Modeling and validation of continuous high shear wet granulation and continuous extrusion processes

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GOALS AND DELIVERABLES

Granulation:

- Develop a 2D compartmental population balance model (PBM) for dry binder granulation process in a continuous high shear granulator
- Show that the model is able to reproduce experimental observations by comparing with data acquired for a Lodige CM5 granulator

Extrusion:

- Develop a model for twin screw extrusion process using computational fluid dynamics (CFD)
- Show that this model is capable of predicting the experimental trends in the process

DESCRIPTION

- The traditionally batch pharmaceutical industries have been shifting towards continuous manufacturing recently
- Mathematical models can be good tools to help outline design spaces of the equipment and processes

Granulation:

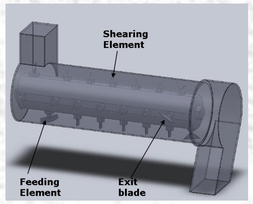
- Powdered particles aggregate in the presence of a liquid binder to from larger granules in wet granulation
- Improves flowability, compressibility and also reduces dusting and segregation
- Dry binder addition - liquid added in the granulator dissolves the binder

Extrusion:

- Hot melt extrusion - powdered materials are passed through a heated extruder and forced through a die
- Helps to stabilize the API, modulate drug release and also increase the drug's dissolution rate

EQUIPMENT

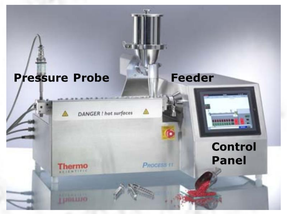
Lodige CM5 is a high shear granulator:



- High speed rotating element enclosed within a horizontal cylindrical casing
- Mixing shaft - cylindrical with three different blade elements
- Operates at a speed of 1000 – 4000 rpm and between 10 - 40kg/hr throughput

ThermoScientific Pharma 11 Twin Screw Extruder:

- Two parallel co-rotating 11mm screws housed in a extruder barrel
- Modular design- flexibility with screw configuration and temperature control
- Can operate between throughput range of 20 g/hr to 2.5 kg/hr



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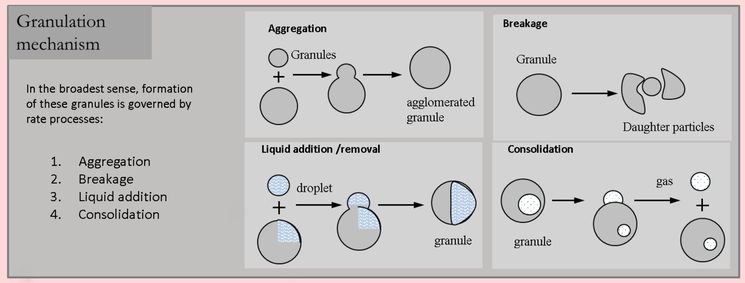
MODEL DEVELOPMENT

Granulation:



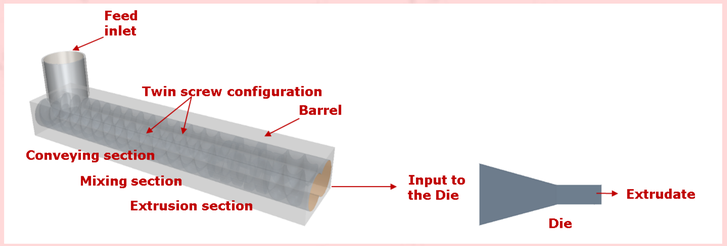
- PBM tracks changes in particle properties over time
- 2D compartmental PBM:
  - ❖ Tracks 2 solids (API & Excipient) with lumped liquid and gas
  - ❖ Rate processes: Aggregation, breakage, liquid addition and consolidation

$$\frac{dF(S_1,S_2,z,t)}{dt} = R_{agg}(S_1,S_2,z,t) + R_{break}(S_1,S_2,z,t) + \dot{F}_{in}(S_1,S_2,z,t) - \dot{F}_{out}(S_1,S_2,z,t)$$

- Composition dependent semi mechanistic aggregation kernel [1], [2]
- Binder dissolution model [3]

Extrusion:

- In a twin screw extruder materials undergo shearing between the rotating screws and the heated wall of the barrel as they are conveyed
- CFD model for the process will be built using Star CCM+



Process Parameters & Operational conditions	Output variables
Screw rotational speed	Material temperature
Barrel temperature	Flow rate of extrudate
Material throughput	Pressure drop across the Die
Formulation (polymer to drug ratio)	Screw temperature
Screw config. (pitch and Helix angle)	Material filling ratio
RTD of the polymer solution	

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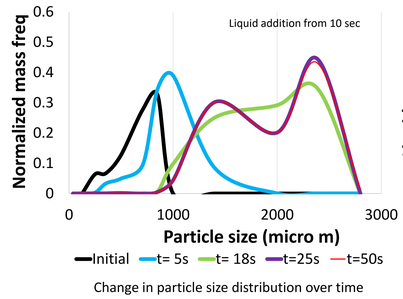
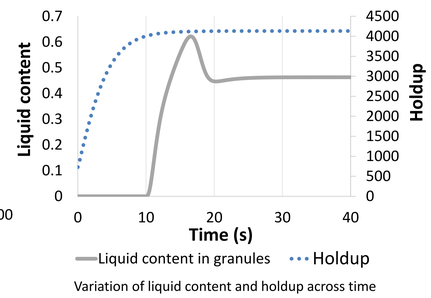
GRANULATION: PRELIMINARY RESULTS



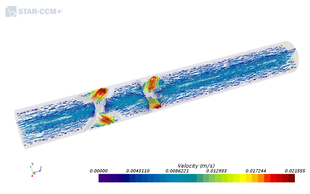
Change in particle size distribution over time



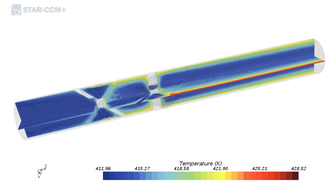
Variation of liquid content and holdup across time

- Particle size increases for up to 10 seconds after liquid addition and distribution profile changes from uni-modal to bi-modal
- Granulator holdup profile shows that steady state is reached around 15 seconds
- Plot shows the liquid content of 1.6 mm sized granules

EXTRUDER: EXPECTED RESULTS



The velocity profile of polystyrene



Temperature profile of polystyrene in a static mixer

- Shows that there is an increase in velocity of the fluid at the blades
- It can be seen that the temperature of the fluid is higher closer to the walls

Conclusion

1. The granulator model is able to predict granule size distribution and liquid content in its preliminary stage of development

Future Work

1. Parameter estimation and sensitivity studies for the granulator model
2. Model will be validated against experimental data
3. A CFD model will be developed for the twin screw extruder

REFERENCES

1. A. Chaudhury, H. Wu, M. Khan, R. Ramachandran, A mechanistic population balance model for granulation processes: Effect of process and formulation parameters, 2014, Chemical Engineering Science, 107, 76-92
2. T. Matsoukas, T. Kim, K. Lee, Bicomponent aggregation with composition-dependent rates and the approach to well-mixed state, Chemical Engineering Science 64 (4) (2009) 787–799.
3. A. Chaturbedi, C. K. Bandi, , D. Reddy, P. Pandey, A. Narang, D. Bindra, L. Tao, J. Zhao, J. Li, M. Hussain, R. Ramachandran, Compartment Based Population Balance Model Development of a High Shear Wet Granulation Process via Dry & Wet Binder Addition, Chemical Engineering Research and Design (submitted)