Design and manufacture of Delivery forms for Small Particles

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Outline

• Background
• Using modeling and simulation
  – Particle modification
  – Multiscale modeling of compaction processes
  – Multiscale modeling of wet granulation
• Some concluding comments
Some example applications

• Micronized poorly soluble drugs
• Dry powder aerosol delivery of drugs to the lungs
• Catalyst particles in chemical processing
• Detergent granules
Micronized drugs

- Emend (aprepitant, Merck)
  - antinausea
- Tricor (fenofibrate, Abbott)
  - cholesterol lowering
- Rapamune (sirolimus, Wyeth)
  - immunosuppressant
- Megace ES (megestrol acetate, Par)
  - anorexia

Van Eerdenbrugh et al., Molecular Pharmaceutics 2010
Dry powder aerosol delivery

- 2 to 5 \( \mu m \) particles preferred for delivery to the lung
- Commonly delivered on larger lactose particles via inhalers
- Dispersion of the powder aerosol is often poor

*Drug Delivery to the Lung*, Zanen and Laube
Packaging small particles in dry delivery forms

<table>
<thead>
<tr>
<th>Reason</th>
<th>Typical Application</th>
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<tbody>
<tr>
<td>To produce useful structural forms</td>
<td>powder metallurgy</td>
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<tr>
<td>To provide a defined quantity for dispensing and metering</td>
<td>agricultural chemical granules, pharmaceutical tablets</td>
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<td>To eliminate dust handling hazards or losses</td>
<td>briquetting of waste fines</td>
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<td>To improve product appearance</td>
<td>food products</td>
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<tr>
<td>To reduce caking and lump formation</td>
<td>fertilisers</td>
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<tr>
<td>To improve flow properties for further processing</td>
<td>pharmaceuticals, ceramics</td>
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<tr>
<td>To increase bulk density for storage</td>
<td>detergents</td>
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<tr>
<td>To control dispersion and solubility</td>
<td>instant food products</td>
</tr>
<tr>
<td>To control porosity and surface-to-volume ratio</td>
<td>catalyst supports</td>
</tr>
<tr>
<td>To improve permeability for further processing</td>
<td>ore smelting</td>
</tr>
<tr>
<td>To create non-segregating blends of powder ingredients</td>
<td>ore smelting, agricultural chemicals, pharmaceuticals</td>
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Approaches to creating delivery forms
Methodology

Research: Learning Pathway

Change in Process or Formulation → Change in Rate Processes → Change in evolution of structure

Selection of Suitable Process and Formulation ← Control of Rate Processes ← Required Structure

End Goal: Product & Process Design

Final Granule Properties

Mike Hounslow, Sheffield University
Barriers to progress

- Quantitative understanding of how microstructure is developed during processing of complex multiphase delivery forms is lacking.
- There is an absence of predictive and quantitative scaling rules between macroscopic properties and single particle properties.
- Process design models that track multidimensional distributions of properties are still relatively rare.
- Carefully designed and executed experiments at laboratory scale and in test bed pilot plants to validate the design models are generally absent.
- Robust on-line techniques for measuring microstructure and distributions of important properties are lacking.
- Current equipment designs are based on heuristics, rather than in depth process understanding and batch process equipment is not easily converted to continuous processing.

These comments are especially true when the primary particle size is less than 10µm.
Fine powders behave differently!

Fine powder (5µm)

Coarse powder (70µm)

Talay, Emady, Litster. Purdue University
An Engineering Design Approach
Multiscale Approaches in Compaction Modeling

Cuitino et al., Rutgers University, CSOPS
Example 1: designer micron sized API particles

- Dispersible -5 µm
- 95% API particles

Delivery vehicles
Particle Coatings for Modification of Powder Properties

Aluminum particles for adhesion force study.
Left: uncoated aluminum (UC1)
Center: with hydrophilic nanosilica coating (CL1)
Right: with hydrophobic nanosilica coating (CB1)

Sparse nanosilica coating acts to prevent close approach of aluminum to steel. Coating sparse composition does not affect adhesion, it simply acts as a spacer.

S. Beaudoin, D. Balachandran (Purdue); R. Dave, L. Jallo (NJIT)
Example 2: Design models for roll compaction

Sinha, Muliadi, Zarate, Litster, Wassgren. Purdue University

Decreasing lubrication
Strategy: a multi-scale approach

- Single particle property measurements (adhesion, Young’s modulus, etc.)
- Mixing algorithm via MP-FEM, computes mechanical properties of pharmaceutical mixtures.
- FEM model simulates the roll compaction process.
- Ribbon density prediction via powder visco-elastic properties
- Model validation through measurements of ribbon density (NIR spectroscopy), and normal and shear forces (via “instrumented” roller).
Particle properties to bulk compaction behavior

- DEM is used to transfer the initial positions and contact neighbor information to Abaqus/Explicit for MPFEM simulations.

- True particle deformations can be seen after compaction is applied.

- *Ideal elasto-plastic material properties are used in current model.*
  - *Ultimately, experimentally measured properties will be used.*
Particle properties to bulk compaction behavior

- Simulation results can be used to determine yield surfaces and elastic properties for binary pharmaceutical mixtures.
  - The influence of concentration, particle packing structure, and particle size will be studied.
  - Particle properties will be measured experimentally via Atomic Force Microscopy and nano-indentation.

Stages in a MPFEM simulation.
Example 3: Combined DEM/PBM modeling of granulation

Freireich, Li, Wassgren, Litster; Purdue University
DEM simulation of a paddle mixer

Freireich, Li et al.; posters 15,16
Residence time data from DEM

Spray Compartment Residence Time Distribution, $E_s(t_s) (s^{-1})$

Bed Compartment Residence Time Distribution, $E_p(t_p) (s^{-1})$

$E_s(t_s)$ and $E_p(t_p)$ are shown for spray and bed compartments, respectively. The distributions are compared to compartment models.

Freireich, Li et al.; posters 15,16
Compartment model for PB

Freireich, Li et al.; posters 15,16
Concluding comments

• End performance of small particles depends critically on how they are “packaged”

• Many challenges remain to predict product structure and performance from formulation properties and process variables

• Multiscale approaches to both characterization and modeling hold promise for better engineered products