THE EFFECT OF LOT-TO-LOT PARTICLE SIZE VARIATION IN AVICEL® PH GRADES OF MICROCRYSTALLINE CELLULOSE (MCC) ON BULK POWDER AND COMPACT PROPERTIES

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OBJECTIVE

Understand lot-to-lot particle size variation in Avicel® PH grades of microcrystalline cellulose and its impact on bulk powder and compact properties.

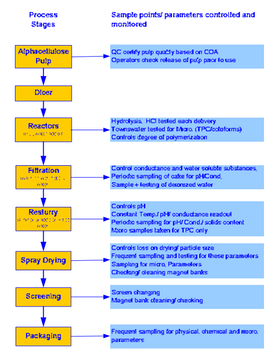
INTRODUCTION

Microcrystalline cellulose, MCC, is a common and often high percentage ingredient in solid dosage forms. As received from its manufacturers, it is subject to slight lot-to-lot variation in its particle size distribution. This variability could lead to differences in its bulk properties and potentially variation in performance during powder processing operations for dosage form manufacture.

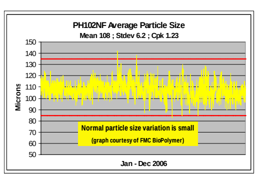
FMC BioPolymer manufactures the Avicel® PH brand of microcrystalline cellulose and markets each lot only after passing many controls, including particle size. For this study, FMC provided samples of PH102, PH200 and PH105 from the high and low ends of their particle size target ranges so the effect of this normal variation on their bulk powder and compact mechanical properties could be determined. FMC Ireland provided samples of PH102 outside the normal operating range to exaggerate the difference between high and low for the purposes of this study. FMC US provided material sampled from the normal production process and represents the normal variability in particle size.

MCC MANUFACTURING PROCESS

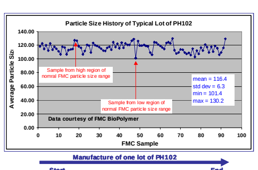
Courtesy of FMC BioPolymer



PARTICLE SIZE CONSISTENCY ACROSS MULTIPLE BATCHES



PARTICLE SIZE CONSISTENCY WITHIN ONE BATCH



MATERIALS & METHODS

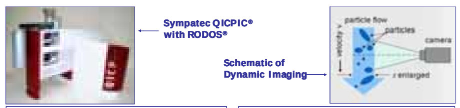
Avicel Grade	Lot	Mfg Site	Position in PS Range
PH102	P206816966-32989	US	low end
PH102	P206817009-2000	US	high end
PH102	70634C (sample A)	Ireland	low end
PH102	70634C (sample B)	Ireland	high end
PH200	M0630C	Ireland	high end
PH200	M625C	Ireland	low end
PH105	5613C	Ireland	low end
PH105	50630C	Ireland	high end

All samples represent normal production variability except for the "atypical" (highlighted) samples collected from transitions between runs of different grades.

Methods

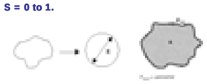
- SEM (particle morphology)
- Dry dispersion laser diffraction (particle size distribution)
- Dynamic Image Analysis (particle size and shape distributions)
- Shear cell (powder flowability and bulk density)
- Helium pycnometry (true density)
- Compact mechanical properties (tableting indices)

DYNAMIC IMAGE ANALYSIS



Sphericity (S) = ratio of perimeter of circle with equivalent projected area, P_{EQPC}, to perimeter of real particle, P_{real}.

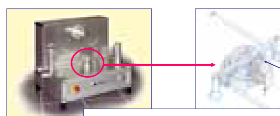
S = 0 to 1.



Aspect ratio (A) = ratio of minimum Feret diameter to maximum Feret diameter.

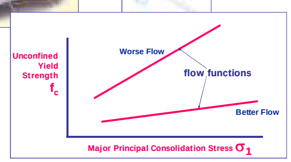
A = 0 to 1.

SCHULZE RING SHEAR TESTER (RST)



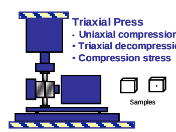
Bulk density determined from powder mass and powder volume (determined from position of cell lid)

- **Flow function** (ff) describes flow behavior under a range of consolidation stresses & can be used to rank relative powder flow performance.
- The **flow function coefficient** (ffc) is the ff at one consolidation stress



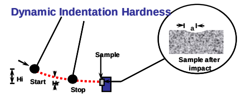
f_c & σ_1 determined from powder yield locus

TABLETING INDICES

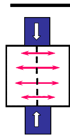


Triaxial Press
- Uniaxial compression
- Triaxial decompression
- Compression stress

Dynamic Indentation Hardness



$$H_0 = \frac{4\,mgrh_r}{\pi a^4}\left[\frac{h_i}{h_r} - \frac{3}{8}\right]$$



Tensile Strength

$$\sigma_T = \frac{F_{break}}{W_p T} \times PTF$$

Brittle Fracture Index

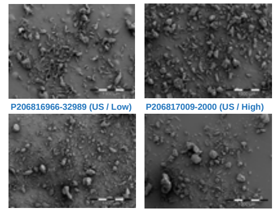
$$BFI = 0.5\left(\frac{\sigma_T}{\sigma_{T0}} - 1\right)$$

Bonding Index

$$BI_w = \frac{\sigma_T}{H_0}$$

PARTICLE MORPHOLOGY

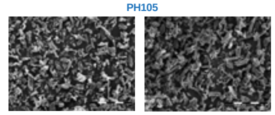
PH102



P206816966-32989 (US / Low) P206817009-2000 (US / High)

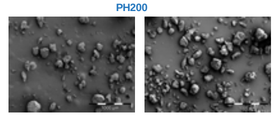
70634C (Ireland / Low) 70634C (Ireland / High)

PH105



5613C (Ireland / Low) 50630C (Ireland / High)

PH200

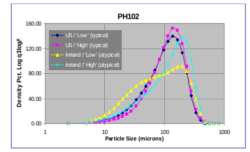


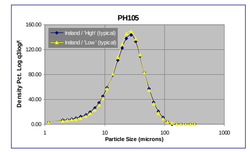
M0630C (Ireland / Low) M625C (Ireland / High)

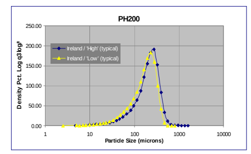
Particle Microscopy

Particles from 'low' and 'high' lots show similar size range, shape and morphology, regardless of site of manufacture

PARTICLE SIZE DISTRIBUTIONS



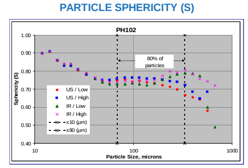


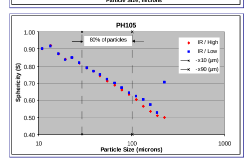


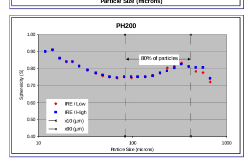
Particle Size Distributions Within Grade

Normal production lots exhibited
- small variation in particle size
- very similar distribution shapes.

PARTICLE SPHERICITY (S)

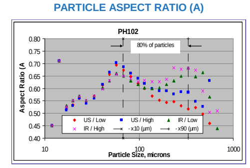


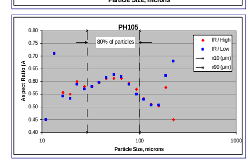


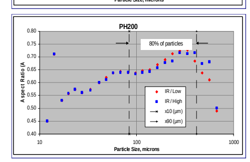


Particle Sphericity (S):
- Decreased with particle size within one lot
- Varied slightly between "normal" lots
- Varied across grades

PARTICLE ASPECT RATIO (A)

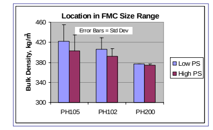






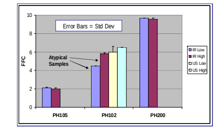
Particle Aspect Ratio (A):
- Increased/decreased with particle size within one lot
- Varied slightly between "normal" lots
- Varied across grades

BULK DENSITY



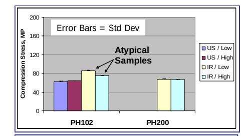
Bulk Density:
- Lot-to-lot differences probably not significant
- Most variation with PH102 & PH105; least in PH200
- Across grades, bulk density decreases with increasing particle size
- Note that bulk density from Schulze shear cell method may differ from USP method

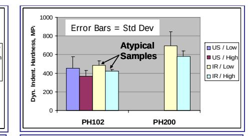
POWDER FLOWABILITY

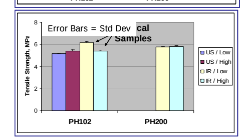


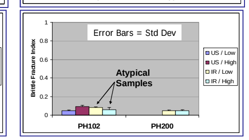
Flow Function Coefficient:
- Variation across lots: PH102 > PH105 = PH200
- Differences between "normal" samples in each grade probably not significant
- Strong relationship between FFC and grade (i.e., particle size)

COMPACT MECHANICAL PROPERTIES









Observations:
- Lot-to-lot differences in all properties for "normal" samples were probably not significant.
- All CS values were considered to be moderate.
- All DIH values were considered to be high.
- All TS values were considered to be high
- All BFI values were considered to be low.

DATA SUMMARY

- Lot-to-lot variation was quantified in particle size distributions and particle shape distributions for PH102, PH200 and PH105.
  - As expected, the largest particle size variation was measured between the "high" PH102 and "low" PH102 with higher than normal fines.
  - Excluding the atypical lots, PH102 size variation in particle size was similar to PH105 and PH200.
- Lot-to-lot variation in powder flowability and bulk density were observed within each MCC grade but the differences were not statistically significant.
  - As expected, grade-to-grade differences in powder flowability were significant.
  - Grade-to-grade differences in bulk density were not significant.
- The influence of lot-to-lot variability on compact mechanical properties was small compared to bulk powder properties.

CONCLUSIONS

- Normal lot-to-lot particle size variation in PH102, PH200 and PH105 probably has no significant impact on tablet manufacturability.
- However, switching to another particle size (i.e., another grade) will require process adjustments.

FUTURE WORK

The results of these experiments suggest further investigations. Examples include the evaluation of
- Additional lots of PH102, PH200 and PH105
- Other MCC grades
- Other MCC suppliers
- Other excipients (e.g., lactose, DCP, etc.)

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