Investigation of Mechanical Property Variability in Lactose Products

Kristine Alston and Carl Wassgren
School of Mechanical Engineering
Purdue University

In association with
Steve Hoag and Ting Wang
University of Maryland
Ann Christine Catlin, Sumudinie Fernando, and Sudheera Fernando
Purdue University

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Improving quality and lowering costs of pharmaceuticals

Overview

- Importance of understanding excipient properties
- Properties of interest
- Background
- Properties measured and test methods
- Materials
- Results
- Conclusions

Importance of Measuring Excipient Properties

- Component properties have significant impact on drug product performance and manufacturability
  - Create a database of properties for use in models, correlations and quality control
- Derived from natural sources; variation may occur due to
  - Geographic origin
  - Seasonal climate variations
  - Storage and processing
- Formulations and manufacturing processes regulated by FDA
  - Variable input + constant process = variable output

Some Properties of Interest

Particle	Powder	Compact
size distribution	Hausner ratio	elastic modulus
shape	compressibility	yield strength
true density	flow function	fracture strength
apparent density	effective angle of internal friction	indentation hardness
specific surface area	poured and tapped bulk density	critical stress intensity factor
elastic modulus		
Poisson's ratio		
yield strength		
fracture strength		
adhesion		

Background

- Literature survey
  - Large scatter in the data
  - Range of test methods used
  - Details of testing conditions and procedures are rarely reported
    - Difficult to determine the source of discrepancies
- Few studies have been performed on the variability of lactose (Gamble et al., 2010; Kushner et al., 2011; Whiteman et al., 1990)
  - Common excipient
  - Purpose: diluent, filler-binder
- Objective: study the variability in particle, powder, and compact level properties of lactose
  - Though a wide range of lactose grades were studied, only select results are presented here.

Materials Tested

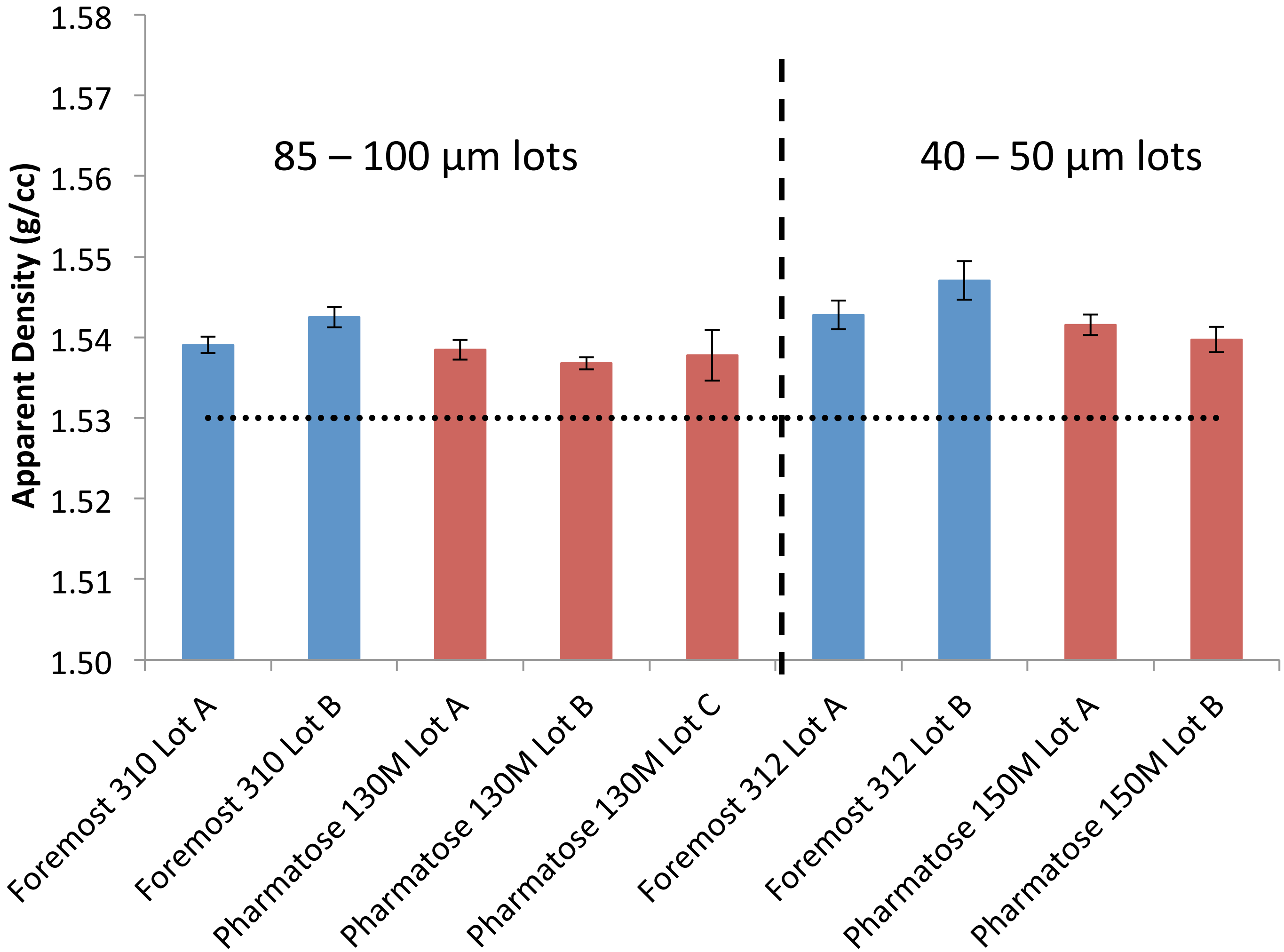
- Crystalline milled α-lactose monohydrate
- “Equivalent” products
  - 85 – 100 µm nominal particle size
    - Lactose Monohydrate 310 (Foremost Farms, USA)
    - Pharmatose 130M (DMV – Fonterra Excipients)
  - 40 – 50 µm nominal particle size
    - Lactose Monohydrate 312 (Foremost Farms, USA)
    - Pharmatose 130M (DMV – Fonterra Excipients)

Product Name	From	Manufacturing Site	Lot no.
Lactose Monohydrate 310	Kerry Bioscience (Foremost Farms, USA)	Rothschild, WI	8510122310
Lactose Monohydrate 310	Kerry Bioscience (Foremost Farms, USA)	Rothschild, WI	8511061010
Lactose Monohydrate 312	Kerry Bioscience (Foremost Farms, USA)	Rothschild, WI	8510101512
Lactose Monohydrate 312	Kerry Bioscience (Foremost Farms, USA)	Rothschild, WI	8510101712
Pharmatose 130M (NZ)	DMV-Fonterra Excipients	Fonterra Limited, Kaponga, New Zealand	NZ000542
Pharmatose 130M (NZ)	DMV-Fonterra Excipients	Fonterra Limited, Kaponga, New Zealand	NZ000570
Pharmatose 130M (NZ)	DMV-Fonterra Excipients	Fonterra Limited, Kaponga, New Zealand	NZ000667
Pharmatose 150M	DMV-Fonterra Excipients	FrieslandCampina DMV BV, Veghel, The Netherlands	10498250
Pharmatose 150M	DMV-Fonterra Excipients	FrieslandCampina DMV BV, Veghel, The Netherlands	10544872

Properties and Test Methods

Property	Test Method	Equipment	Standard
Apparent Density	Helium pycnometry	Accupyc II 1340 Pycnometer Helium gas	ASTM B923-10
Particle Size Distribution	Laser diffraction	Malvern Mastersizer 2000 Particle Size Analyzer Hydro µP wet dispersion unit Malvern Mastersizer 2000E Particle Size Analyzer Scirocco M dry powder feeder	ASTM B822-10
Poured Bulk Density	-	Graduated cylinder	ASTM D7481-09
Tapped Bulk Density	-	Agilent Technologies 350 Tapped Density Tester	ASTM D7481-09
Shear Cell Flowability	Ring shear cell	Schulze Ring Shear Tester RST-XS	ASTM D6773-08
Elastic Modulus	Three point bending	Carver Hydraulic Press Instron ElectroPuls E1000 Custom three point bend fixture	ASTM B925-08 ASTM D790-07
Tensile Strength	Three point bending	Carver Hydraulic Press Instron ElectroPuls E1000 Custom three point bend fixture	ASTM B925-08 ASTM D790-07
Critical Stress Intensity Factor	Three point bending	Carver Hydraulic Press Instron ElectroPuls E1000 Custom three point bend fixture	ASTM B925-08 ASTM E399-09

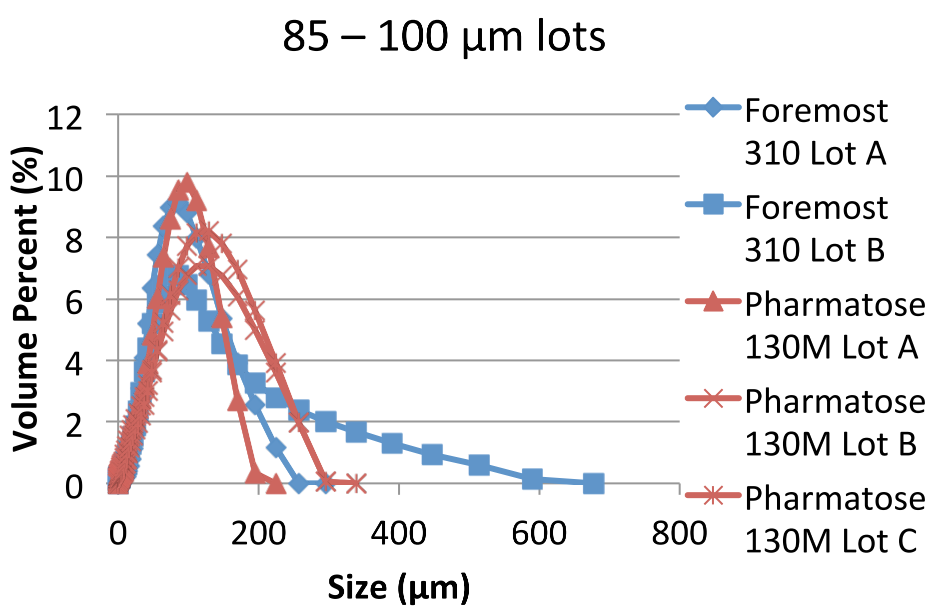
Results – Apparent Density

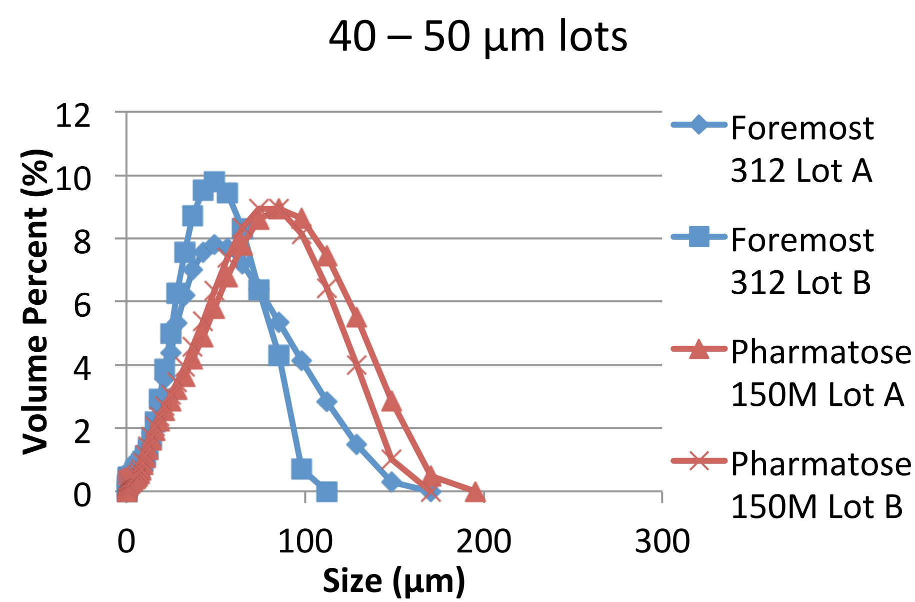


True density of α-lactose monohydrate: 1.53 g/cc

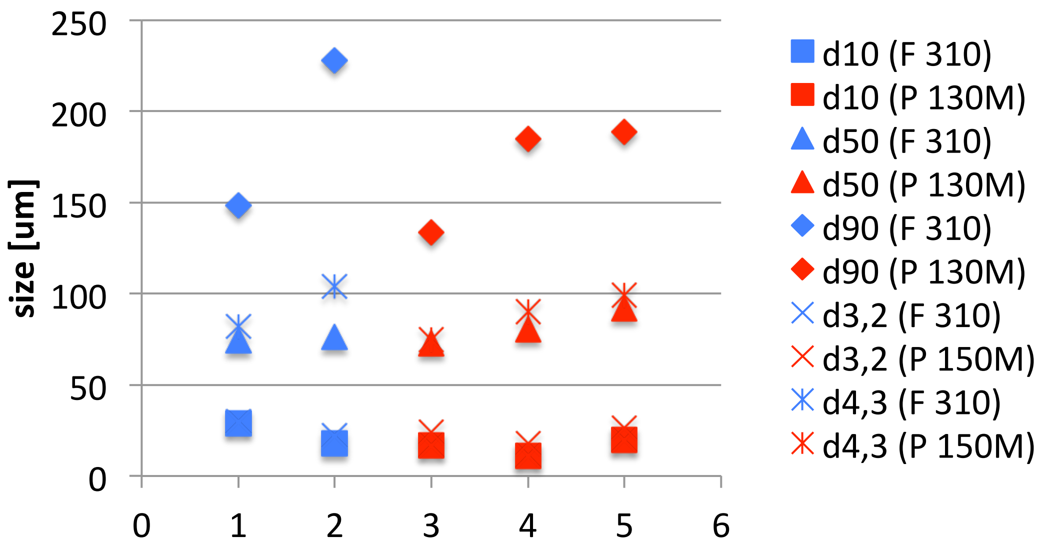
Determined from 20 measurements ± 1 standard deviation

Results – Particle Size Distribution



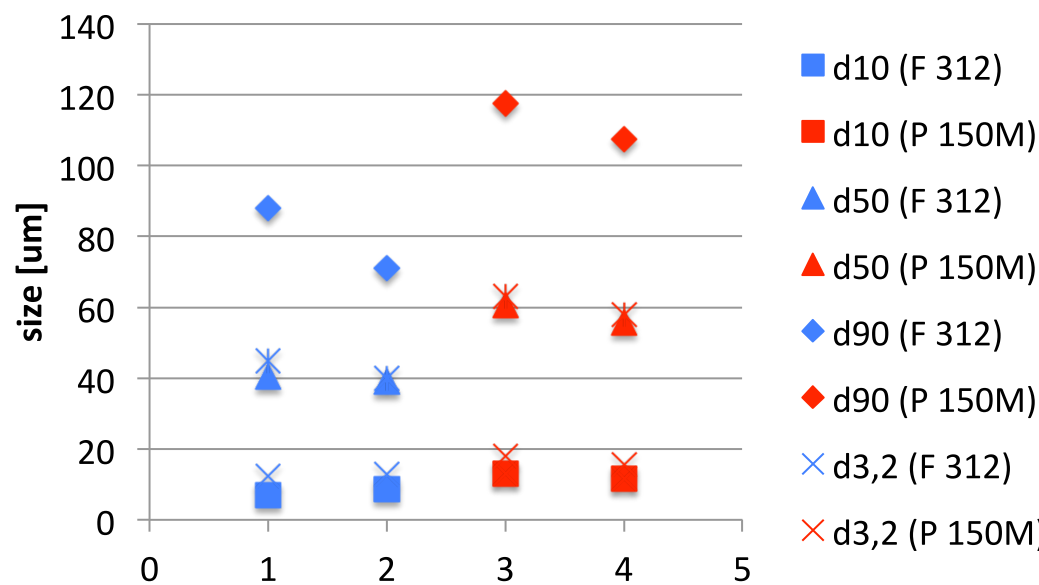


Results – Particle Size Distribution

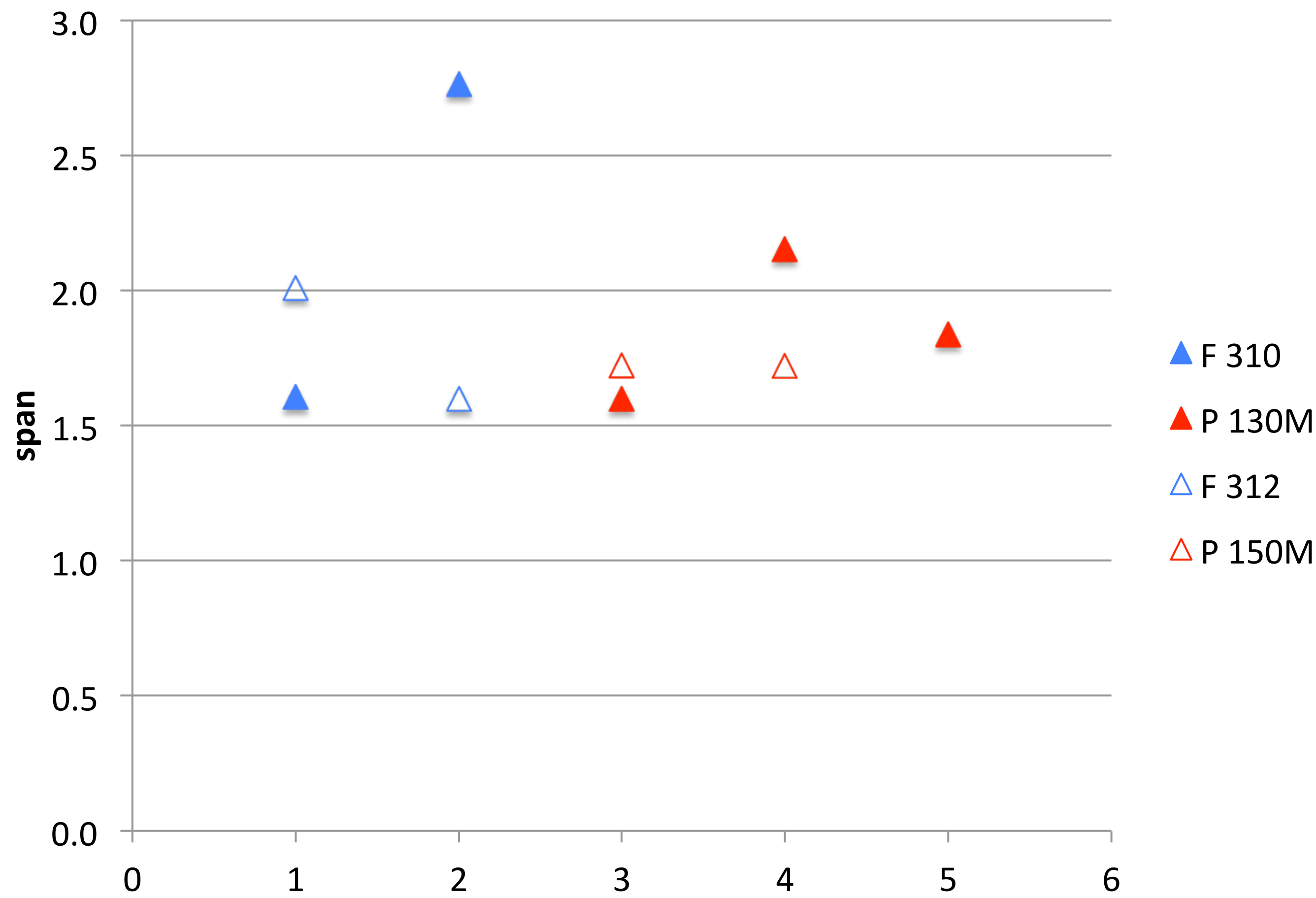


85 – 100 μm lots

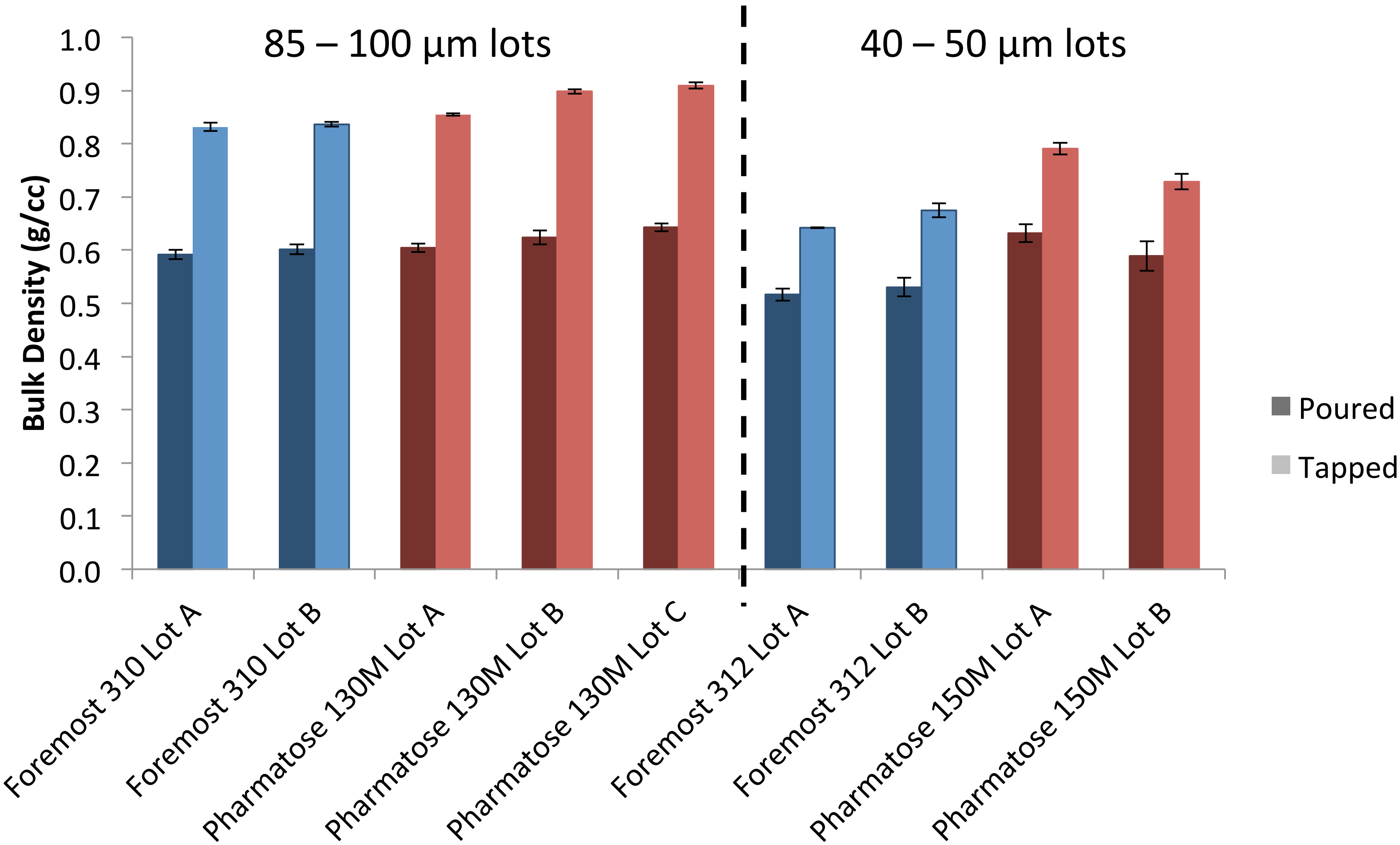
40 – 50 μm lots



Results – Particle Size Distribution

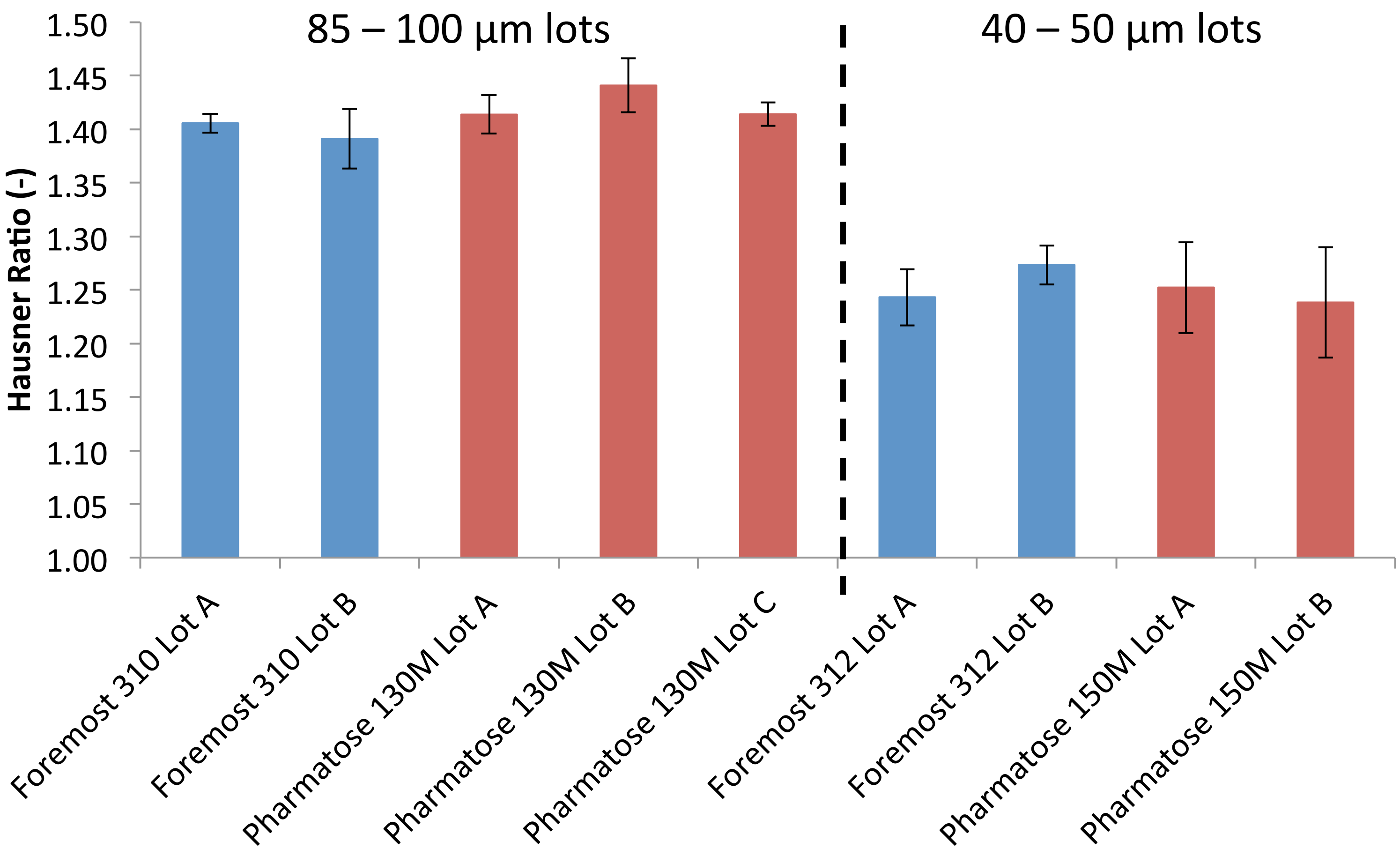


Results – Poured and Tapped Bulk Density



Determined from 3 measurements ± 1 standard deviation

Results – Hausner Ratio

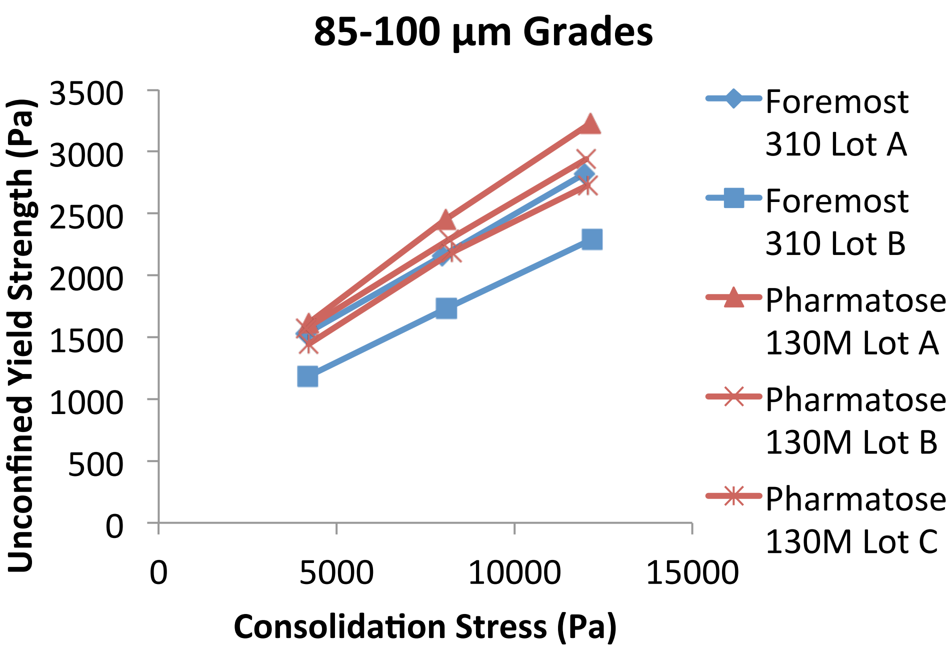


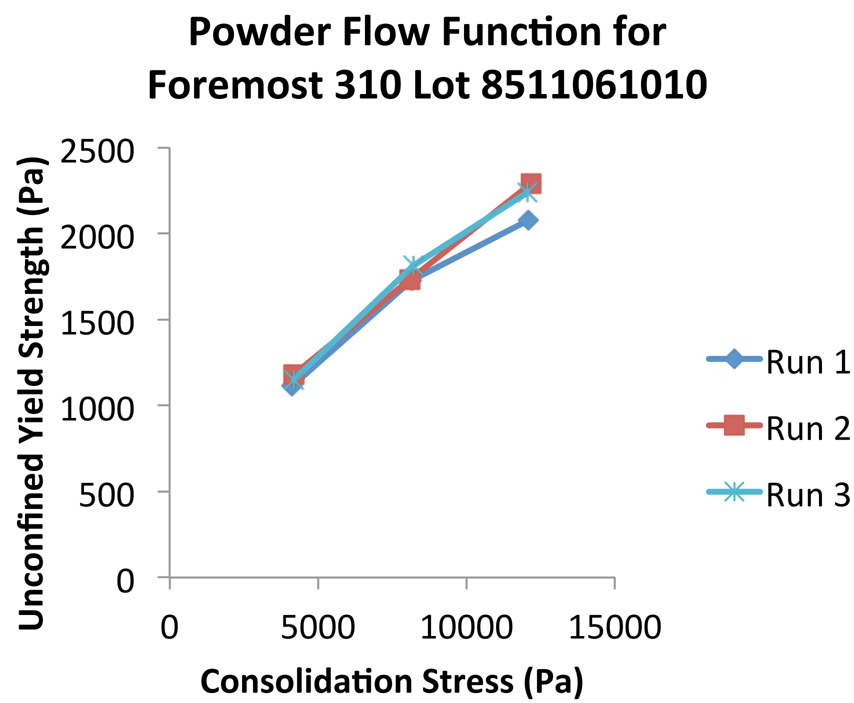
$HR = \rho_{tapped} / \rho_{bulk}$

Smaller HR = better flow

Determined from 3 measurements
± 1 standard deviation

Results – Shear Cell Flowability

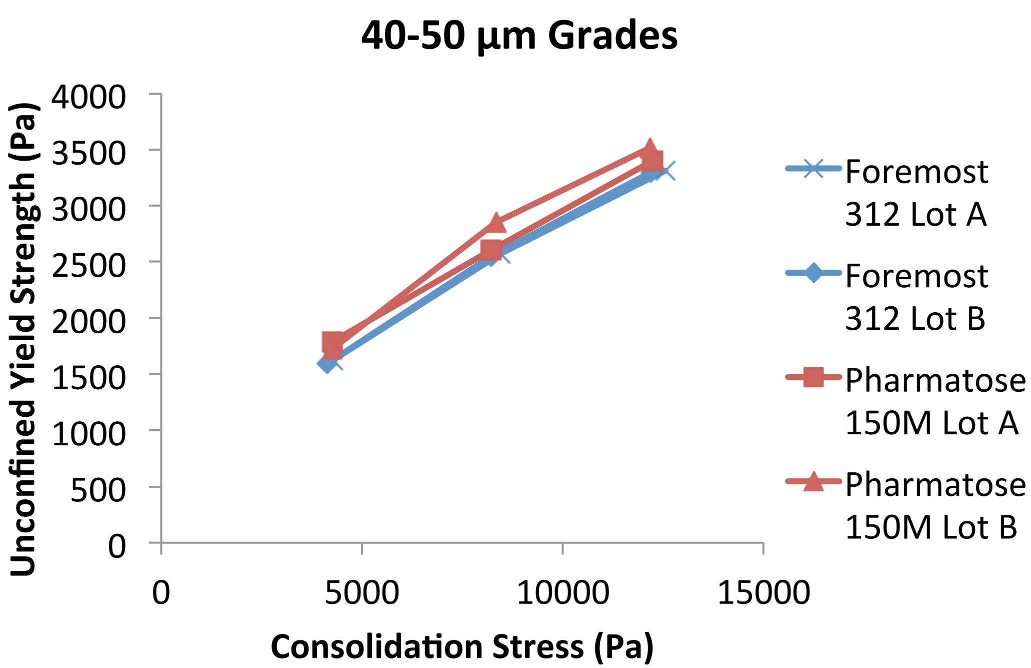




Grade	Lot Number	Flow Factor at ~8000 Pa (-)
Foremost 310	A	3.69
Foremost 310	B	4.67
Pharmatose 130M	A	3.28
Pharmatose 130M	B	3.56
Pharmatose 130M	C	3.77

Larger flow factor => better flow

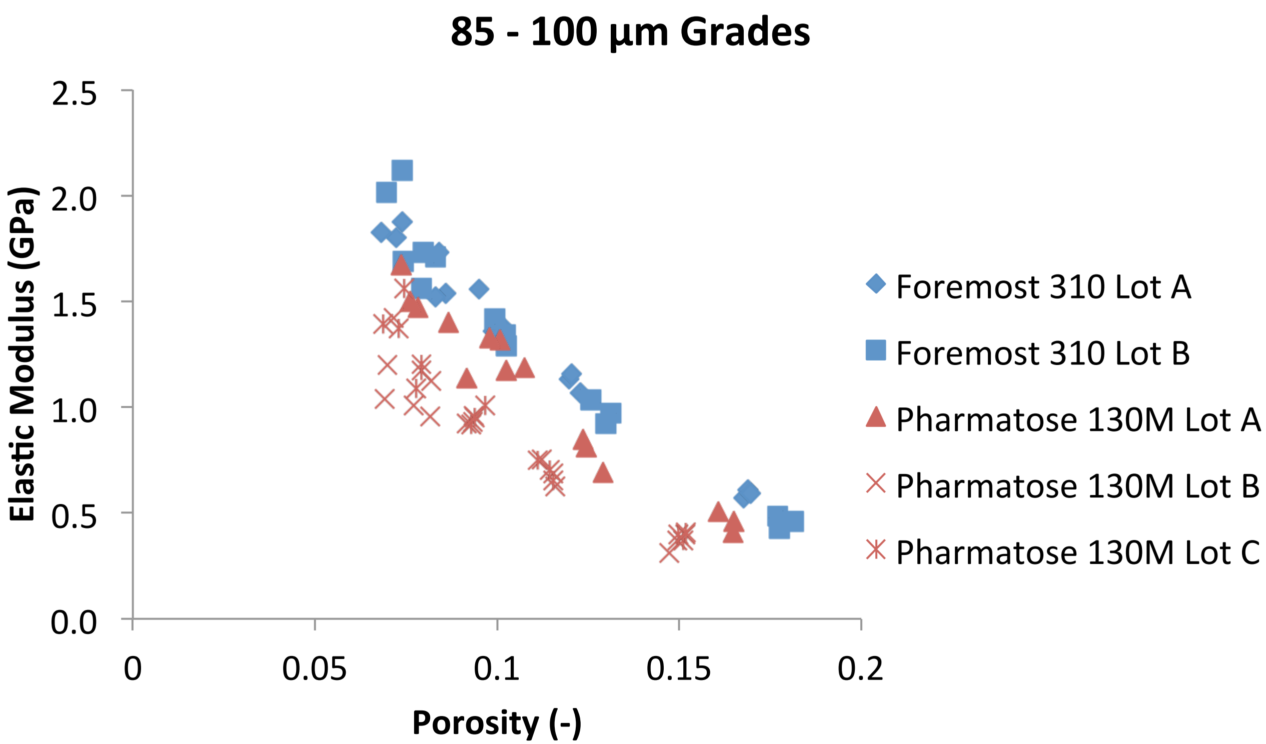
Results – Shear Cell Flowability



Larger flow factor => better flow

Grade	Lot Number	Flow Factor at ~8000 Pa (-)
Foremost 312	A	3.29
Foremost 312	B	3.22
Pharmatose 150M	A	3.15
Pharmatose 150M	B	2.93

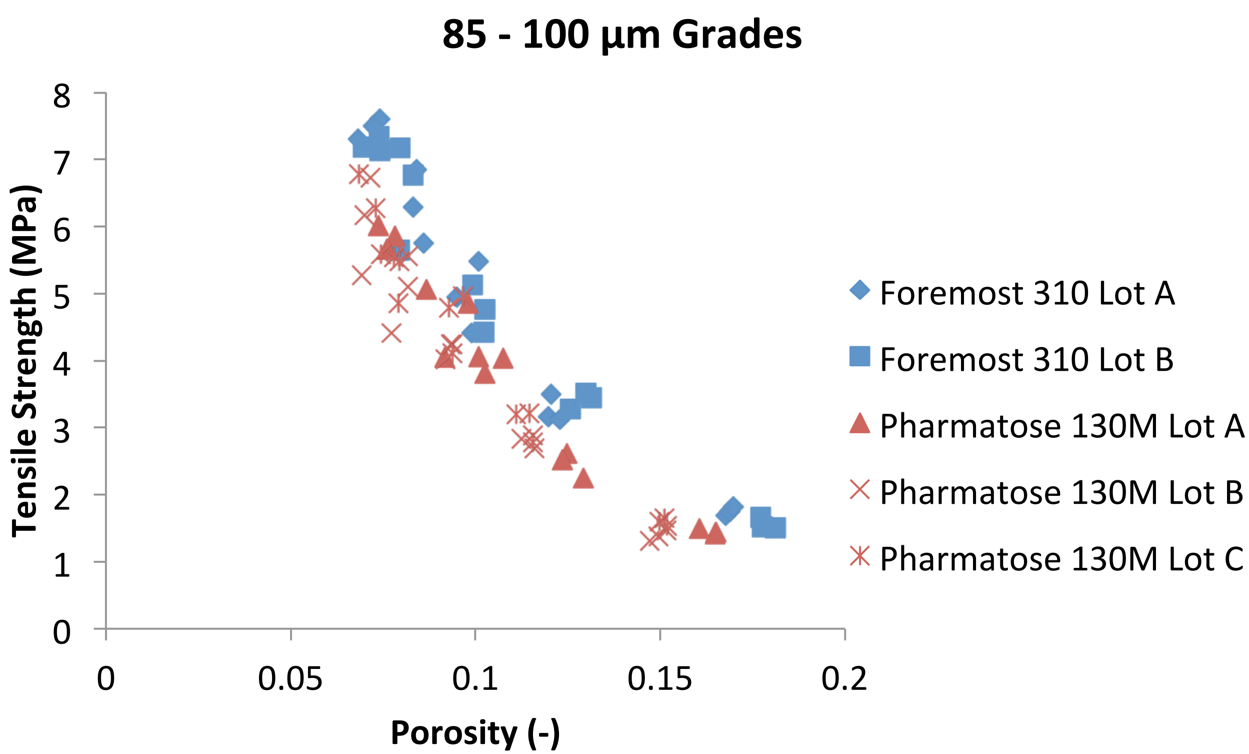
Results – Elastic Modulus



Grade	Lot Number	E_0 (GPa)	b (-)	R^2
Foremost 310	A	4.3	11.6	0.98
Foremost 310	B	5.1	13.3	0.98
Pharmatose 130M	A	4.9	14.4	0.96
Pharmatose 130M	B	3.6	15.0	0.94
Pharmatose 130M	C	4.2	15.8	0.98

Sprigg's Equation: $E=E_0 e^{-b\epsilon}$

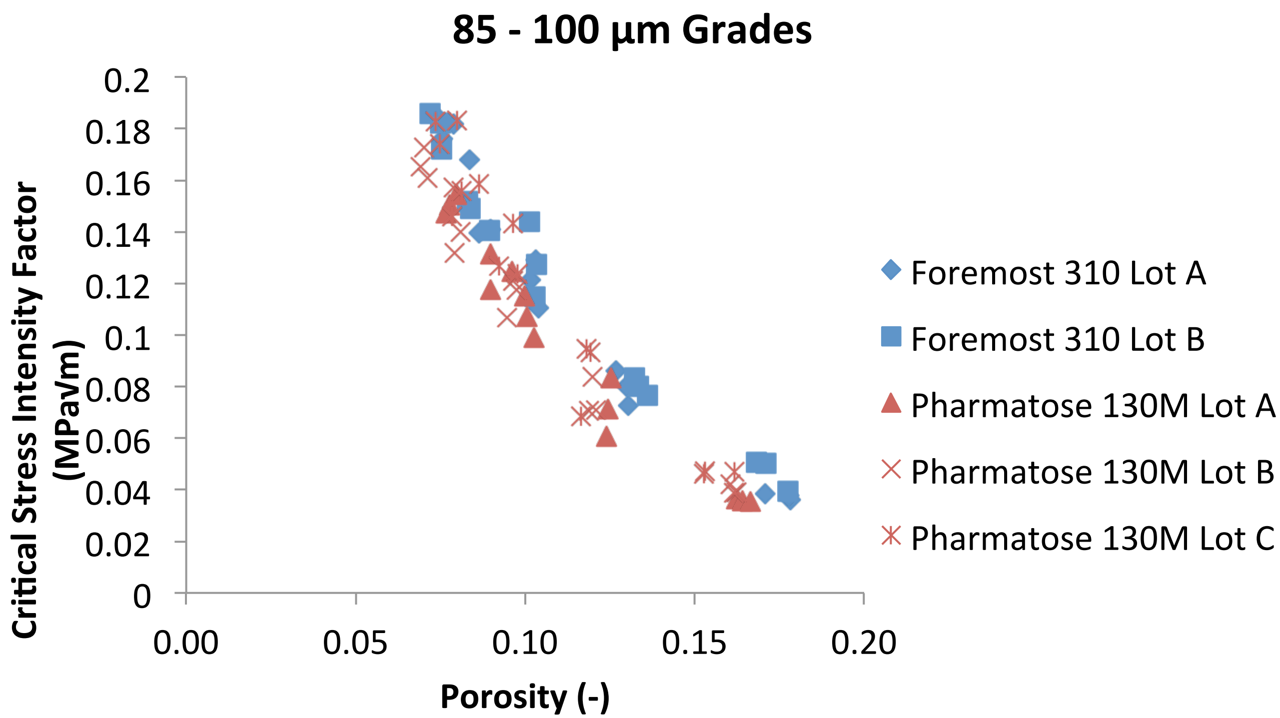
Results – Tensile Strength



Grade	Lot Number	σ_0 (MPa)	b (-)	R^2
Foremost 310	A	21.8	15.1	0.98
Foremost 310	B	20.6	14.3	0.98
Pharmatose 130M	A	20.4	16.3	0.98
Pharmatose 130M	B	22.2	18.3	0.97
Pharmatose 130M	C	21.4	17.1	0.98

Sprigg's Equation: $\sigma=\sigma_0 e^{-b\epsilon}$

Results – Critical Stress Intensity Factor



Grade	Lot Number	K_{IC0} (MPa√m)	b (-)	R^2
Foremost 310	A	0.59	15.7	0.99
Foremost 310	B	0.50	13.7	0.99
Pharmatose 130M	A	0.57	16.8	0.98
Pharmatose 130M	B	0.50	15.7	0.99
Pharmatose 130M	C	0.61	16.5	0.96

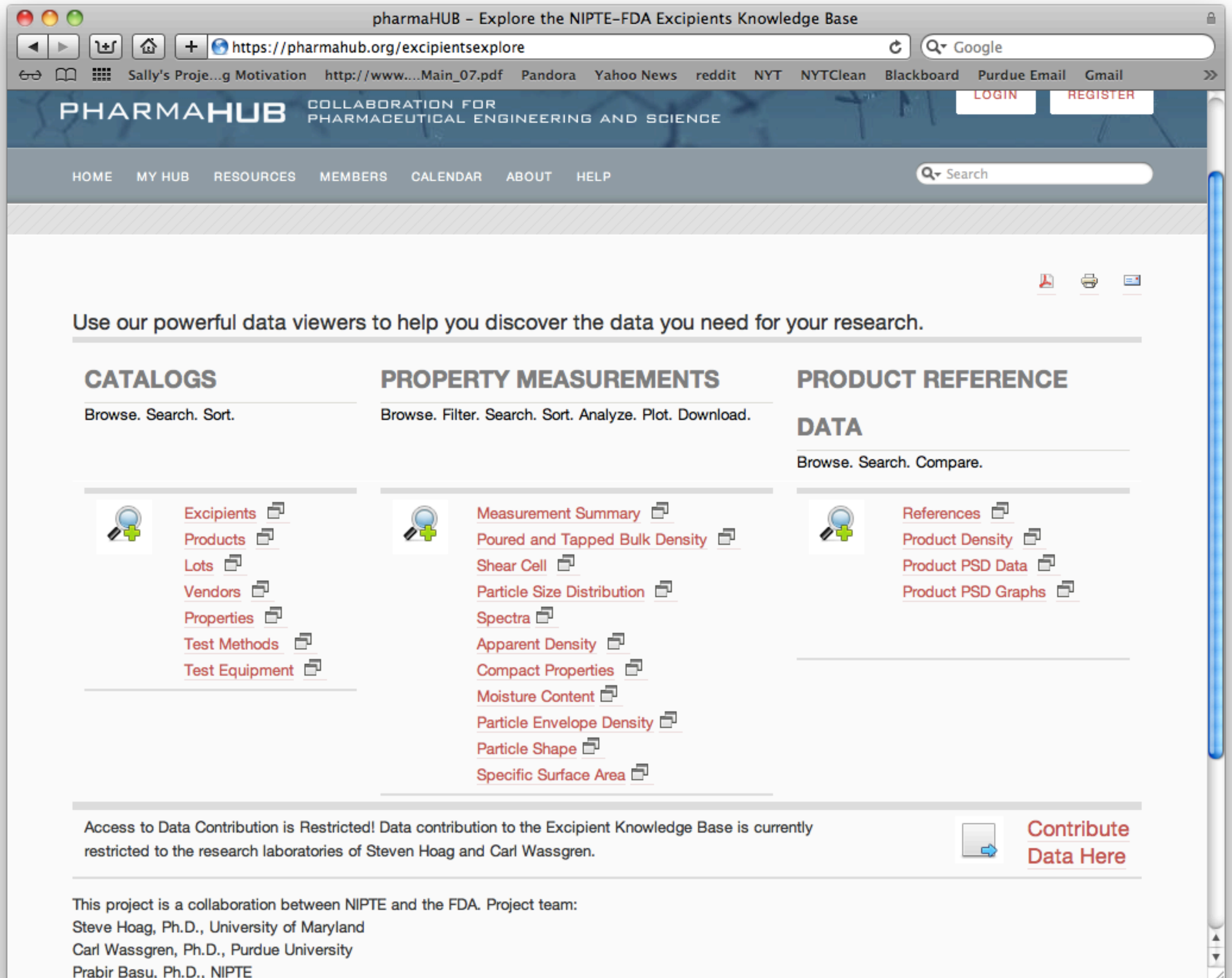
Sprigg's Equation: $K_{IC} = K_{IC0}\, e^{-b\epsilon}$

Conclusions

- Apparent density
  - Larger than the true density; small variability
- Particle size distribution
  - Considerable lot-to-lot variability
  - Particle size distribution is more skewed for Foremost products
  - Median size distributions quite different than stated by the manufacturer
- Bulk Density
  - 85-100 µm: Pharmatose poured and tapped density slightly larger than Foremost
  - More lot and vendor variability for 40-50 µm products
  - Both poured and tapped bulk densities smaller for 40-50 µm products
  - Hausner Ratio smaller for smaller particle sizes
- Shear cell
  - Flow function: low variability between lots and products, except for Foremost 310 lot B
  - Flow factors suggest cohesive material, except for Foremost 310 lot B
  - Flow factor and Hausner Ratio give conflicting results.
- Compact properties
  - Elastic modulus , tensile strength, and critical stress intensity factor follow Sprigg's equation quite well
  - Foremost gives consistently larger elastic modulus, tensile strength, and critical stress intensity factor
    - However, the variability in data points is close to these differences
  - Difficult to discern any differences between lots

- Data available at: pharmahub.org/excipientsexplore

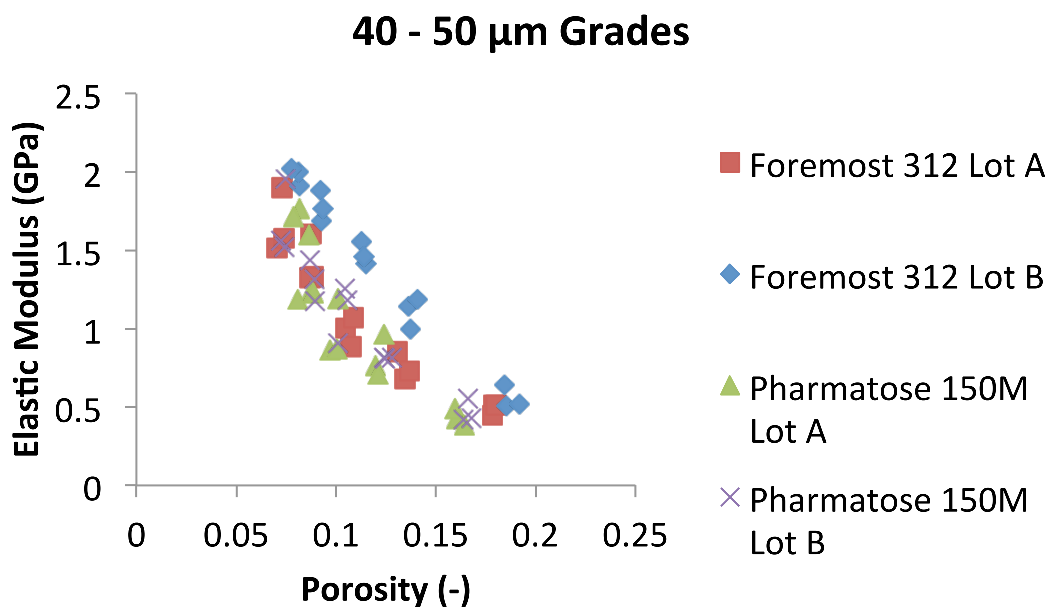
Pharmahub Excipients Database



Questions?

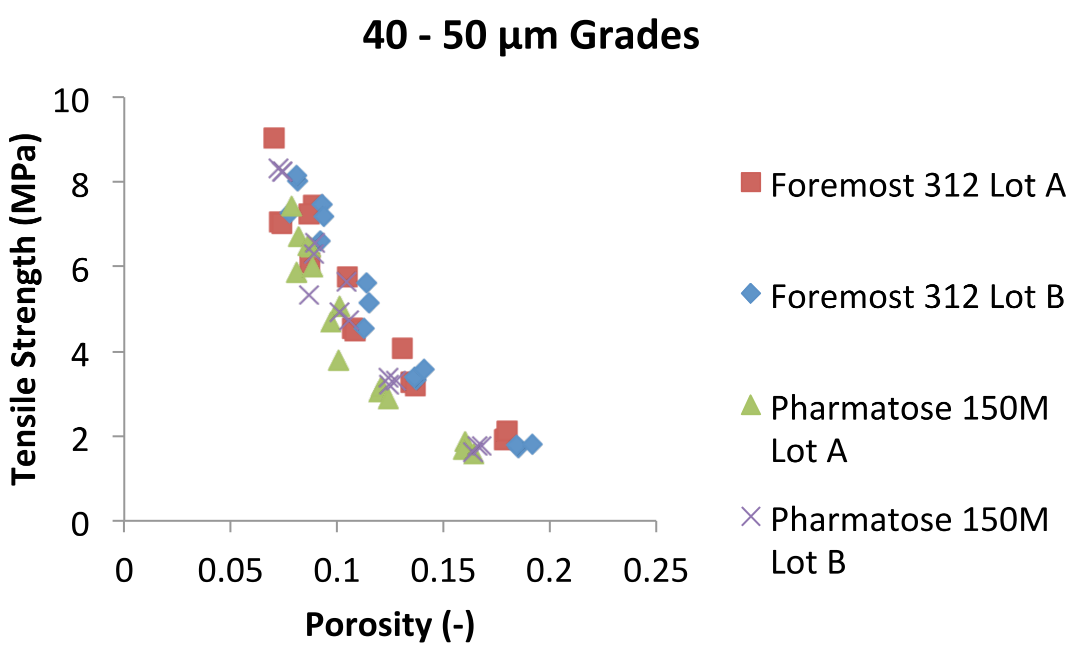
BACKUP SLIDES

Results – Elastic Modulus



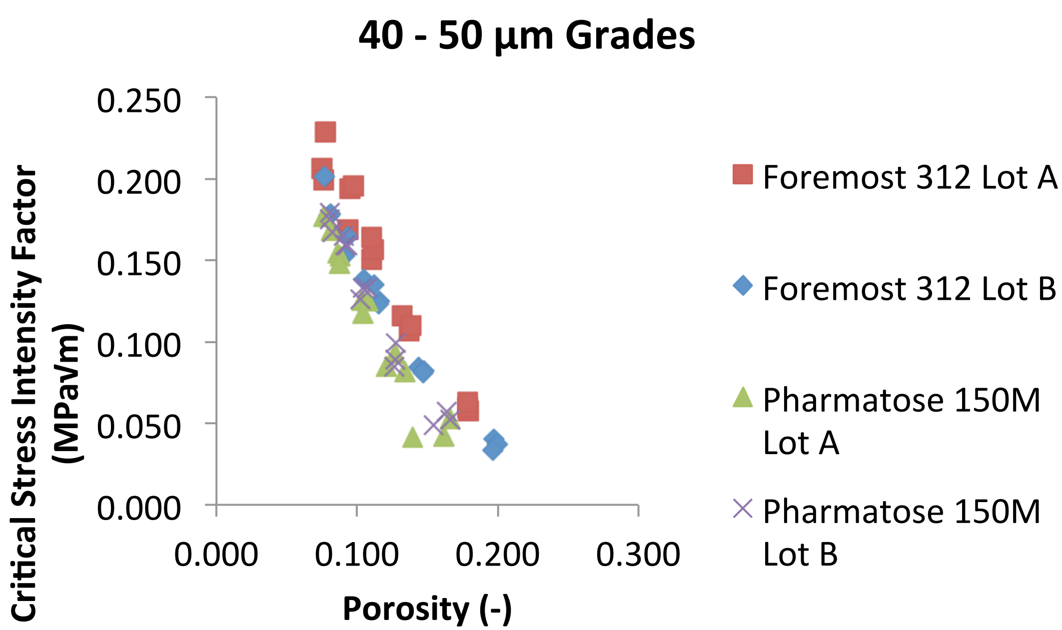
Grade	Lot Number	E_0 (GPa)	b (-)	R^2
Foremost 312	A	3.7	11.5	0.95
Foremost 312	B	5.5	12.0	0.97
Pharmatose 150M	A	4.9	15.1	0.89
Pharmatose 150M	B	4.5	13.6	0.94

Results – Tensile Strength



Grade	Lot Number	σ_0 (MPa)	b (-)	R^2
Foremost 312	A	20.4	13.1	0.97
Foremost 312	B	25.1	14.2	0.98
Pharmatose 150M	A	26.2	17.2	0.97
Pharmatose 150M	B	27.9	16.8	0.98

Results – Critical Stress Intensity Factor



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