Modelling high shear wet granulation in pharmaceutical production: batch to continuous

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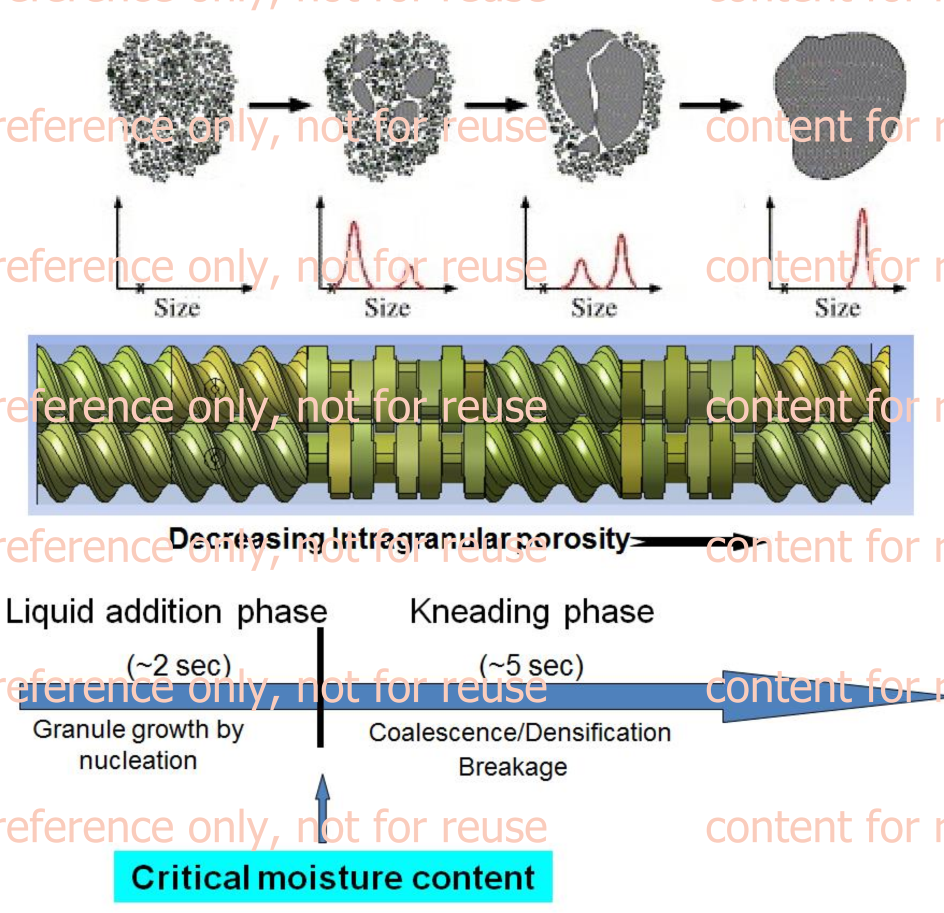
Introduction

- Continuous wet granulation performed using twin-screw granulators (TSG) is an important part of future continuous manufacturing of pharmaceutical solid dosage forms.
- First-principles and data-driven modelling approaches are important for process design, optimisation and control of critical quality parameters.
- Important interactions among various sub-processes in granulation circuits should be incorporated in the working models.
- The target of real-time control of quality requires a high degree of development and reliability in the process models.

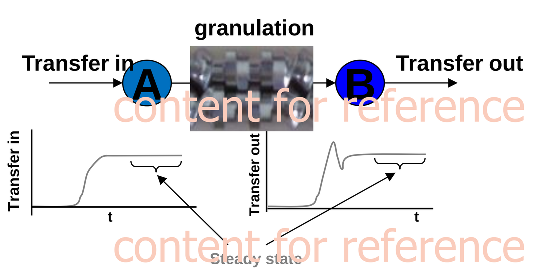
Continuous high shear wet granulator

Working principle



From dynamic system to steady-state

- Dynamics are transient
- At appropriate time-scales and conditions, granulation is in steady state



$$\frac{d[F_m]}{dt} \approx 0 \approx \frac{d[G_m]}{dt}$$

Two key implications

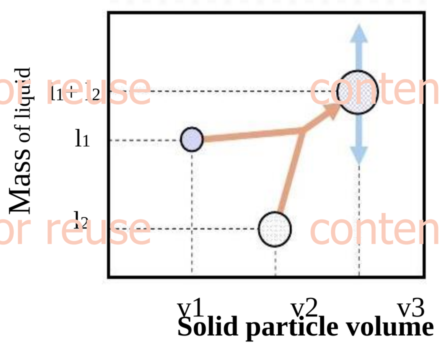
1. Fluxes are roughly constant
2. Internal concentrations are constant, solid, liquid, gas

Modelling approach

Population balance equation

Population phenomena:

+ Size growth
  + Aggregation
  + Layering, etc.
- Size reduction
  - Breakage
  - Consolidation , etc.



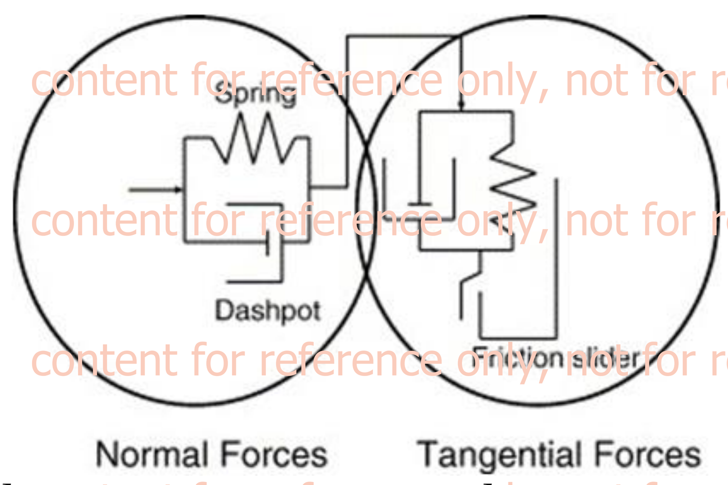
$$\frac{\partial}{\partial t}n(x,z,t)+\underbrace{\frac{\partial}{\partial x}\left[n\frac{dx}{dt}\right](x,z,t)}_{\text{Growth term}}=\underbrace{\frac{1}{2}\int_0^x\beta(x-y,y)n(x-y,z,t)n(y,z,t)dy-n(x,z,t)\int_0^\infty\beta(x,y)n(y,z,t)dy}_{\text{Aggregation term}}$$

$$\underbrace{+\int_0^\infty K_{break}(y)\zeta_{break}(y,x-y)n(y,z,t)dy-K_{break}(x)n(x,z,t)}_{\text{Breakage term}}\underbrace{-\frac{\partial}{\partial z}[\dot{Z}n(x,z,t)]}_{\text{Flux term}}$$

where, the spatial velocity in the external coordinate is defined as $\dot{Z}=\frac{dz}{dt}$

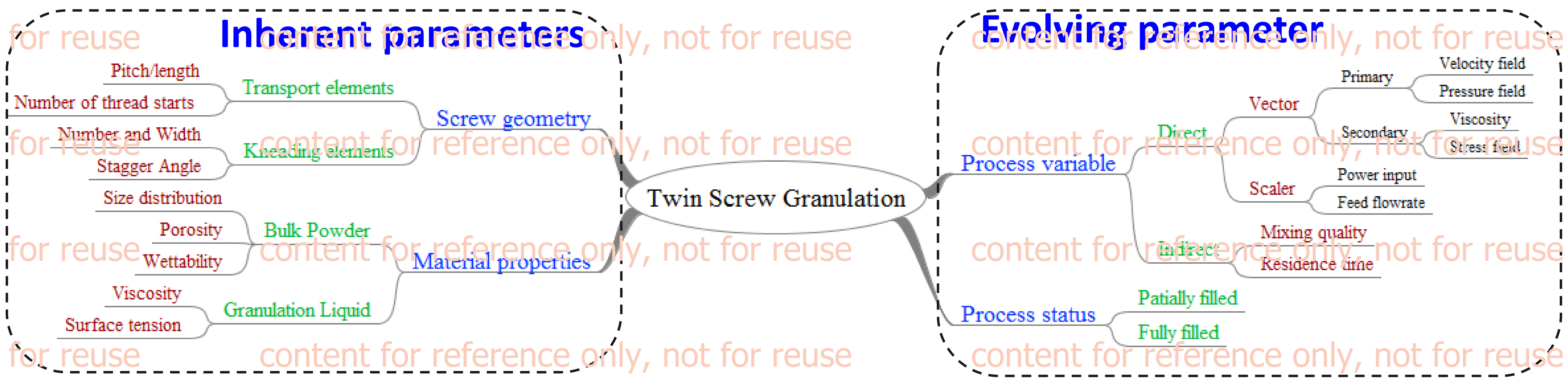
Discrete element method

The DEM approach bridges the gap between micro- and meso-scales modelling of granulation processes. The linear and angular momentum associated with each particle in the granulator is computed to give the status of the process at each stage.



$$m_i\frac{dv_i}{dt}=mg+F_p+F_w \qquad I_i\frac{d\omega_i}{dt}=M_p+M_w$$

Measurement Approach



- Detailed information about "field" variables in the screw cross-section using flow visualization techniques such as positron emission particle tracking(PEPT) in a barrel is now possible.
- 0-dimensional measurements such as torque are easy to measure, but do not provide local information required for a detailed process study.
- Higher dimensional measurements are hard-to-measure on-line but are mandatory for development of improved and more detailed process knowledge.
- Application of soft-sensing methods based on spectroscopic techniques such as NIR have shown potential , but their application needs more investigation before introduction soft-sensors for field application.

Conclusions

- Understanding granulation along the screw geometry in twin screw granulator requires higher dimensional modelling and in-process measurements providing local information. The modular structure of the twin-screw granulator lies in the center of modelling and measurement techniques applied.
- A single simple model cannot predict the complex granulation behaviour with shifting granulation regimes. Therefore, different parts of the granulation process should be described by different mechanistically based structural models.
- Although simulation substantially increases the understanding of the processes involved, not all process steps of granulation process can be modelled due to high computational burden.
- The main challenge in the area of TSG measurements exists in the development of new measurement techniques which are able to measure the fundamental granule properties, preferably in situ.
- The available modelling methods show performance limitations as the dimensions of the model increase. This motivates the need to develop more reliable and computationally efficient numerical methods to provide solutions which can be applied in future for online model based control.

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