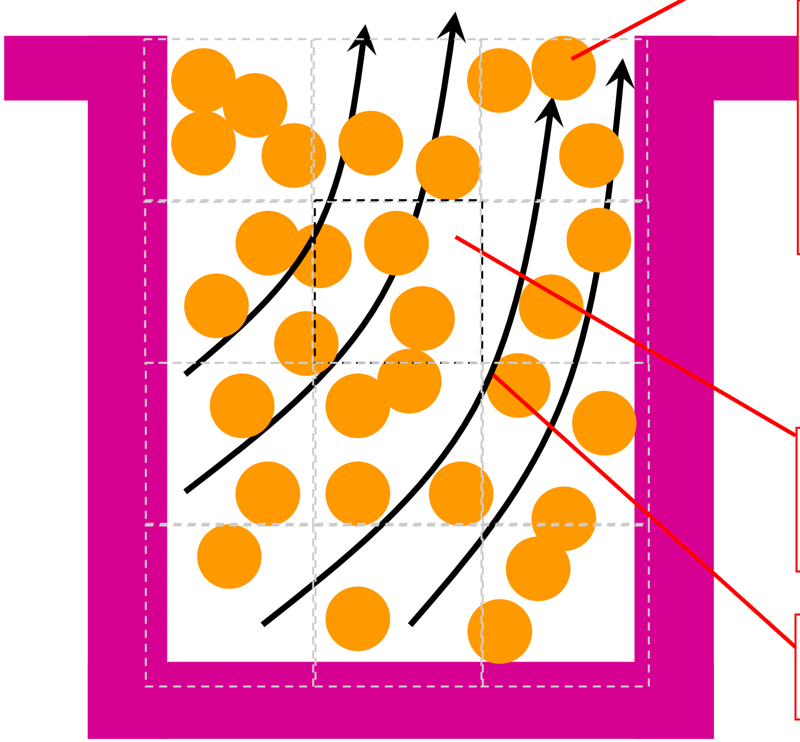


The flow of particles is modelled using **DEM.**

The interaction between particles are rigorously modelled using theoretical contact mechanics:

- Hertz-Mindlin-Deresiewicz for elastic particles
- JKR for adhesive particles

The interaction between air and particles is considered.

The flow of air is modelled using **CFD.**

Particle equations of motion:

$$F_i = F_i^c + F_i^{fp} + F_i^e + m_i g = m_i \ddot{x}_i$$

$$T_i = I_i \ddot{\theta}_i$$

fluid-particle interaction force

$$F_i^{fp} = -V_{pi} \nabla p + V_{pi} \nabla \cdot \tau_f + \varepsilon f_{di}$$

Total fluid-particle interaction force per unit volume

$$F_{fp} = \frac{\sum_{i=1}^{n_c} F_i^{fp}}{\Delta V_c}$$

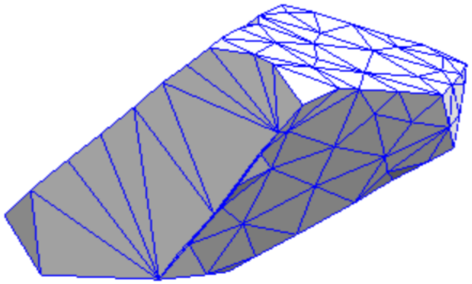
Fluid continuity and momentum equations

$$\frac{\partial(\varepsilon \rho_f)}{\partial t} + \nabla \cdot (\varepsilon \rho_f u) = 0$$

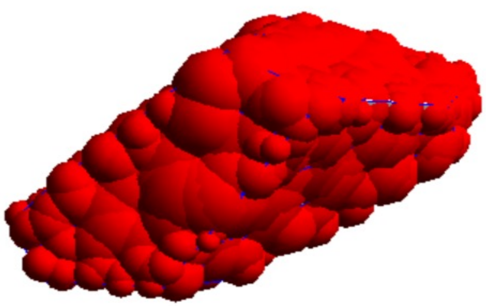
$$\frac{\partial(\varepsilon \rho_f u)}{\partial t} + \nabla \cdot (\varepsilon \rho_f u u) =$$

$$-\nabla p_f + \nabla \cdot \tau_f - F_{fp} + \varepsilon \rho_f g$$

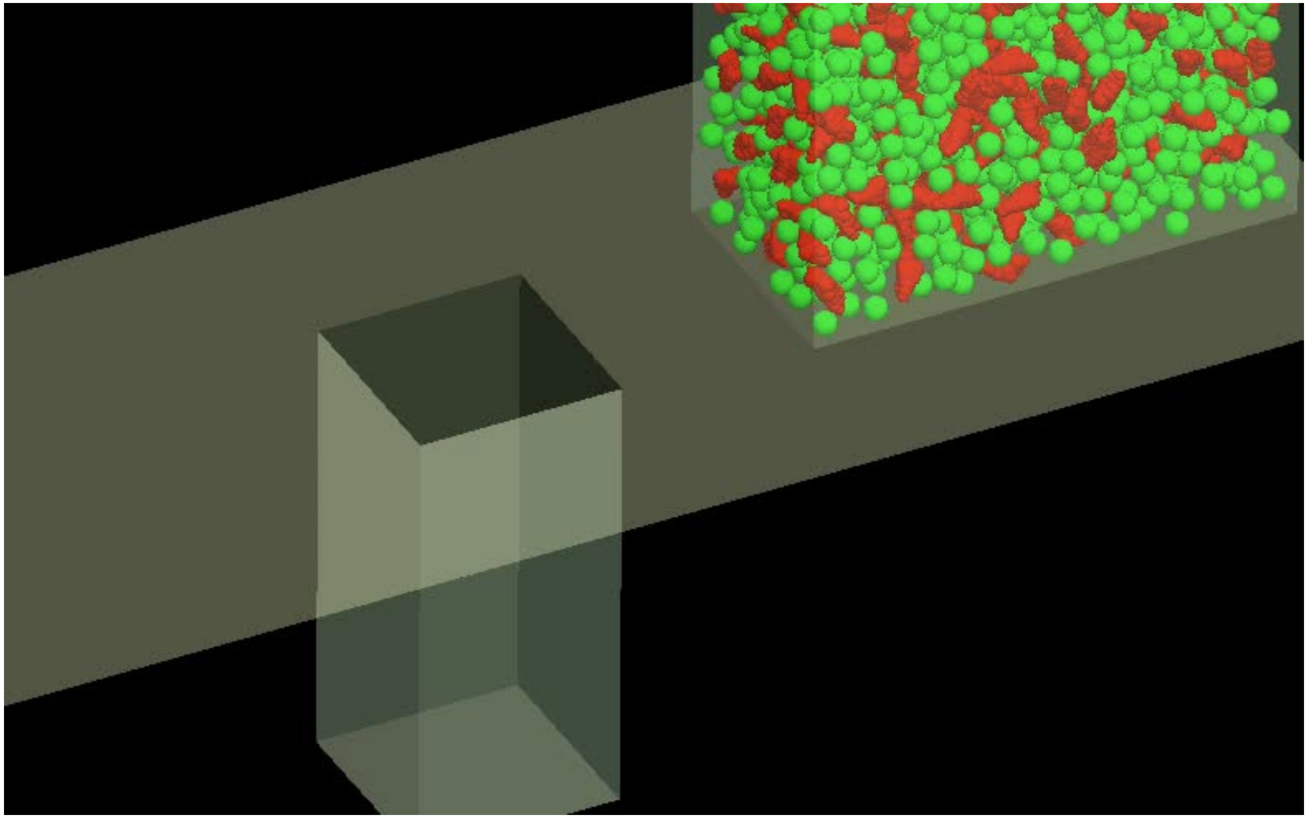
DEM with real particles (Wu et al. 2016)



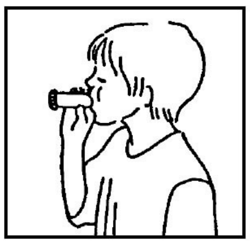
Real crystal



DEM approximation

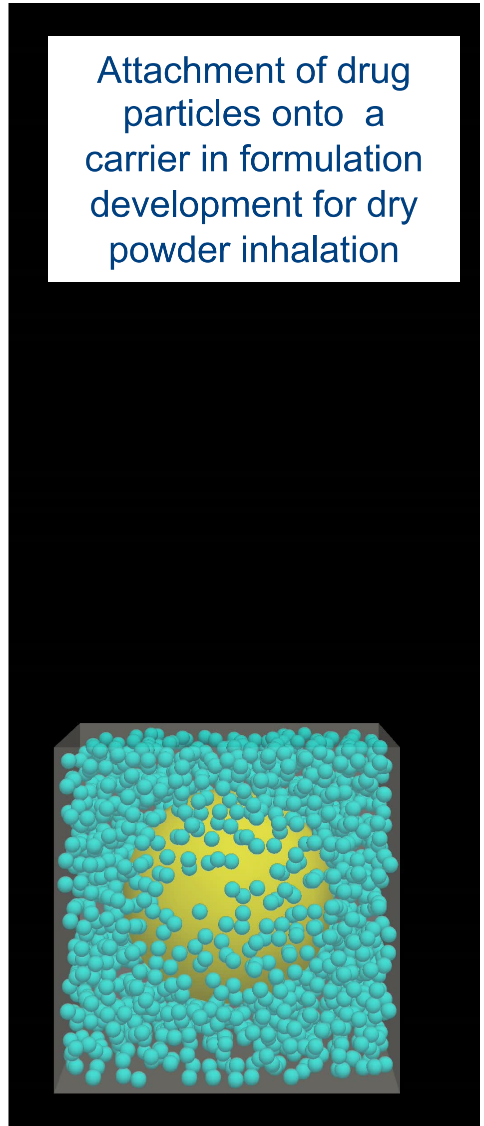


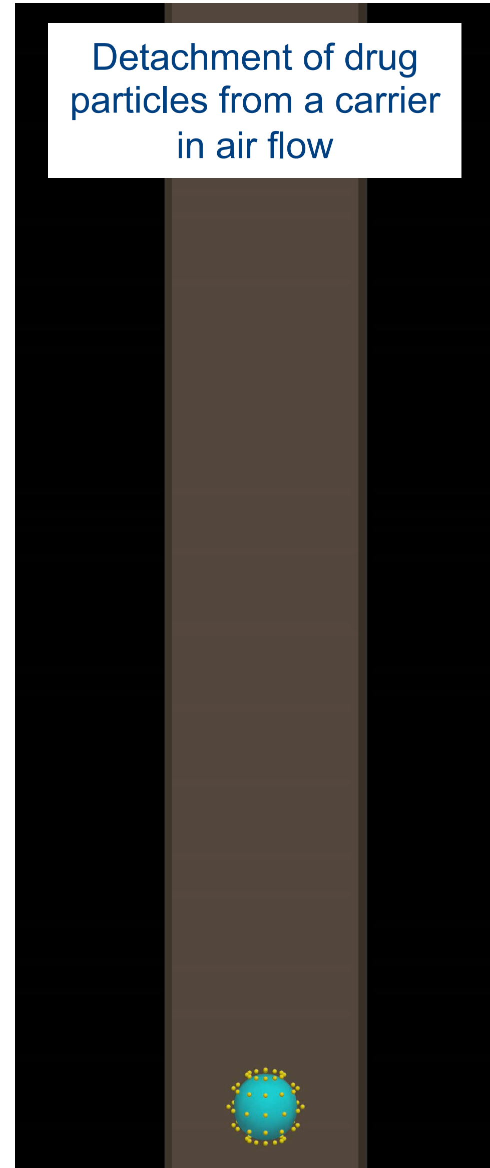
DEM-CFD for mechanistic understanding: Dry Powder Inhalation



Deliver medicines directly to the lungs and airways in the form of dry powders;

For treating pulmonary and respiratory diseases, such as asthma, bronchitis and emphysema.





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J Yang, CY Wu, M Adams. 2014. Acta Pharmaceutica Sinica B 4 (1), 52-59I.

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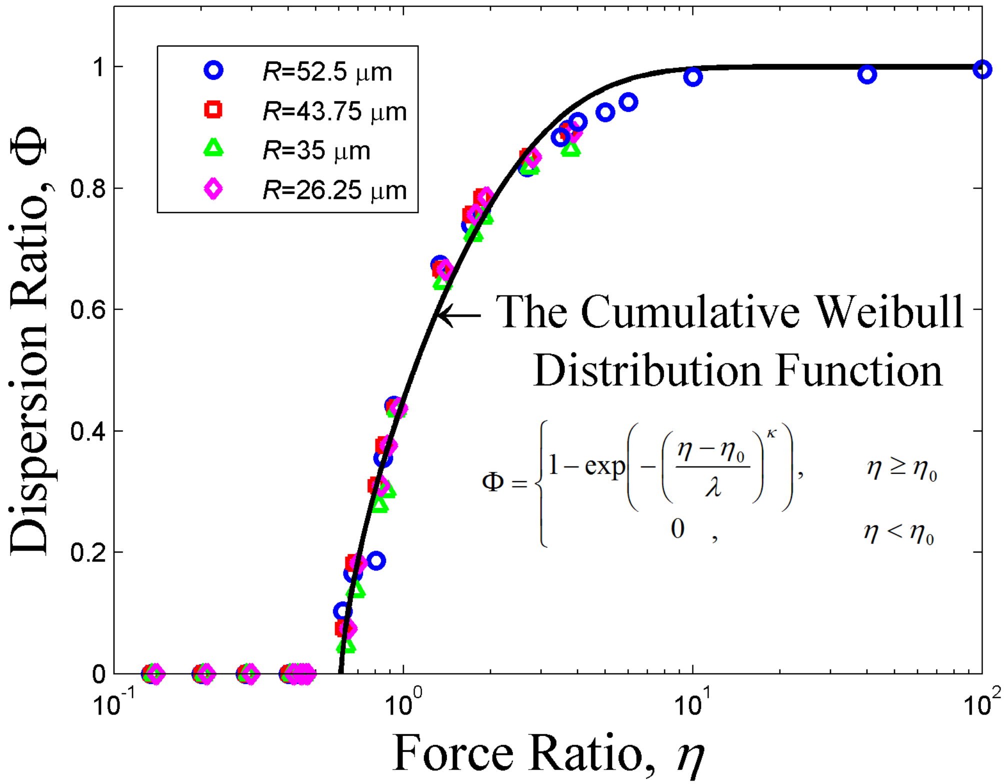
Detachment Mechanism

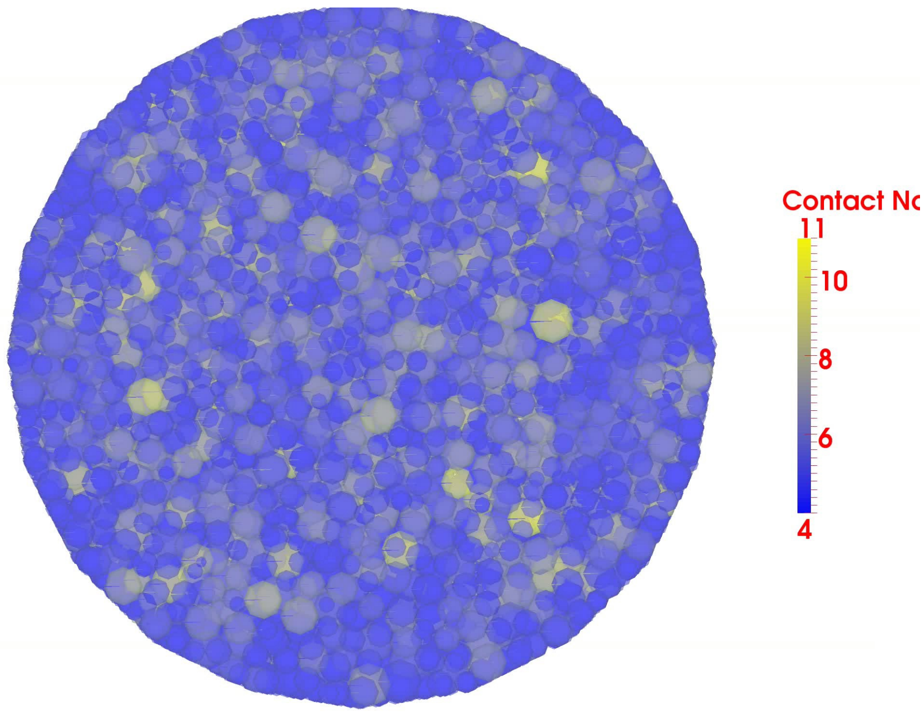
DPIs Performance is the result of the balance of the removal force and adhesive force.

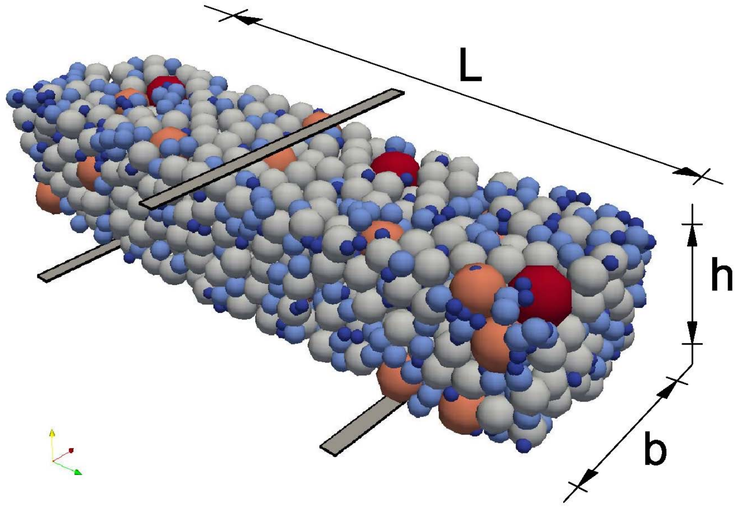
$$\eta = \frac{F_d}{F_c}$$

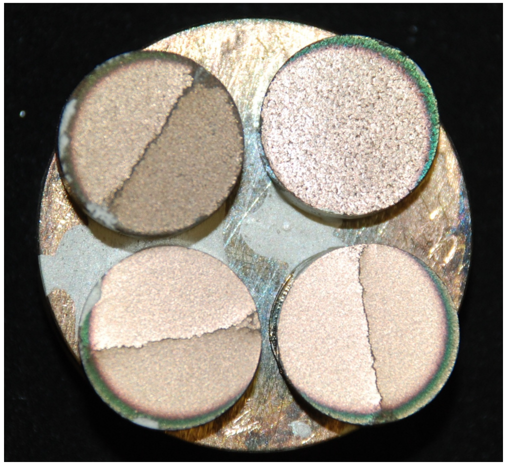


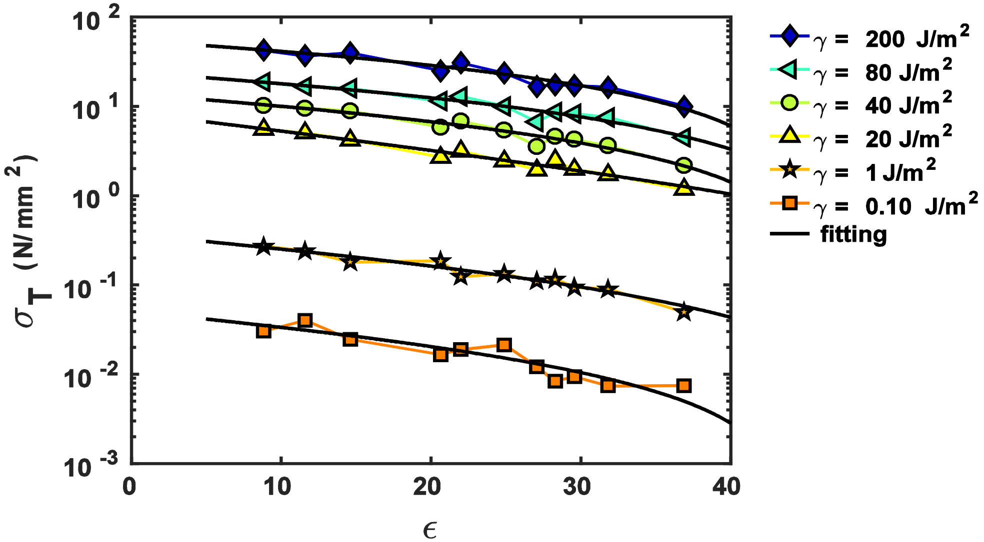
J Yang, CY Wu, M Adams. 2014. Acta Pharmaceutica Sinica B 4 (1), 52-59I.

DEM for mechanistic understanding: Mechanical Characterisation









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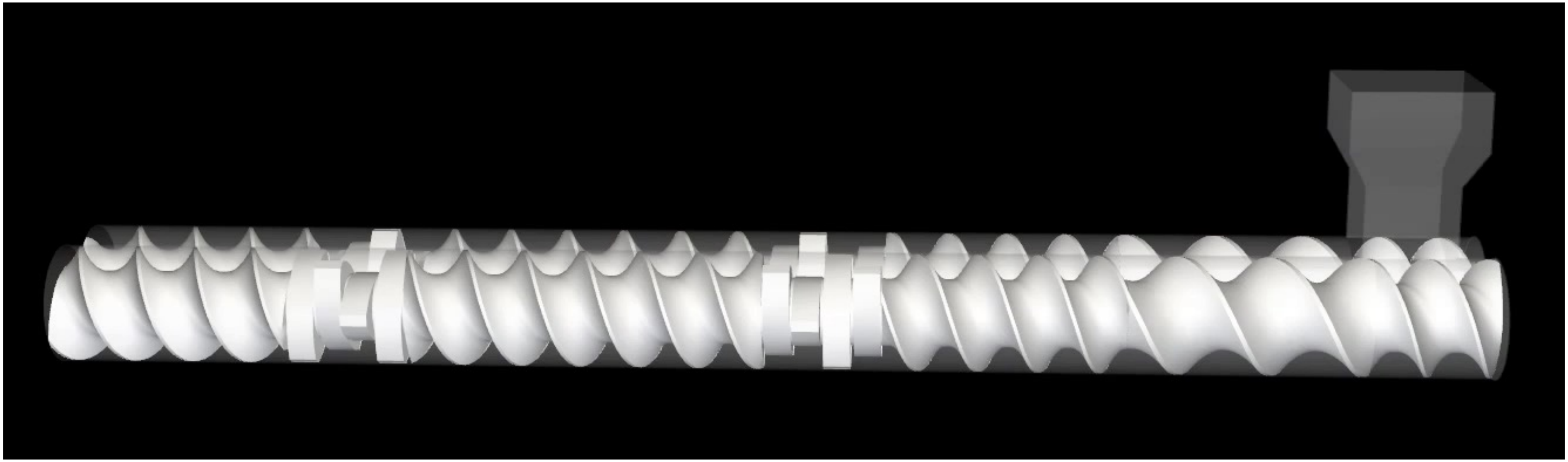
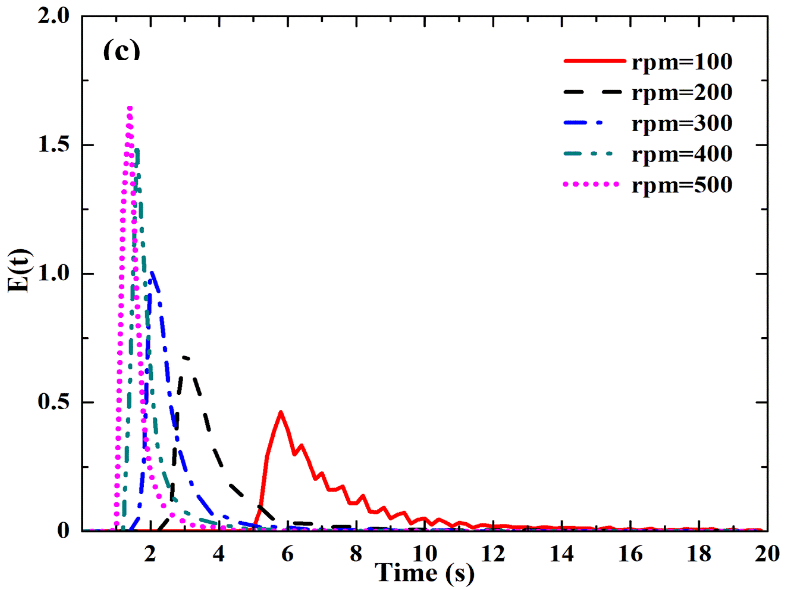
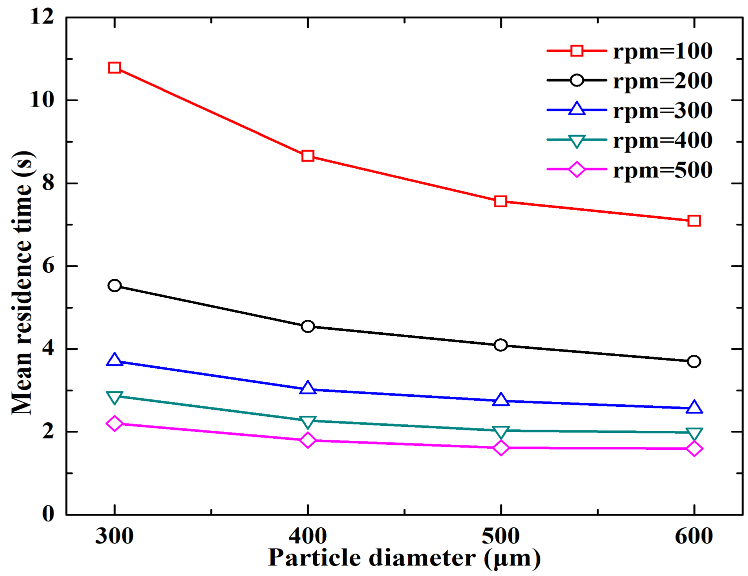
DEM for Process Modelling: Twin Screw Granulation

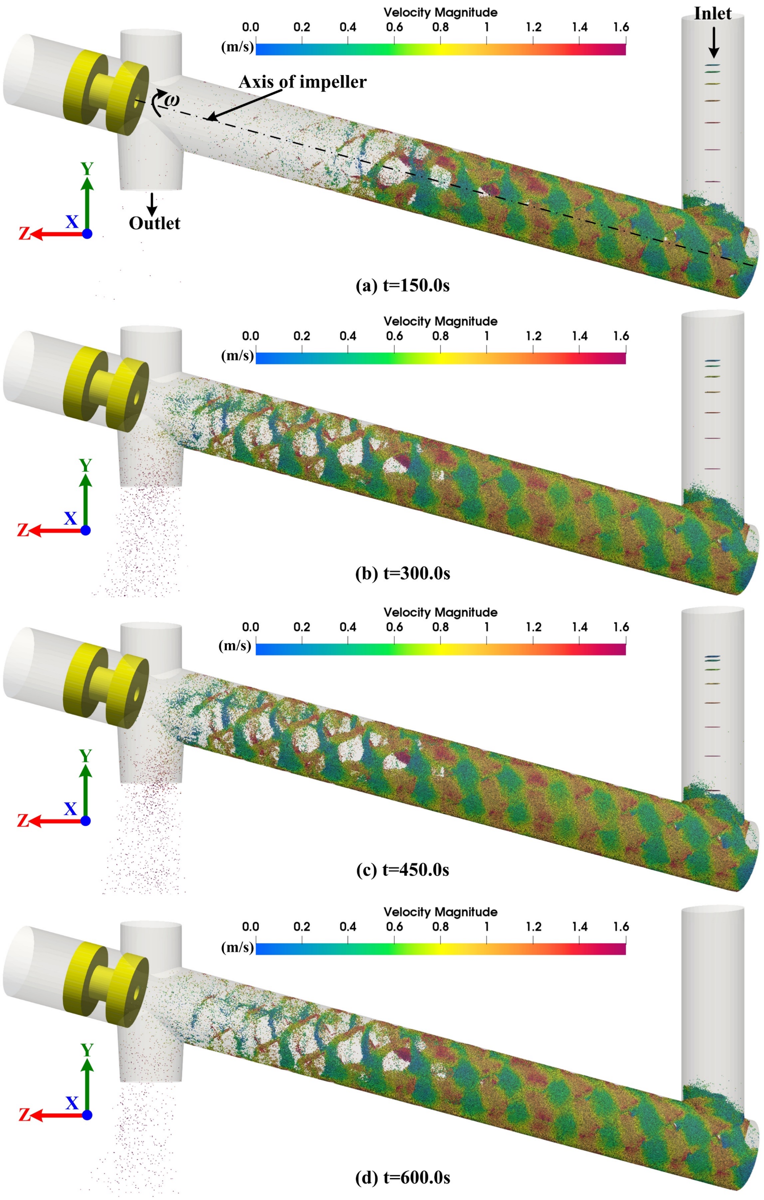


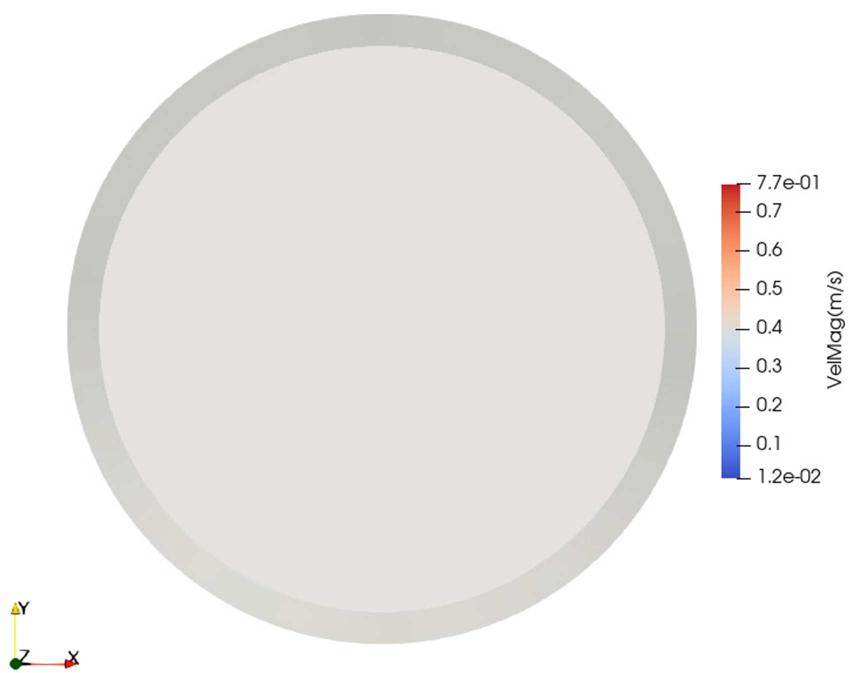




Chao Zheng; Ling Zhang; Nicolin Govender; Chuan-Yu Wu. 2021. DEM analysis of residence time distribution during twin screw granulation. Powder Technology. 377:924-938

DEM for Process Modelling: Continuous Blending & Film Coating





C Zheng, L Li, BJ Nitert, N Govender, T Chamberlain, L Zhang, CY Wu. Powder Technology 412 (2022) 117968

Mechanistic modelling of die filling in a rotary tabletting system

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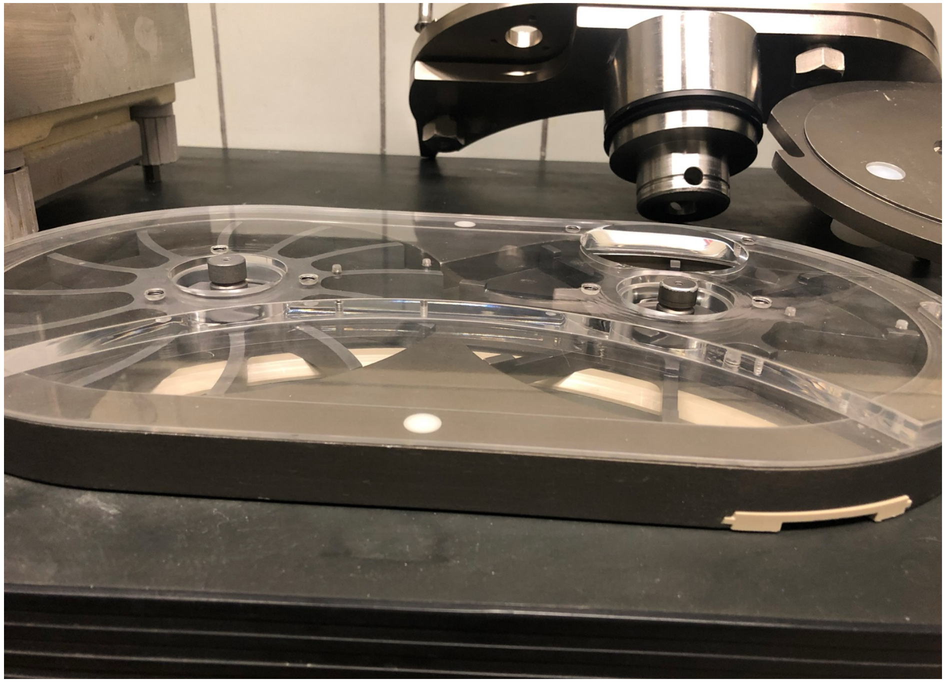
Side view

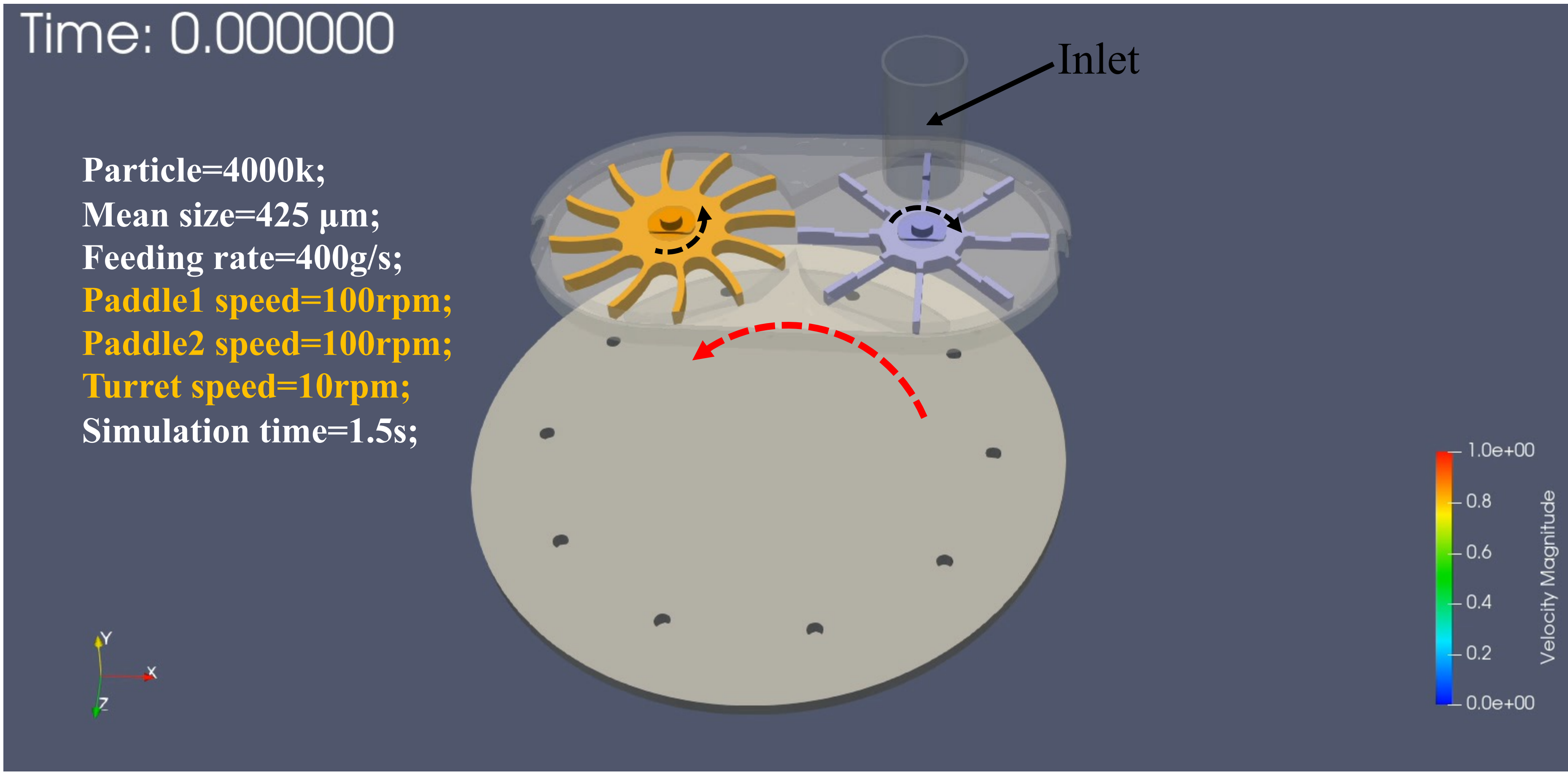


Photos of feed frame

Top view

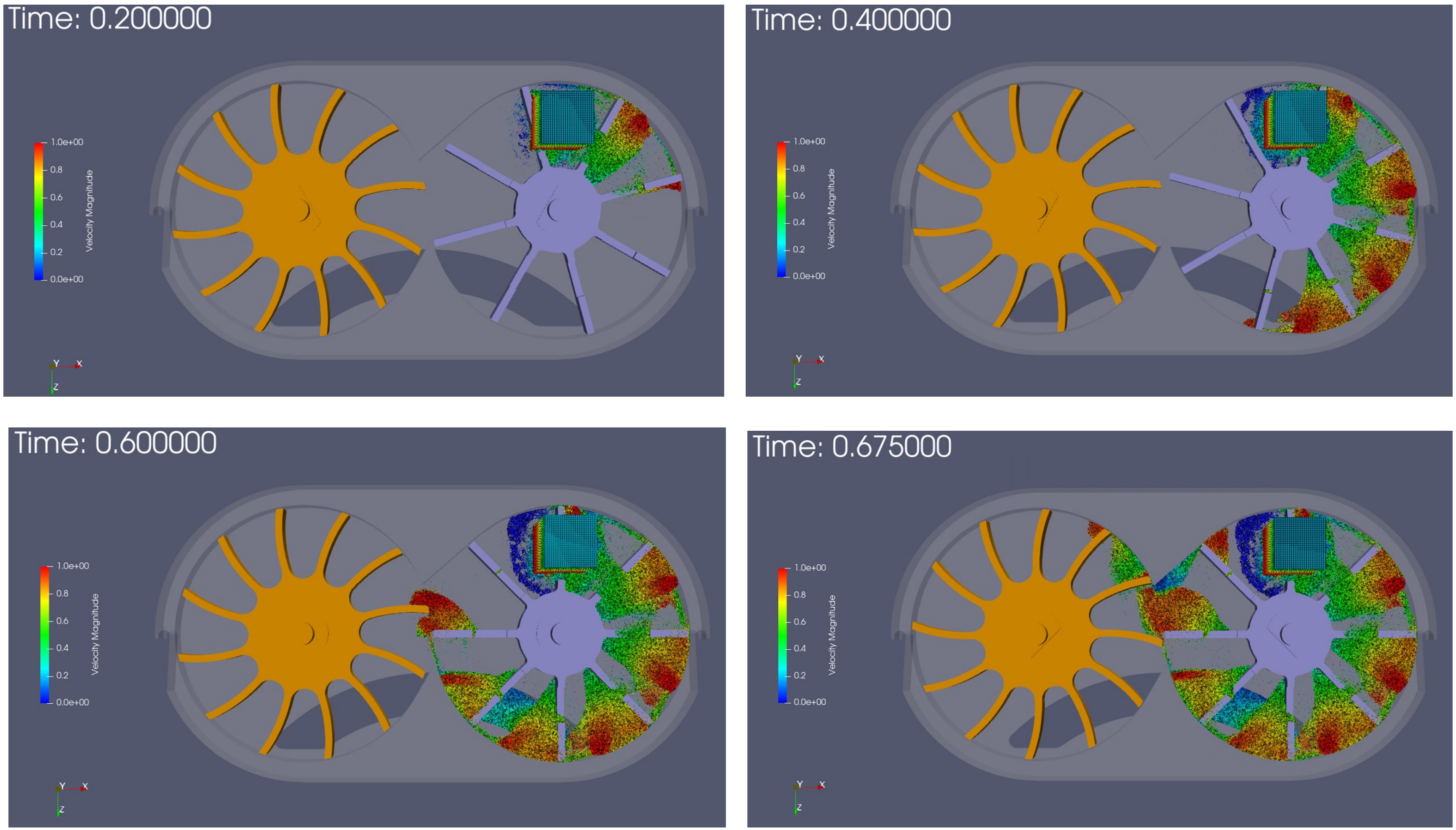
Photos of feed frame

DEM modelling of the feed frame



Animation of initial DEM model for feed frame

Particle flow patterns



Snapshots of powder distribution in feed frame (Top view)

Impact of cohesion

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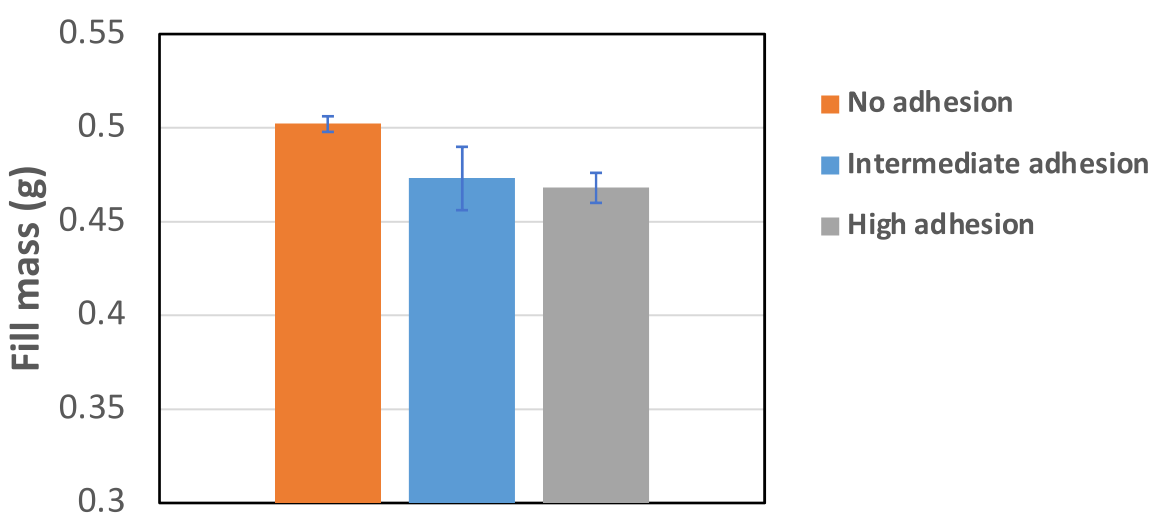
Particle size ratio	Cohesion	Turret speed (rpm)	Paddle 1 speed	Paddle 2 speed	Average mass (g)	RSD (%)	Hold-up mass (g)
1.6	intermediate	55	57.5	69	0.474	1.46	294
1.6	**No adhesion**	**10**	**15**	**18**	**0.502**	**0.83**	**293**
1.6	**Intermediate**	**10**	**15**	**18**	**0.473**	**3.57**	**287**
1.6	**High**	**10**	**15**	**18**	**0.468**	**1.71**	**278**

Cohesion number

$$= \frac{\text{Work of cohesion}}{\text{Gravitational potential energy}}$$

$$Coh = \frac{1}{\rho g}\left(\frac{\Gamma^5}{E^{*2} R^{*8}}\right)^{1/3}$$

$$\Gamma_2 = \Gamma_1 \left(\frac{R^*{}_2}{R^*{}_1}\right)^{\frac{8}{5}}$$



Finite Element Modelling

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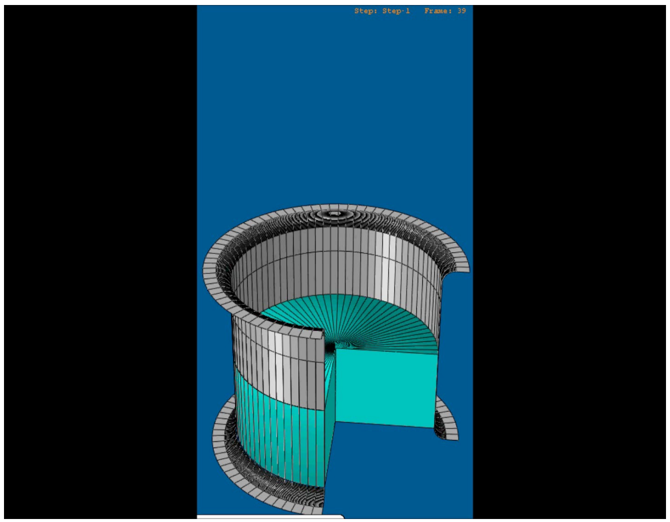
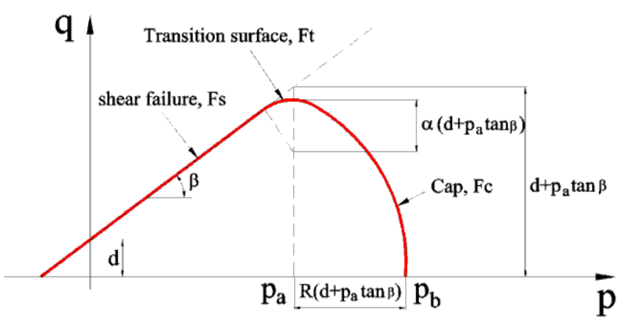


Powder is regarded as continuum elastic-plastic media.

Compaction behaviour is modelled by solving a boundary value problem, i.e. partial differential equations representing:

- Balance laws (mass, energy, momentum);
- Constitutive laws (stress-strain, friction).



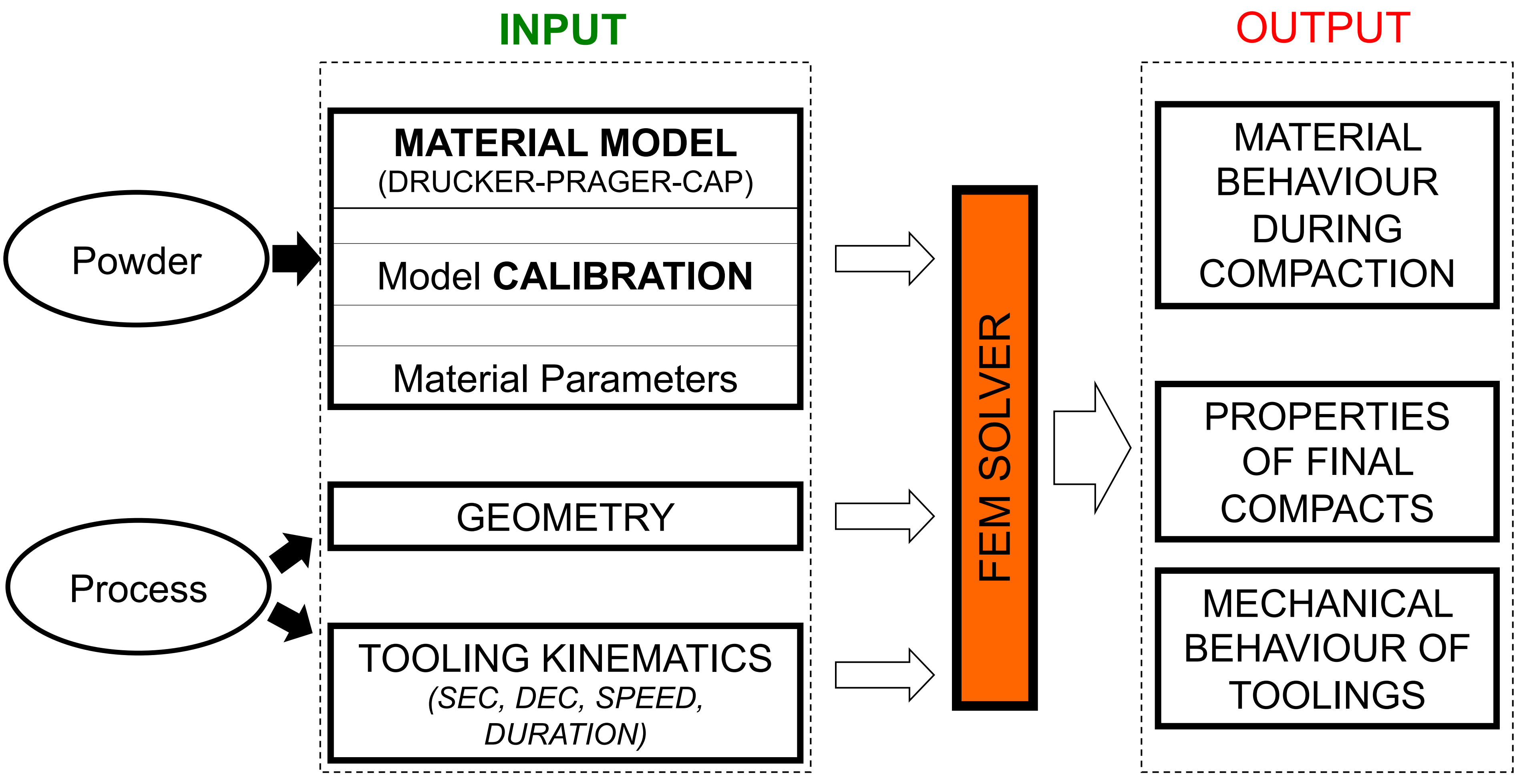
Drucker-Prager-Cap model

Drucker-Prager-Cap model:

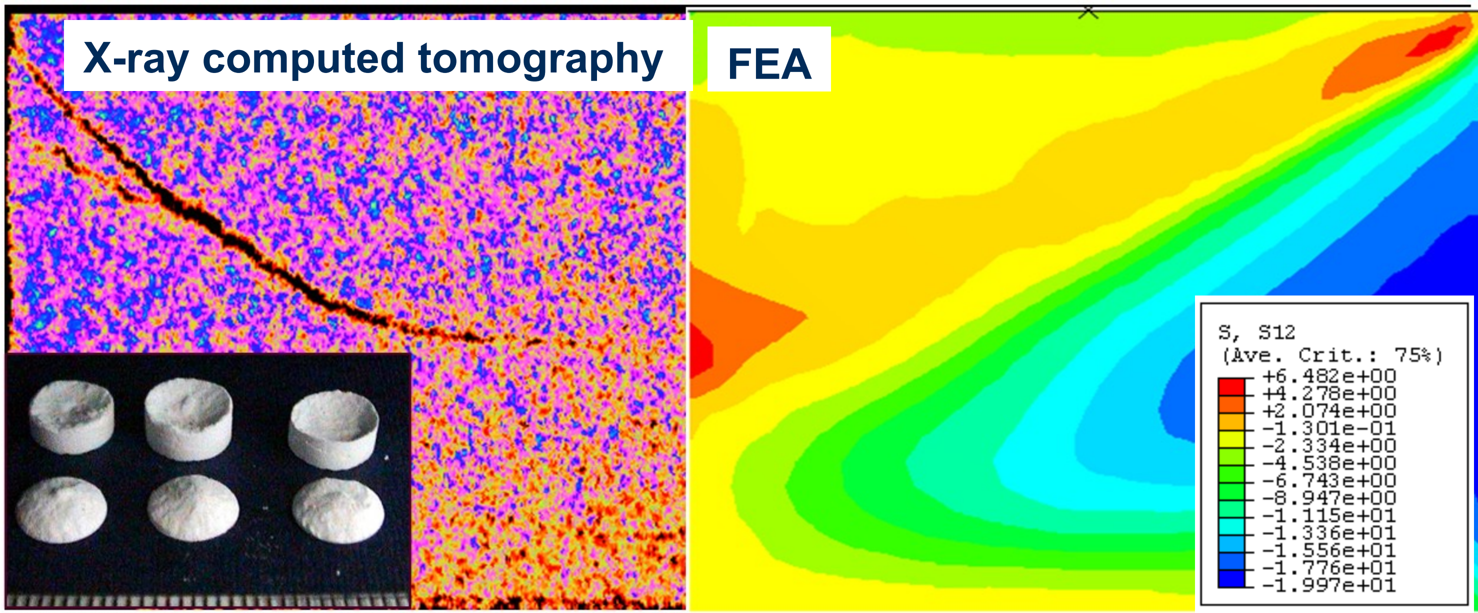
- A reasonable representation of the powder behaviour.
- Easy for numerical implementation and experimental calibration.

- Widely used for metallic and ceramic powders.
- Recently for pharmaceutical powders (Michrafy 2002; Sinka 2001, 2002, Wu et al. 2005,2008, Frenning et al. 2007).

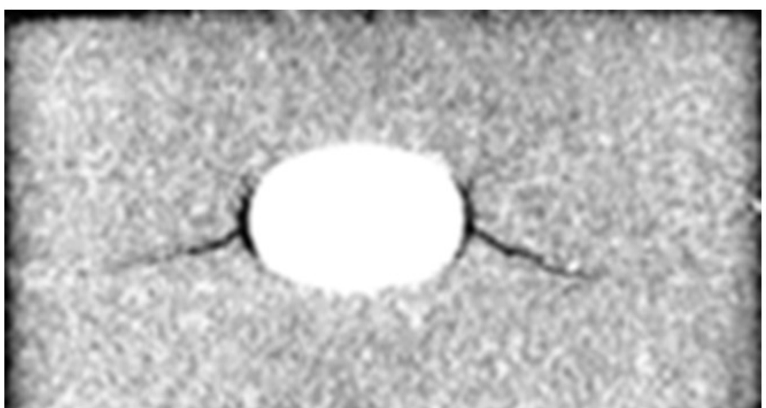
Finite Element Modelling of Powder Compaction

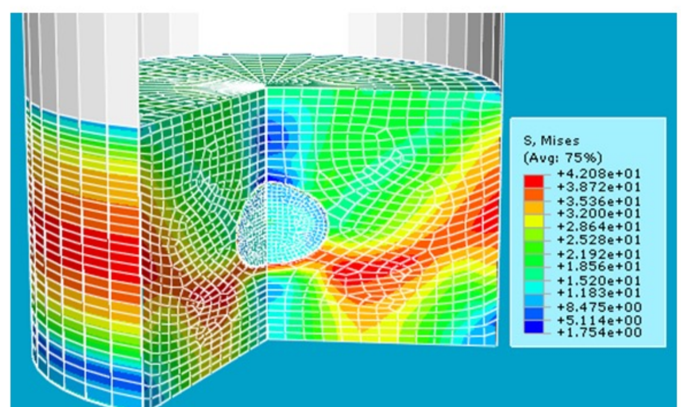


Indicating problems associated with manufacturing

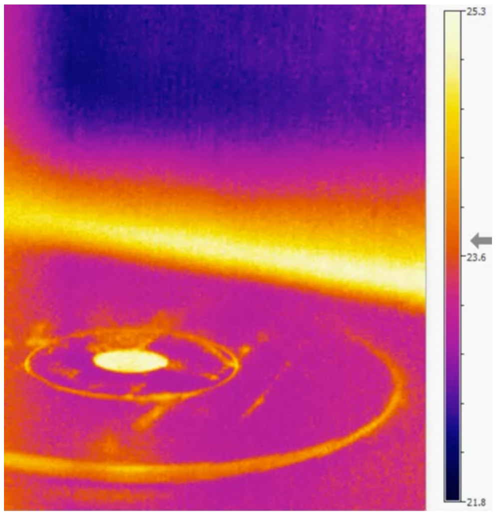


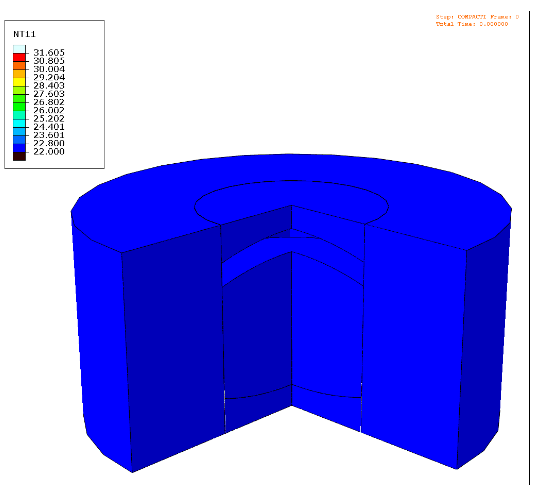
Wu C.Y., Ruddy O., Bentham A.C., Hancock B.C., Best S.M. and Elliott J.A. (2005), “Modelling the mechanical behaviour of pharmaceutical powders during compaction”. *Powder Technology*, 152(1-3):107-117

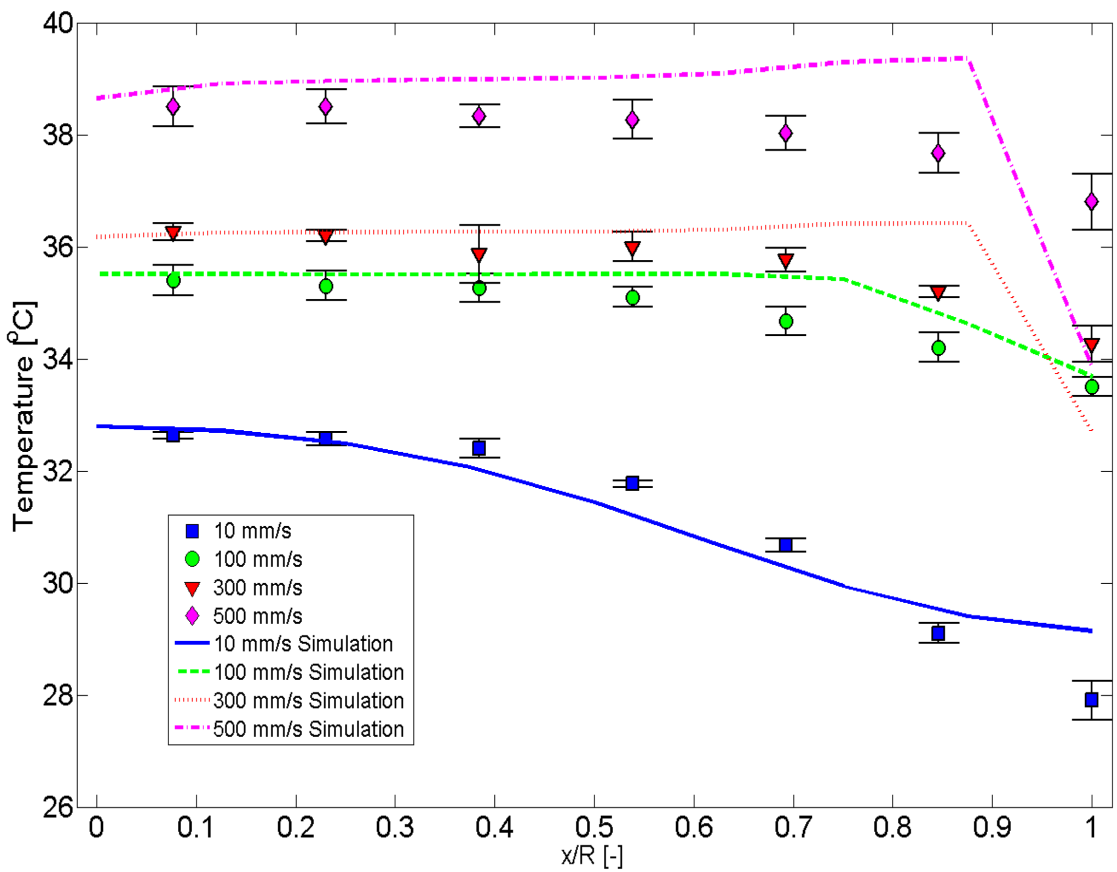




Heat Generation and temperature rise

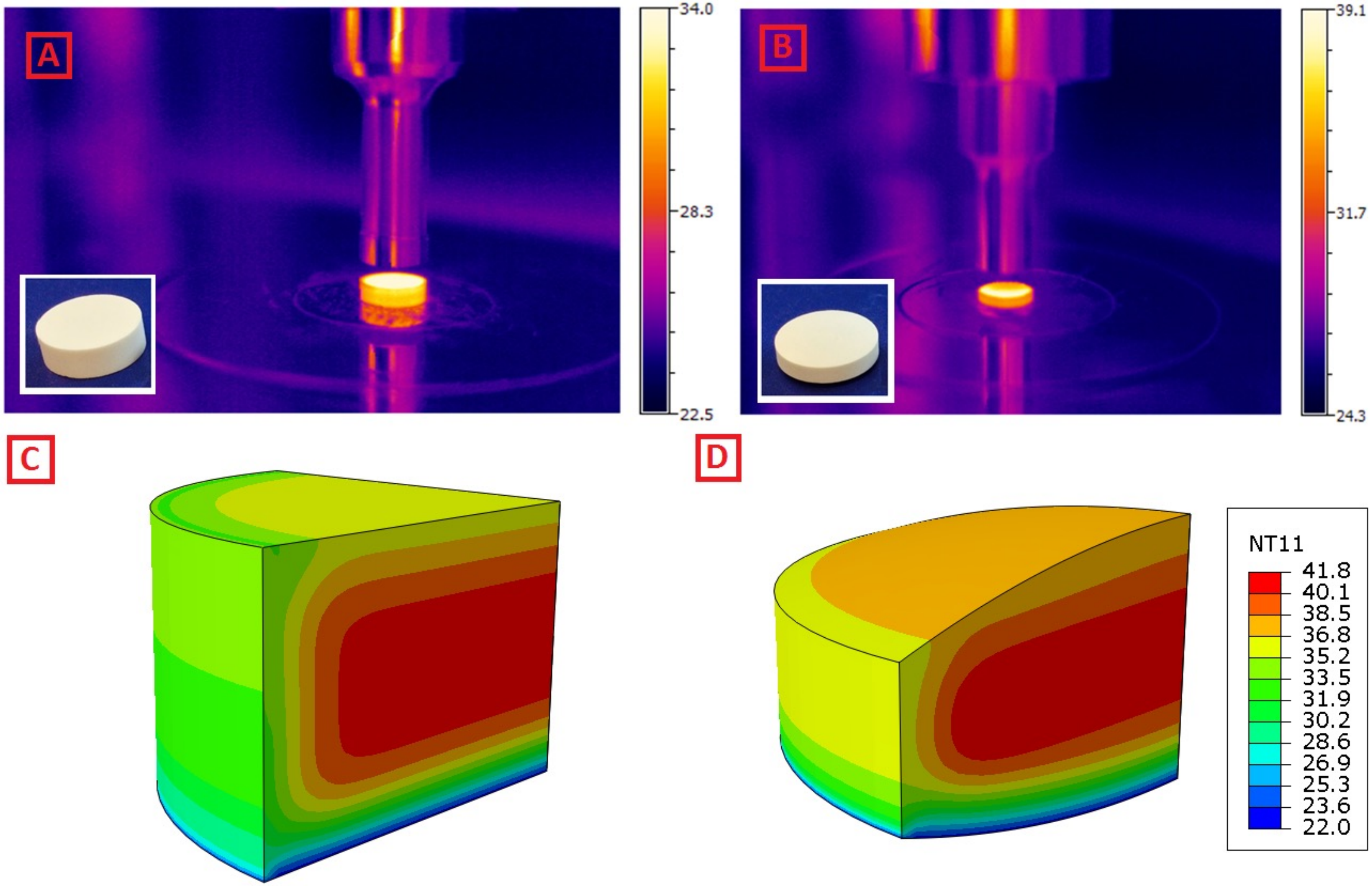






A Krok, P Garcia-Trinanes, M Peciar, CY Wu. 2016. Finite element analysis of thermomechanical behaviour of powders during tabletting. Chemical Engineering Research and Design 110, 141-151

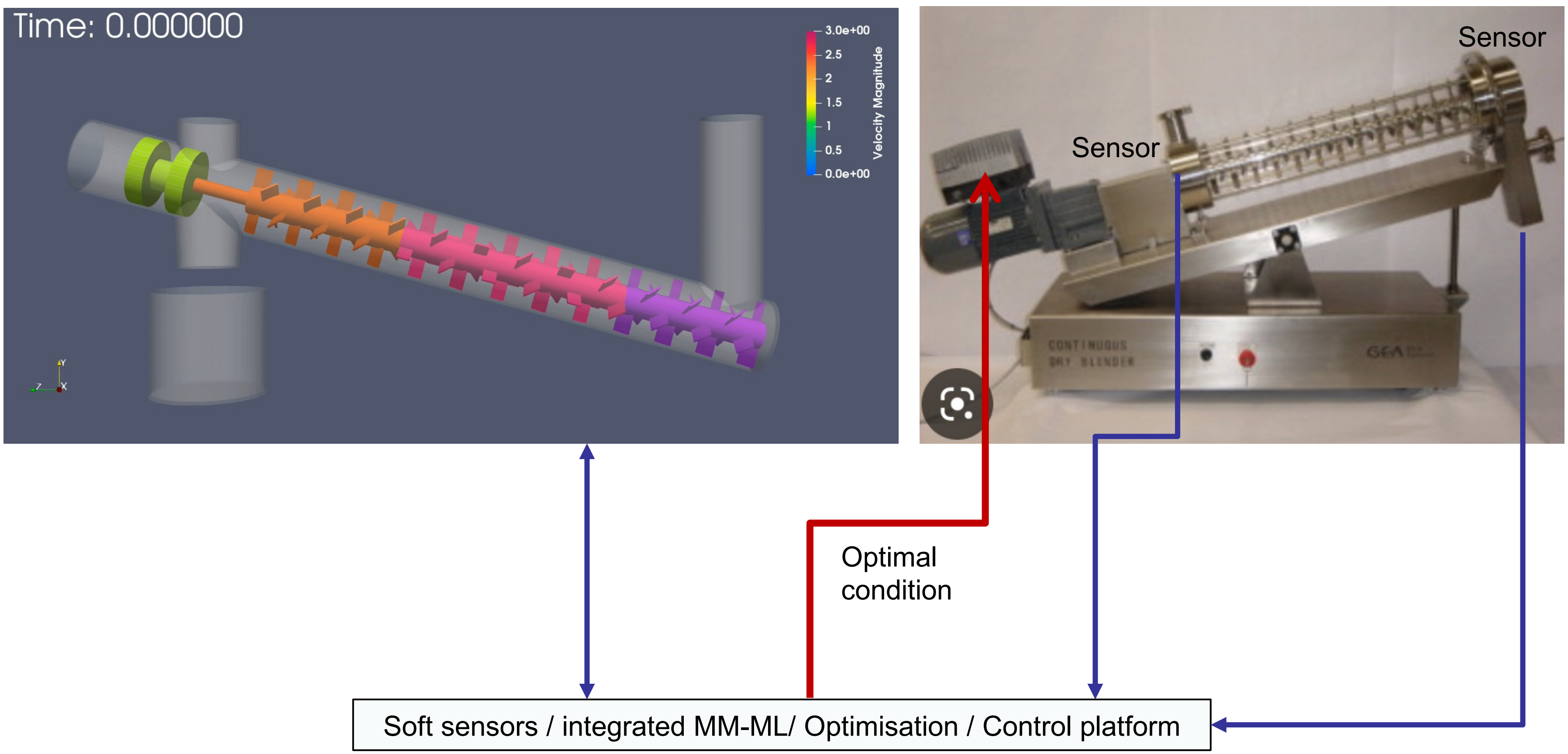
Heat Generation and temperature rise



A Krok, A Mirtic, GK Reynolds, S Schiano, R Roberts, CY Wu. 2016. An experimental investigation of temperature rise during compaction of pharmaceutical powders International journal of pharmaceutics 513 (1-2), 97-108

Towards Digital Twins

- ❑ Rapid decision-making
- ❑ High fidelity



Mechanistic modelling capabilities

Strengths:

- ❑ Accurate representation of underlying physical and chemical processes.
- ❑ Enables a deep understanding of the system's behavior and interactions.
- ❑ Well-defined parameters allow for precise predictions and control.

Limitations:

- ❑ Complexity in incorporating all variables and interactions.
- ❑ Parameter identification are often extensive.
- ❑ Difficulty in adapting to new scenarios or system changes without significant re-calibration.

Remarks & Perspectives

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- Duly consideration of different mechanical behaviours of powders at various process stages is essential in applying different computational methods.
- **Mechanistic modelling is versatile with wide applications** in mixing, conveying, powder flow, die filling and tabletting.
- Great potential to **integrate these methods with ML for pharmaceutical formulation development.**
- **Open Data** with robust data infrastructure will significantly enhance the deployment of AI in pharmaceutical product development
- Computational tools will play an important part in pharmaceutical manufacture of the future: Digital twins, Pharm 4.0, continuous manufacturing, etc.

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