Challenges in solids flow and powder handling in pharmaceutical manufacturing

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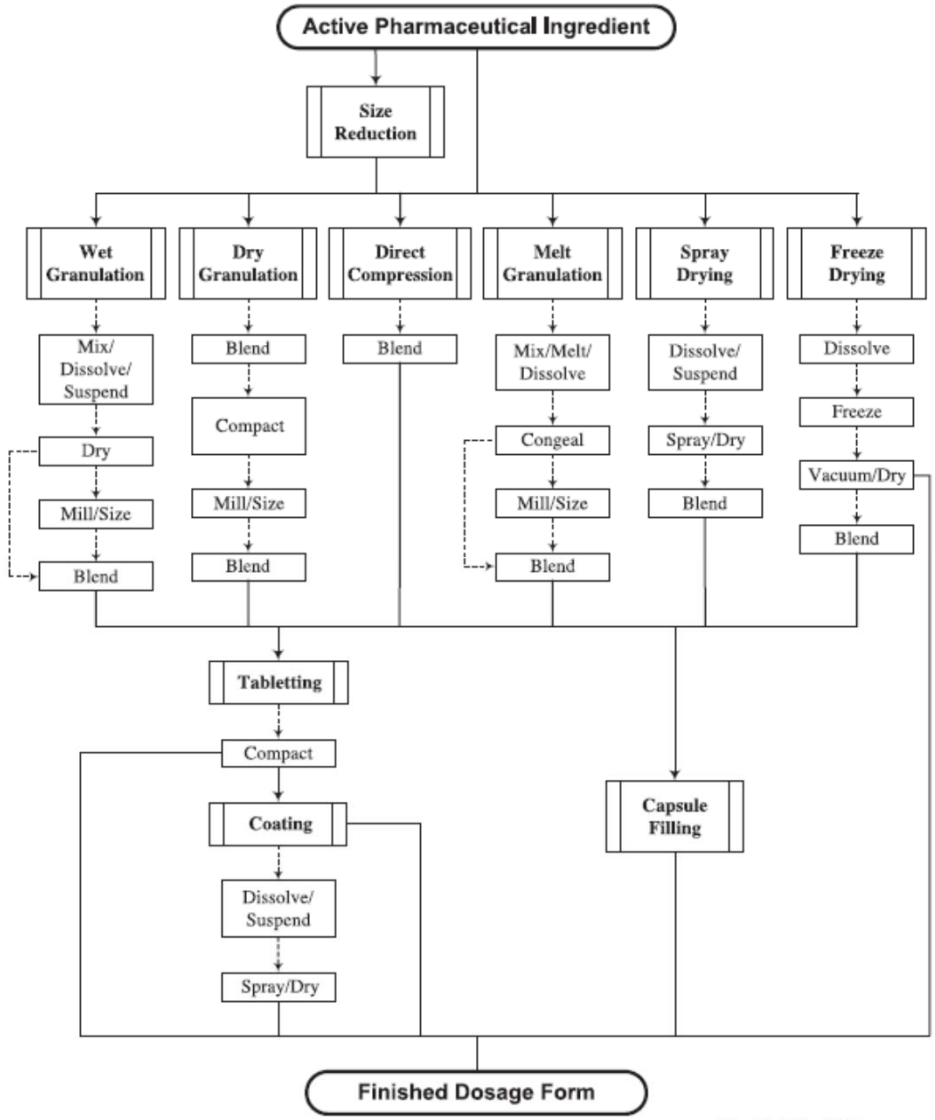
Background and Perspective

- Center for Material Science and Engineering (CMSE) at MSD is a comprehensive material science laboratory
- Supports development, troubleshooting and optimization of new and **in-line products and processes**
- Powder flow and solids handling– a challenging area in pharmaceutical manufacturing – with areas for further research
  - **Segregation (de-mixing)**
  - **Process equipment design**
  - **Characterization**
  - **Modeling flow of powders**
  - **Electrostatics**

Powder flow and solids handling in pharmaceutical operations

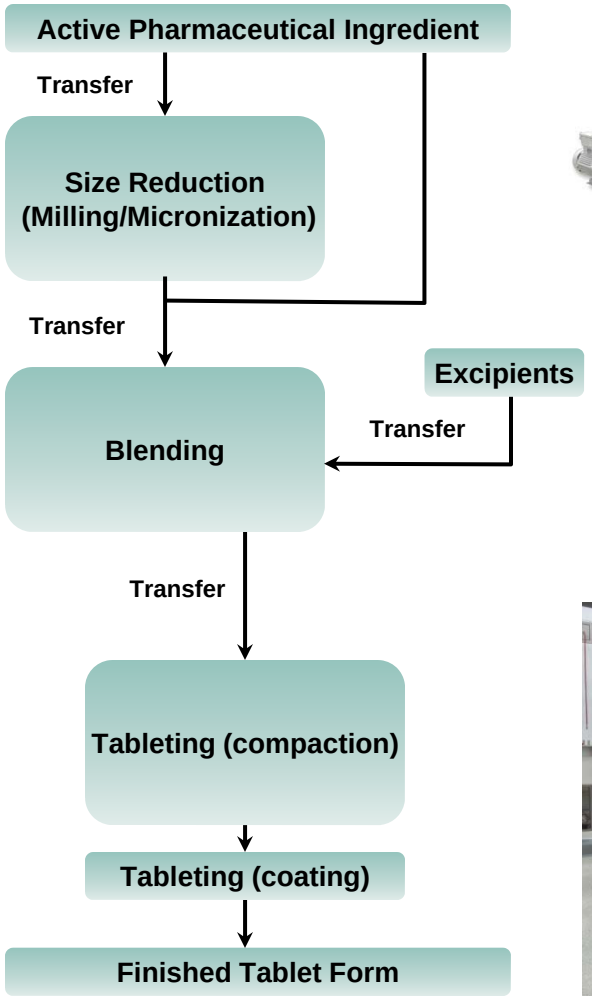
- Relevant to all solid pharmaceutical dosage forms
- Consistent flow, uniformity critical for processability and product attributes
- **Development:** Formulation “optimization”
- **Filed commercial products:** Formulation, material attributes constrained.
- Manufacturing, regulatory, economic considerations



from G. Zhang et. al., Adv. Drug. Deliv. Rev. (2004)

Powder flow and solids handling in pharmaceutical operations (cont.)

Direct compression solid dosage form



- **Size reduction**
  - Solids transfer
  - Electrostatics
- **Blending**
  - Poor blending/dispersion of cohesive powder
  - Solids transfer to/from blender
  - Electrostatics
- **Tableting**
  - Segregation (de-mixing) during transfer
  - Die fill: Uniformity/weight control

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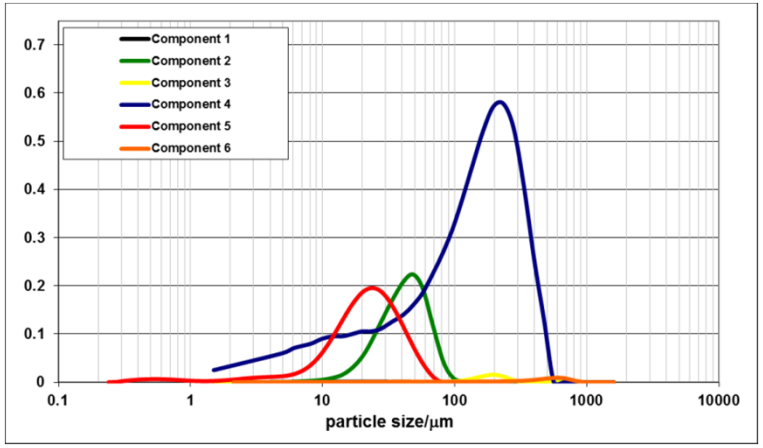
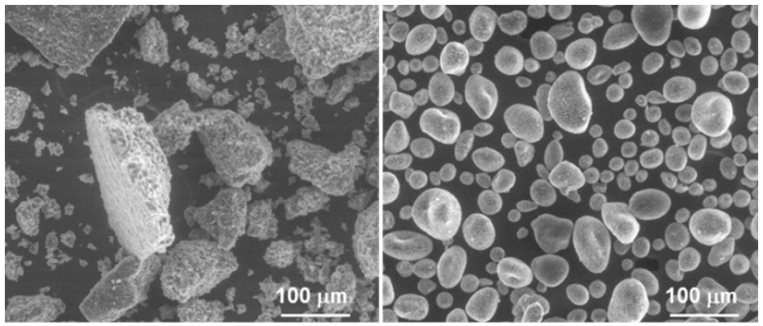
I. Segregation (de-mixing) of multicomponent blends during powder flow

- Pharmaceutical solid dosage forms - multiple components to achieve desired quality and function

- ✓ ***Processability***
- ✓ ***Potency***
- ✓ ***Bioavailability***
- ✓ ***Stability***
- ✓ ***Elegance***

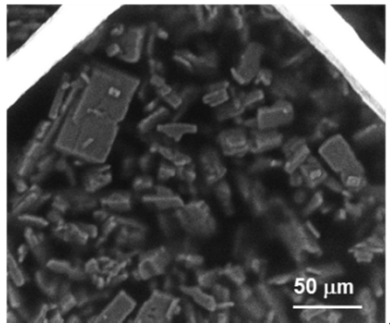


- Wide range of size, density, morphology, and cohesivity



- Segregation (de-mixing) during flow critical to avoid

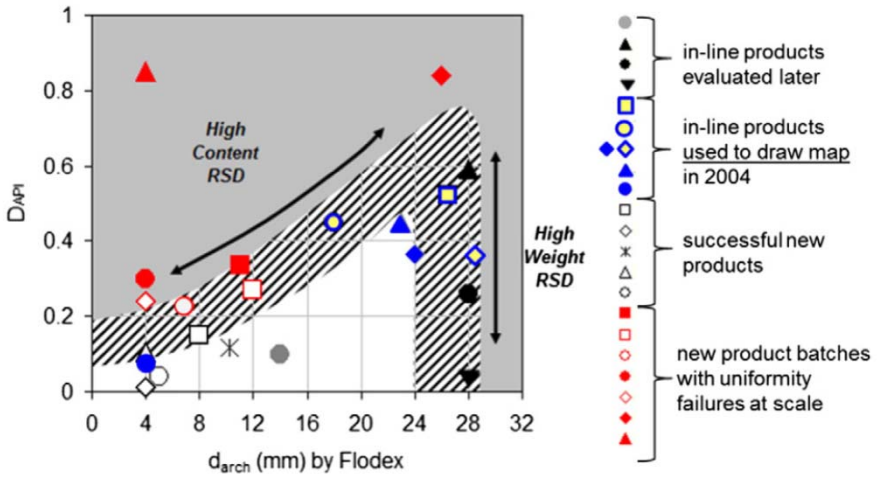
- **Challenges**
  - Highly dependent on process and conveying specifics
  - Highly dependent on process scale
  - “Stylized” small scale testing a poor indicator



I. Segregation (de-mixing) of multicomponent blends during powder flow (cont.)

- Correlative, empirical approaches employed
- One approach – regime map for assessing die fill risk (right)
- Limitations
  - Requires mfg experience/data (~10 years)
  - Non-trivial to translate to different process equipment
  - Conservative: maximum segregation potential

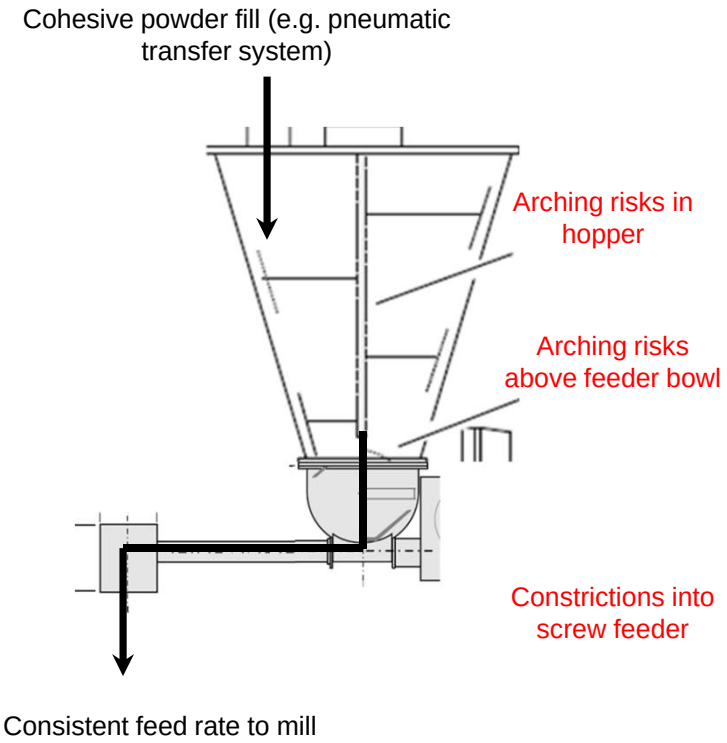
from M. Gentzler et. al. Powder Technology (2015)



II. Design/assessment of powder handling equipment

- Most require flow of cohesive powders
- Material properties, process equipment, conveyance method
- Other phenomena (air flow, electrostatics) to consider
- Predicting and maintaining stable powder flow through realistic manufacturing processes a challenge
- **Examples:**
  - Powder hold-up in hoppers
  - Stable flow into downstream/continuous operations (see right)
  - Pneumatic conveyance of cohesive powders

Hypothetical flow risks of KTron™ loss-in-weight feeder setup



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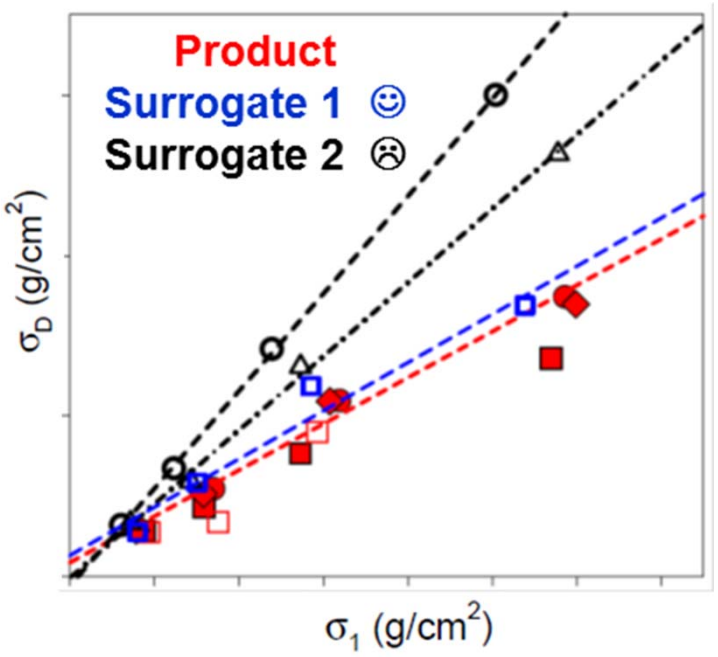
II. Design/assessment of powder handling equipment (cont.)

- **Challenges:**
- Complicated geometries, conveyance systems, and flow regimes
- Cost, time and design constraints
- Modeling approaches limited

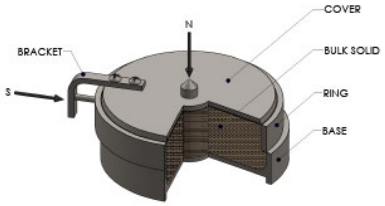
- **Typical approach:**
  - Retrospective analysis
  - Material/process characterization
  - Risk assessment
  - Design modifications (or flexibility)
  - If required, trials (component *or* powder surrogate)
  - Success….or revisit….



- The (hopeful) future – modeling of cohesive powder systems….

III. Experimental characterization of fine cohesive powders

- Standard “bulk” characterization techniques typically used provide limited information

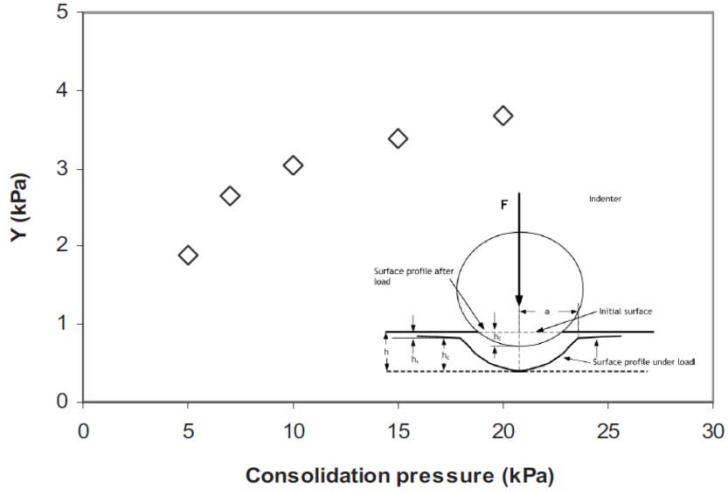


- Flow characterization of weakly consolidated powders challenging

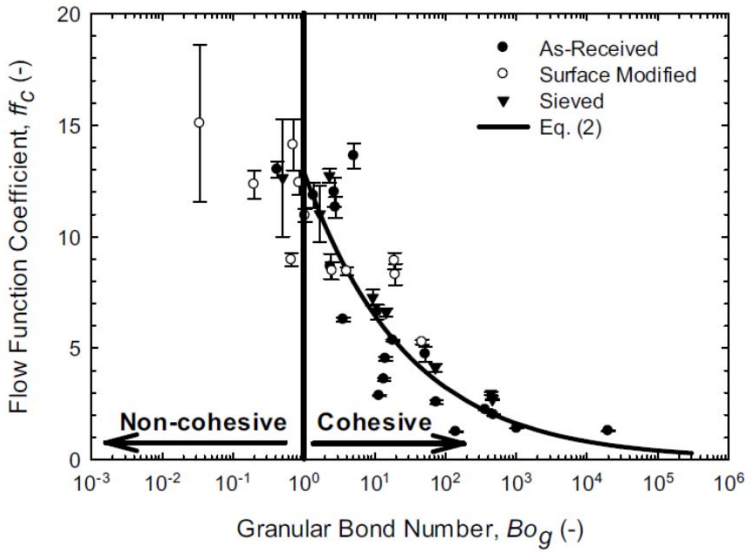
- Semi-empirical correlations to flow behavior

- Characterization at particle contacts difficult
  - Surface forces, roughness, local compliance

from Hassanpour et. al. Part. Part. Syst Charact 2007



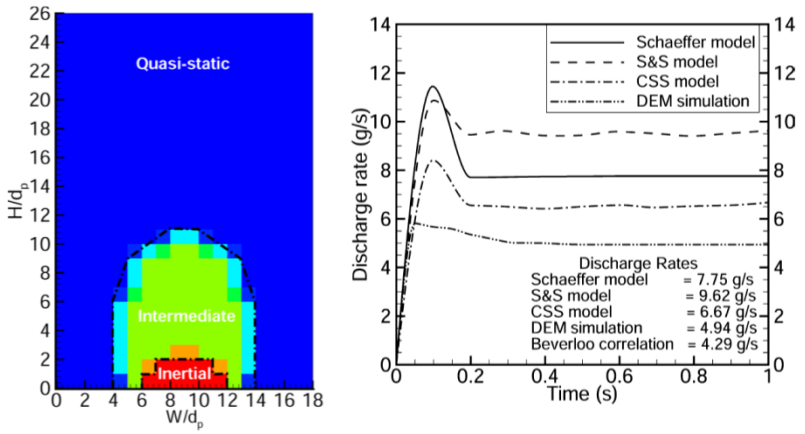
from Capece et. al. Int. J. Pharmaceutics 2016



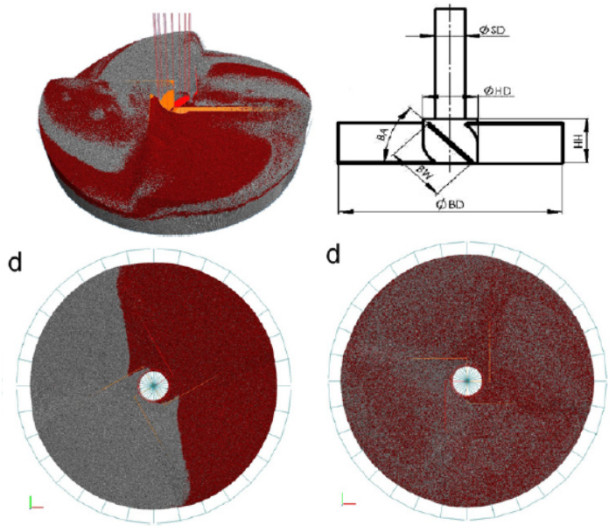
IV. Challenges in modeling flow of powders

- Complexity and lack of comprehensive constitutive models makes modeling of powder flow challenging
- Approaches
  - Jenike hopper analyses
  - Stress analyses including pressure (air) gradients [*e.g. Johanson 2004*]
  - Continuum modeling methods (top right)
  - Discrete element methods (DEM or coupled CFD-DEM) (bottom right)

from V. Vidyapati et. al. Ind. Eng. Chemistry Res. 2013



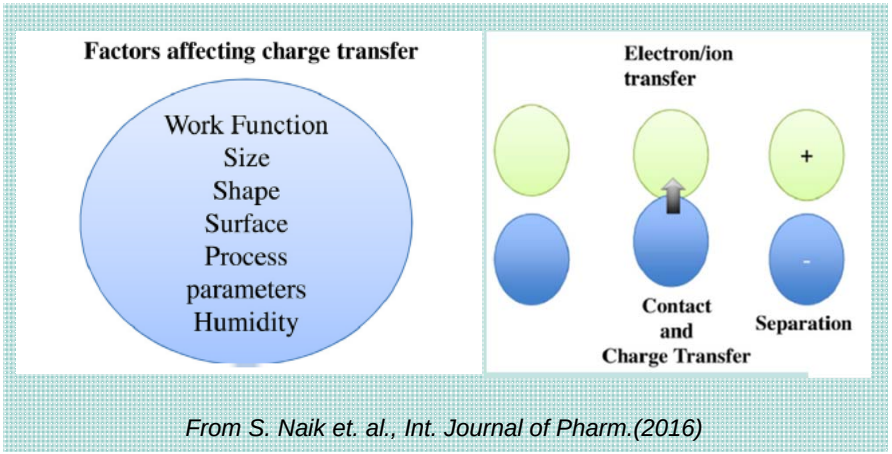
from Radeke et. al. Chem. Eng. Sci. 2010



V: Impact of electrostatic charging on powder flow and agglomeration

- Electrostatic charging of flowing powders can impact product quality and processing
  - Contact electrification
  - Triboelectric charging
- Challenging to characterize and define mechanism
- Standard techniques provided limited insight
- Ideally measurement of charge *distribution*

Poor dispersion (agglomerates) due to triboelectric charging



From S. Naik et. al., Int. Journal of Pharm.(2016)

Conclusions

- Powder flow and solids handling a challenging area in pharmaceutical manufacturing

  - **Segregation (de-mixing)**
  - **Design/assessment of process equipment**
  - **Experimental characterization**
  - **Modeling flow of powders**
  - **Electrostatics during processing**

- Work remains to advance both experimental and modeling approaches to improve our ability to describe and predict flow behavior of cohesive pharmaceutical powders

Acknowledgements and References

- Acknowledgements
  - Michael Gentzler, CMSE members

- References

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