Excipient Mechanical Properties and Measurements

Selection of Properties and Test Methods

- Properties
  - Commonly reported in the literature and/or used in models and correlations
  - Could also include quality control measurements widely agreed upon by users
  - Grouped into three categories
    - particle
    - powder
    - compact
- Test methods
  - Wide variety reported in the literature
  - Try to stick with published standards (e.g., ASTM)

Properties

Particle	Powder	Compact
size distribution	**bulk density**	**elastic modulus**
apparent density	**flowability**	**tensile strength**
microscope images	**moisture content**	**critical stress intensity factor**
shape and surface roughness	**spectra**	surface hardness
adhesion/cohesion	compressibility	visco-elasticity and visco-plasticity
elastic modulus, tensile strength, etc.	specific surface area	
	permeability	
	constitutive model parameters (*e.g.*, Drucker Prager Cap)	

All powder samples sub-divided using spin riffling.

Sample and Measurement Reports

Sample Report	Measurement Report
sample ID	tester's name
excipient type	testing date
vendor	test method
product	equipment make and model
lot #	*SOP*
	RH and temperature*

*@ Purdue, RH and temperature are not controlled, but they are recorded.

Particle Level Properties

Particle	Powder	Compact
size distribution	**bulk density**	**elastic modulus**
apparent density	**flowability**	**tensile strength**
microscope images	**moisture content**	**critical stress intensity factor**
shape and surface roughness	**spectra**	surface hardness
adhesion/cohesion	compressibility	visco-elasticity and visco-plasticity
elastic modulus, tensile strength, etc.	specific surface area	
	permeability	
	constitutive model parameters (*e.g.*, Drucker Prager Cap)	

Examples of the Importance of Particle Size Distribution

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

Particle Size Distributions

- Many different size definitions
  - best definition depends on application

maximum chord diameter	equivalent sphere surface area diameter
Feret's diameter	equivalent sphere specific surface diameter
Martin's diameter	sieve diameter
equivalent circle area diameter	equivalent Stokes diameter
equivalent sphere volume diameter	

- Distributions presented in terms of
  - frequency and cumulative distributions
  - by number, by surface area, by volume, by mass
    - type of distribution usually a function of measurement method
    - converting between distributions should be avoided

Particle Size Distribution…

- Derived quantities
  - x_{10}, x_{50}, x_{90}, span
  - weighted average surface area diameter, *i.e.,* Sauter mean diameter ($x_{1,2}$)
  - weighted average volume diameter ($x_{1,3}$)

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
    - ASTM B822-10, "Standard test method for particle size distribution of metal powders and related compounds by light scattering"

Examples of the Importance of Apparent Density

- Segregation
- Fluidization
- Flowability
- Bulk density

Apparent Density

- Apparent density = mass/(volume including internal pores)
  - = true density if no internal pores are present
- Gas (He) pycnometry
  - most common apparent density measurement technique
  - @Purdue: Micromeritics Accupyc II 1340
    - ASTM B923-10, “Standard test method for metal powder skeletal density by helium or nitrogen pycnometry”

Powder Level Properties

Particle	Powder	Compact
size distribution	**bulk density**	**elastic modulus**
apparent density	**flowability**	**tensile strength**
microscope images	**moisture content**	**critical stress intensity factor**
shape and surface roughness	**spectra**	surface hardness
adhesion/cohesion	compressibility	visco-elasticity and visco-plasticity
elastic modulus, tensile strength, etc.	specific surface area	
	permeability	
	constitutive model parameters (*e.g.*, Drucker Prager Cap)	

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
  - tapped bulk density: Agilent Technologies 350 Tapped Density Tester
    - ASTM D7481-09, "Standard test method for determining loose and tapped bulk densities of powders using a graduated cylinder"
- Often used to qualitatively characterize a powder's flowability using the following derived quantities
  - Hausner ratio (HR) = $\rho_{tapped}/\rho_{poured}$
  - Carr's compressibility index = $1 - 1/HR$
  - larger HR (larger compressibility) implies worse flow

"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 predictive 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
  - ASTM D6773-08, “Standard test method for bulk solids using Schulze Ring Shear Tester”

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…

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

Compact Level Properties

Particle	Powder	Compact
size distribution	**bulk density**	**elastic modulus**
apparent density	**flowability**	**tensile strength**
microscope images	**moisture content**	**critical stress intensity factor**
shape and surface roughness	**spectra**	surface hardness
adhesion/cohesion	compressibility	visco-elasticity and visco-plasticity
elastic modulus, Poisson's ratio, etc.	specific surface area	
	permeability	
	constitutive model parameters (*e.g.*, Drucker Prager Cap)	

Compact properties are typically a function of the compact porosity and the method of producing the compact.

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
  - critical stress intensity factor performed in a similar manner, but with a notched specimen
- Brinell and Vicker's hardness testing common
  - usually quasi-static, can also be performed dynamically
- @Purdue:
  - punch/die set for producing rectangular compacts with and without
  - three-point testing apparatus
  - Brinell hardness tester recently acquired
  - ASTM D790-07, "Standard test methods for flexural properties of unreinforced and reinforced plastics and electrical insulating materials"
  - ASTM E399-09, "Standard test methods for linear-elastic plane-strain fracture toughness KIC of metallic materials"
  - ASTM E10-07a, "Standard test method for Brinell hardness of metallic materials"

QUESTIONS?

Tests to Date

Grade	Lot Number	Vendor	Particle Size Distribution	Apparent Density	Microscope Images	Shear Cell	Bulk/Tapped Density	Elastic Modulus	Tensile Strength	Critical Stress Intensity Factor	Hardness
Pharmatose 130M (NZ)	NZ000542	DMV-Fonterra Excipients	Complete	Complete	Complete	Complete	Complete	Complete	Complete	Complete	Incomplete
LubriTose MCC	1320015799	Kerry Bioscience (Sheffield Bioscience)	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete
LubriTose MCC	1320015207	Kerry Bioscience (Sheffield Bioscience)	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete
LubriTose AN	1320015797	Kerry Bioscience (Sheffield Bioscience)	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete
LubriTose AN	1320014615	Kerry Bioscience (Sheffield Bioscience)	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete
LubriTose SD	1320015798	Kerry Bioscience (Sheffield Bioscience)	Complete	Complete	Complete	Complete	Complete	Complete	Complete	Complete	Incomplete
LubriTose SD	1320014643	Kerry Bioscience (Sheffield Bioscience)	Complete	Complete	Complete	Complete	Complete	Complete	Complete	Complete	Incomplete
Lactose Anhydrous NF 120M	1320009301	Kerry Bioscience (Sheffield Bioscience)	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete
Lactose Monohydrate 310	8510122310	Kerry Bioscience (Foremost Farms, USA)	Complete	Complete	Complete	Complete	Complete	Complete	Complete	Complete	Incomplete
Lactose Monohydrate 310	8511061010	Kerry Bioscience (Foremost Farms, USA)	Complete	Complete	Complete	Complete	Complete	Complete	Complete	Complete	Incomplete
Lactose Monohydrate 312	8510101512	Kerry Bioscience (Foremost Farms, USA)	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete
Lactose Monohydrate 312	8510101712	Kerry Bioscience (Foremost Farms, USA)	Complete	Complete	Complete	Complete	Complete	Complete	Complete	Complete	Incomplete
Lactose Monohydrate 316	8510111661	Kerry Bioscience (Foremost Farms, USA)	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete
Lactose Monohydrate 316	8510111761	Kerry Bioscience (Foremost Farms, USA)	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete
Avicel PH101	P109821003	FMC Corporation	Complete	Complete	Complete	Complete	Complete	Incomplete	Incomplete	Incomplete	Incomplete
Avicel PH102	P208819026	FMC Corporation	Complete	Complete	Complete	Complete	Complete	Incomplete	Incomplete	Incomplete	Incomplete
Avicel PH200	PN08819580	FMC Corporation	Complete	Complete	Complete	Complete	Complete	Incomplete	Incomplete	Incomplete	Incomplete