Excipient Mechanical Properties and Measurements

Selection of Properties

- Commonly reported in the literature and/or used in models and correlations
- Grouped into one of three categories
  - particle
  - powder
  - compact

Sample and Measurement Reports

- Sample report includes
  - sample ID, excipient type, manufacturer, product, lot number
- Measurement report includes
  - tester's name, date of test, test method, equipment make and model, humidity and temperature, SOP, and measurements
  - @Purdue: humidity and temperature not controlled

Particle Properties

- Particle size distribution
- Apparent density
- (Envelope density)
- (Shape and roughness)
- (Adhesion / cohesion)
- (Elastic modulus, Poisson's ratio, …)

Examples of the Importance of Particle Size Distribution

- Powder porosity
- Content uniformity
- Blending / segregation
- Dissolution
- Liquid drop penetration (e.g., wet granulation)
- Flowability
- Geldart fluidization
- Compact strength

Particle Size Distribution

- Multiple size definitions
  - maximum chord diameter, equivalent sphere volume diameter, equivalent sphere volume-to-surface area diameter, equivalent circle area diameter, sieve diameter, Stokes diameter, …
  - Most useful definition depends on usage
- Distribution of sizes presented in terms of
  - frequency distribution
  - cumulative distribution
  - can be by number, by surface area, by volume, or by mass

Particle Size Distribution…

- Laser diffraction is the most common measurement technique used in the pharmaceutical industry
  - wet or dry
  - equivalent sphere volume diameter
  - frequency distribution by volume
  - @Purdue (dry): Malvern Mastersizer 2000E with Sciroco M dry dispersion unit
  - @Purdue (wet): Malvern Mastersizer 2000

Particle Size Distribution…

- Input into the database for each sample
  - (size bin_i, % of total particle volume in this size bin_i)
- Output from the database
  - plots and tables
    - frequency and cumulative distributions
  - derived quantities
    - x_{10}, x_{50}, x_{90}, $x_{3,2}$, $x_{4,3}$, span

Examples of the Importance of Apparent Density

- Segregation
- Geldart fluidization
- Flowability
- Bulk density

Apparent Density

- Gas (He) pycnometry
  - most common apparent density measurement technique
  - apparent density = true density if no internal pores are present
  - @Purdue: Micromeritics Accupyc II 1340
- Input to and output from the database
  - apparent density value

Powder Properties

- Poured and tapped bulk densities
- Flowability
- (Compressibility)
- (Specific surface area)
- (Permeability)
- (Drucker-Prager Cap parameters)

Examples of the Importance of Poured and Tapped Bulk Density

- Flowability
- Permeability, fluidization
- Filling efficiency
- Dosage form size

Poured and Tapped Bulk Densities

- Purdue measurements
  - poured bulk density: determined from a mass of material poured into a graduated cylinder (use FT4 rheometer instead?)
  - tapped bulk density: Varian Tap Density Tester
- Often used to qualitatively characterize a powder's flowability using the following derived quantities
  - Hausner ratio (HR) = $\rho_{tapped}/\rangle_{poured}$
  - Carr's compressibility index = 1 – 1/HR
  - larger HR (larger compressibility) implies worse flow

Poured and Tapped Bulk Densities…

- Input into the database for each sample
  - poured or tapped bulk density
  - one or both can be provided
- Output from the database
  - poured or tapped bulk density
  - Hausner ratio and Carr’s compressibility index (if both poured and tapped bulk density are provided simultaneously)

“Flowability”

- Flowability is a measure of a powder’s tendency to flow
- Important for any situation involving flow
  - e.g., blending, granulation, die filling, transport, …
- Many definitions proposed
  - Hausner ratio and Carr’s compressibility index
  - avalanche frequency, flow through an orifice, …
  - flow function (from shear cell measurements)
- To date, only the powder flow function is useful for quantitative design

Powder Flow Function

- Found using a shear cell, e.g.,
  - Schulze shear cell
  - Freeman FT4 rheometer shear cell
  - Jenike shear cell
- Measurement consists of
  - failure shear stress for an applied normal stress for a powder bed prepared at several pre-shear normal stresses (or bulk densities)
  - referred to as a “yield locus”
- @Purdue: Schulze Shear Tester RST-XS and Freeman FT4 rheometer

Powder Flow Function…

- From the yield locus, can determine
  - powder angle of internal friction
  - powder effective angle of internal friction
  - powder bulk cohesion
- From several yield loci, can obtain
  - powder kinematic friction angle
  - powder flow function (unconfined yield strength as a function of major consolidation stress)
  - powder flow factor (inverse slope of the powder flow function, usually reported for a specific consolidation stress)
    - the larger the flow factor, the better the flow

Powder Flow Function…

- Input into the database for each sample
  - (pre-shear normal stress$_i$, pre-shear shear stress$_i$; normal stress$_j$, yield shear stress$_j$)
  - (consolidation stress$_i$; bulk density$_i$, effective angle of internal friction$_i$, powder flow factor$_i$, bulk cohesion$_i$)
  - powder flow function (consolidation stress$_i$, unconfined yield strength$_i$)
- Output from the database
  - plots and tables for
    - (pre-shear normal stress$_i$, pre-shear shear stress$_i$; normal stress$_j$, yield shear stress$_j$)
    - (consolidation stress$_i$; bulk density$_i$, effective angle of internal friction$_i$, powder flow factor$_i$, bulk cohesion$_i$)
    - powder flow function (consolidation stress$_i$, unconfined yield strength$_i$)

Powder Flow Function…

- Could also use the shear cell for
  - different degrees of time consolidation
  - powder-wall kinematic friction angle
- Haven’t performed these tests

Compact Properties

- Typically a function of the compact porosity and method of producing the compact

- Elastic modulus
- Poisson’s ratio
- Tensile strength
- Fracture toughness / critical stress intensity factor
- Surface hardness
- (Visco-elastic / visco-plastic parameters)

Examples of the Importance of Compact Properties

- Tablet friability
- Tablet breakage strength
- Tableting performance
- Tablet relaxation

Compact Testing

- Several methods for determining these properties have been proposed
- Three point bending is common
  - form a thin, rectangular compact using a Carver press
  - measure elastic modulus and tensile strength from applied load and corresponding deflection/failure
  - fracture toughness (critical stress intensity factor) performed in a similar manner, but with a notched specimen
    - produced using a corresponding punch
- Brinell and Vicker's hardness testing common
  - usually quasi-static, can also be performed dynamically
- @Purdue:
  - designing and ordering punch/die sets for three-point bending
  - designing and machining three-point testing jig for use with Instron testing equipment
  - designing and ordering Brinell hardness tip for Instron
  - have access to existing quasi-static Brinell and Vicker's testers

Long Term Viability of the Database

- Need to ensure that the data are trustworthy
  - independent organization makes the measurements
  - consistency in the measurements
- Long term support for
  - those making the measurements
  - those maintaining the database
- Funding to purchase and maintain measurement equipment and materials
  - access to needed equipment if not able to purchase