Dynamic Image Analysis and pharmaceutical multi-particulates

Particle size distributions
Coat thickness and drug release
Swelling during drug release
Topics

- What are multi-particulates and what is DIA?
- Representative samples
- Applications
  - Raw materials
  - Drug layering
  - Measuring coat thickness
  - Investigating drug release
- Future opportunities
Multi-particulates

- Inert Core
- Drug + Binder
- Polymer Coating
- Drug release

Sugar Sphere
Sugar Sphere Plus Drug Layer
Sugar Sphere Plus Drug Layer Plus Polymer Layer
Ghost After Dissolution, Expansion Noticeable
Sieving facts

- Standard for beads
  - Common, conceptually easy
- Sizes 500, 600, 710, 850, 1000, 1180, 1400 µm
- Tolerances on sieves (e.g. 850 µm)
  - Mean opening 850 ± 35 µm,
    NMT 5% > 925 µm, max individual 970 µm
  - Sieve-to-sieve differences
- Infinite shaking, lengthwise passage
Alternate PSDs

- Microscopes
  - Labor intensive, small sample size, which dimension to measure if irregular

- Dynamic Image Analysis
  - Image dimensions irrespective of orientation
  - Average is larger, conceptually and measured
Dynamic image analysis

Vibrating Chute and Sample

Screen

Light Source

Sample Collection
Measuring shadows
A typical PSD
Particle sizes and distributions

G. Heinicke©
Horiba Instruments Webinar, June 2009
Raw materials, drug layering
Distributions

- Absolute homogeneity – 1 particle is sufficient
- Degree of heterogeneity
  - Span from smallest to largest particle
  - Shape consistency
- Typical multi-particulates
  - Drug layered seed cores (sugar spheres or MCC)
  - Extruded products
  - High shear granulations
- Adequate representation
Representative measurements

- Different distributions
- Size of sample
- Method of sampling
- How representative is the sample?
- Reproducibility of measurement
  - Data from a given sample is reproducible

Fluid bed sampling

- PSD is steady at about 15,000 particles for layered sugar spheres (10-30 g depending on D50 and density)
- Sample port equivalent to thief
- Sample port samples represent the processing

Heinicke & Schwartz, Pharm Dev Tech, 9 (4), 359, 2004
Typical data
Applications
Multi-particulates

Sugar Sphere

Sugar Sphere Plus Drug Layer

Sugar Sphere Plus Drug Layer Plus Polymer Layer

Ghost After Dissolution, Expansion Noticeable

G. Heinicke ©
Horiba Instruments Webinar, June 2009
Drug layering

Heinicke et al., *Pharm Dev Tech*, 10, 85, 2005

G. Heinicke©

Horiba Instruments Webinar, June 2009
Resolve polymer coat addition
These are the particles

13%

15%

G. Heinicke©

Horiba Instruments Webinar, June 2009
Series of coat thickness
Linear Fit
\[ D50Mes \text{ (um)} = 891.86135 + 4.7723849 \times TPCW \% \]

Summary of Fit

- R Square: 0.993486
- R Square Adj: 0.992183
- Root Mean Square Error: 1.777776
- Mean of Response: 955
- Observations (or Sum Wgts): 7
Drug release

G. Heinicke©

Horiba Instruments Webinar, June 2009
**TPCW and drug release**

\[ y = 58.608x - 99.382 \]

\[ R^2 = 0.9986 \]
Coat thickness & drug release

\[ y = 23.637x - 86.566 \]

\[ R^2 = 0.9917 \]
Heinicke et al., Pharm Dev Tech, 10, 85, 2005

G. Heinicke©

Horiba Instruments Webinar, June 2009
How real is it?

Supporting evidence for meaningful data
Effect of batch surface area

- Adjust by altering core charge weight
- Ratio of weights is ratio of area (different weights of same substrate)
- Normalize for TPCW and look at drug release

Effect of raw material PSD (SA) on coat thickness, a contribution to lot-to-lot variation
Experiment with batch size

- 600, 650, 700, 750 and 800 g core charges
- One coating solution
- Same coating solution weight additions of 425, 559, 699, 845, 998, 1158, and 1326 g to each core charge
- Comparison of coat thickness
- Comparison of drug release
Core charge & change in D50

![Graph showing the relationship between Nominal CW and D50 for different Bx IDs (600g, 650g, 700g, 750g, 800g). The graph includes linear fits for each Bx ID.]
Normalize to TPCW

![Graph showing linear fits with ID labels: 600g, 650g, 700g, 750g, 800g]
Explain the single line
Different experiments marked
Novel use of DIA

Heinicke et al., Pharm Dev Tech, 10, 85, 2005
Different SS sieve cuts
Expt 1: Coating constant PSDs

- Same sized particles
- 700 g core charge of each (separately)
- Same coating solution weight additions of 425, 559, 699, 845, 998, 1158, and 1326 g to each core charge
- Sample, measure D50 at each TPCW, plot
- Q: Are the lines coincident, parallel or diverging?
Constant coat thickness

- **Small**
  - High potency

- **Medium**
  - High potency

- **Large**
  - Low potency
Expt 1: Slopes aren’t equal

![Graph showing coat thickness vs. TPCW with linear fits for different cores](image_url)
Heinicke et al., *Pharm Dev Tech*, 10, 85, 2005

G. Heinicke©  
Horiba Instruments Webinar, June 2009
Adjust for surface area

\[ C_2 = \frac{\rho_2}{\rho_1} \frac{d_2}{d_1} C_1 \]

\( C_x = \text{Core Charge Weight (1 or 2)} \)

\( \rho_x = \text{Bulk Density of Cores} \)

\( d_x = \text{Diameter of Cores} \)

Heinicke et al., *Pharm Dev Tech*, 10, 85, 2005
Expt 2: Adjust Core Charge

- Same sized particles
- 636g, 700 g, 775 g sprayed separately
- Same coating solution weight additions of 425, 559, 699, 845, 998, 1158, and 1326 g to each core charge
- Sample, measure D50 at each TPCW, plot
- Q: Are the lines coincident, parallel or diverging?
Expt 2: Slopes are equal

Coat Thickness (um) vs TPCW (%) graph with linear fits for Core IDs 15, 45, and 64.
Investigating drug release

- Polymer insoluble
- Swelling and stretching
- Coat thickness effects
- Core dependent
Coat thickness and swelling
Constant coat thickness

small

medium

large

High potency

Low potency
Core dependence: release & size

Drug release in 0.1N HCl, same sized cores and same coat thickness

Future opportunities for DIA

- Count, mass per particle, uniformity
- Surrogate dissolution test
- Surface area of core charge
- Bimodal distributions
- Density of drug layer or coating layer as applied
- Application to other multi-particulates
Acknowledgements

- Horiba instruments
- The late Dr. J.B. Schwartz & USP
- Dr. Garth Boehm and Dr. Kristin Arnold
- Anchen Pharmaceuticals Inc.

Questions?