Powder Rheometry for

Optimising Formulations for

Tablet Compression
Due to their simple and convenient use, compressed tablets are the most widely used solid dosage form, representing 70% of all dispensed medicines.

As well as providing the correct API dosage at the correct rate, the final tablet must be easy to handle, administer and store. It should also be a suitable size, hardness, texture, stability and palatability.

In addition to the Active Pharmaceutical Ingredient (API), tablets contain a number of inert materials/ excipients required to aid formulation. These include:

- Diluents
- Binders
- Lubricants & Glidants
- Disintegrants
- Sweeteners & Flavours
- Colouring agents
The Traditional Approach to Pharmaceutical Tablet Manufacture

- Requires each batch process step to be validated and fixed, with quality retrospectively tested.
- Requires all potential variables (including raw material properties) to be consistent, batch to batch, if quality is to be assured.
- Most raw material specifications may list particle size distribution, density, water content and some chemical properties, but not particle shape, surface texture, surface energy, elasticity, or many other likely important parameters.
- These variables all influence bulk powder properties like flow, adhesion, compressibility – therefore perhaps it is not surprising that batch to batch problems are often related to variation in raw materials.
Traditional **Batch Operations used in Tablet Manufacture**

![Diagram of batch operations in tablet manufacture](image-url)
Process Flow for Continuous Tablet Manufacture (Wet & Dry Granulation)
In both batch and continuous, successful product manufacture requires a detailed understanding of the material properties and processes employed.

The relationship between material properties and process conditions determines the critical quality attributes of the tablet.
Attributes Critical to Product Quality

- Tablet quality normally defined by a number of physical and chemical attributes – Critical Quality Attributes (CQA), considered essential to ensure a high quality tablet. Those typically included are:

  - Tablet weight (USP 905)
  - Content uniformity (USP 905)
  - Hardness (USP 1217)
  - Disintegration (USP 701)
  - Dissolution (USP 711)
  - Thickness

- Often tested for after the tablets have been manufactured through the measurement of an appropriate subset of the manufactured batch.

- If quality attributes are not met, further testing or corrective action is required.
Content Uniformity (CU)

- Content uniformity problems occur when the drug, or Active Pharmaceutical Ingredient (API) to excipient ratio changes beyond a defined allowable amount (± 15% by weight – USP 905).

- With some formulations containing just 1% or 2% of API, and total tablet weight in the tens of milligrams, the actual mass of drug in each tablet may be in the order of a few micrograms.

- CU problems occur for two reasons:
  - Incomplete mixing / blending
  - Segregation

- These scenarios occur for different reasons, and resolving them normally requires different approaches. However, from a material properties perspective, they are usually caused by the same variables:
  - Cohesion
  - Density
  - Particle size differences
Blending/Mixing

- Blenders or mixers exist in many forms and scales.

- Their efficiency depends on their design, the amount of energy available to impart in the blend, and the suitability of these process variables for the materials being blended.

- Mixers are often classified into “low shear” or “high shear”, based on the shear energy available to disperse the particles in the blend.
Blending/Mixing

- Ability of a powder to blend with one or more other components is significantly influenced by the strength of the cohesive forces acting between particles, which have the effect of limiting a particle’s independent mobility.

- Cohesive powders normally demonstrate poor flow and can be seen to contain agglomerates.

- In order to uniformly blend one powder with another powder, cohesive forces acting between every particle need to be overcome.

- In a blending process, this is achieved by inducing shear stress and strain, or displacement. Shear stress is normally a mechanically induced phenomena, whether through an impeller, agitator or tumbling.

- However if the shear stress and strain rate are insufficient to overcome cohesive forces, blend uniformity may not be achieved, even with extended process times.
The FT4 Powder Rheometer measures the resistance that the powder, or granules, exerts on the blade, as the blade forces its way through the sample.

This resistance is expressed as “Flow Energy”, which is calculated from the direct measurements of Torque and Force.
**Flow Rate (Strain)**

- Most powders exhibit higher shear stresses (worse flowability) at lower flow rates.
- Cohesive powders are the most flow rate sensitive.
- Non-cohesive powders less flow rate sensitive.
- Powders containing flow additives (mag. st.) often have lower flow energy at lower flow rates (more Newtonian).
Case Study – Mixing
Evaluation of Mixing using PET (Positron Emission Tomography)

Buck Systems Lab Mixer

- A small radioactive bolus (~1-2% by mass) of MCC is added to the substrate.
- The bin is tumbled for 5 revolutions.
- The bin is transferred to the PET camera which evaluates the degree of dispersion of the radioactive particles.
- Bin is returned to blender and the process is repeated.
Views of the blender contents after 5, 20, 55 & 100 revs
**Powder Mixing – Effect of Bin Rotational Speed on Spherical Particles (MCC)**

2% Radioactive MCC in 5L of MCC

Increasing blender speed

- **Faster mixing**
- **Powder becomes more aerated, permitting more efficient dispersion.**

Low RSD = uniform dispersion

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**Powder Mixing – Effect of Bin Rotational Speed on Platelet Particles (Sodium Benzoate)**

2% Radioactive MCC in 5L of Sodium Benzoate

![Graph showing the effect of bin rotational speed on platelet particles](image)

- **Increasing blender speed**
  - Slower mixing

- **Particles lock together more enthusiastically**

- **Low RSD = uniform dispersion**
Quantifying Flow Rate Sensitivity

- Significant difference in the powder’s flow rate sensitivity.

- Platelets experience rotational and translational “frustration” which increases with shear rate (blender speed).

- Flow rate test using powder rheometer identified similar response as observed in-process performance.
Segregation

- Even if blend uniformity is achieved, subsequent handling and processing can result in segregation.
- Mostly due to particle size and density differences, but can also be caused by differences in aerodynamic properties or the propensity to electrostatic charge.
- More pronounced in free-flowing powders.
- The five most common segregation mechanisms are:
  - Sifting – bins, batch blenders and chutes
  - Angle of repose – rotating shell-type blenders, stock piles and bins
  - Fines fluidization – air blenders, high speed ribbon blenders, bins and piles
  - Air currents
  - Chute trajectory
**Segregation**

- Inter-particular cohesion will restrict the mobility of individual particles, reducing the tendency of segregation.

- However, cohesion can also prevent blend uniformity from being obtained.

- Quantifying / measuring powder cohesion is vital to understanding the process performance of a powder / formulation.
Understanding the Interaction with Air

- **Weak cohesive bonds**
- **Strong cohesive bonds**

**Non-Cohesive Powder**

**Cohesive Powder**

AIR SUPPLY
Understanding the Interaction with Air

\[ m_1g \rightarrow f_{\text{coh-c}} \rightarrow m_2g \rightarrow f_{\text{coh-b}} \rightarrow m_3g \rightarrow f_{\text{coh-a}} \rightarrow m_1g \]
Understanding the Interaction with Air

Non-Cohesive Powder

Cohesive Powder

Air in

Air in
Understanding the Interaction with Air

Used for measuring:

- Cohesion
- Segregation
- Blending / mixing
- Low stress, gravitationally induced flow
- Dosing / Mass Uniformity
- Aerosolisation / DPI
- Fluidisation behaviour

INCREASING AIR VELOCITY

FLOW ENERGY

BFE

Cohesive

High Aerated Energy

Non-Cohesive

Low Aerated Energy

Low Aeration Energy

Increased propensity to Segregate

Weak Interparticular Bonds
**Tablet Hardness / Crushing Strength**

- Resistance of the tablet against an applied force until it breaks.
- Tablets must be able to withstand the rigors of handling and transportation experienced in the manufacturing plant, in the drug distribution system, and in the field at the hands of the end users (patients/consumers).
- Manufacturing processes such as coating, packaging, and printing can involve considerable stresses, which the tablets must be able to withstand.
- The mechanical strength of tablets is therefore of considerable importance and is routinely measured.
- Tablet strength serves both as a criterion by which to guide product development and as a quality control specification:
  - Too high – tablet(s) may not disintegrate within the specified time or meet the dissolution specification.
  - Too soft – tablet(s) may not withstand subsequent handling such as coating, packaging and shipping.
**Tablet Hardness / Crushing Strength**

- Tablet Hardness can be altered by either changing the powder properties or changing the applied load.

- Linear relationship between tablet hardness and logarithm of applied pressure:

  \[ \log P = nF_c + C \]  
  
  *(Shotton & Ganderton)*

  Where \( P \) = Applied Pressure, \( nF_c \) = strength of compact and \( C \) = constant

- However increasing the applied pressure can also result in an increase in both capping and lamination.

- May be preferable to change the powder properties – this can be achieved through granulation.
Case Study – Continuous Wet Granulation
**Wet Granulation**

- Converts fine powders into larger granules. Benefits include:
  - Improved flow
  - Reduced segregation
  - Better content uniformity
  - Improved compression properties
  - Reduced dusting

- Granulation via high shear can be a batch or a continuous process
  - In both cases, water is introduced whilst the powder is sheared

- Process variables:
  - Amount of water added
  - Screw speed (continuous)
  - Powder feed rate (cont.)
  - Impeller and chopper speed (batch)
  - Granulation time (batch)
  - Water addition rate (batch)
Influence of Granulation on Flow Properties

- Flow Energy is influenced by:
  - Friction between particles / granules
  - Mechanical interlocking of particles / granules
  - Strength of capillary bonds
  - Strength of cohesive forces

- In high shear wet granulation, the addition of water and work (shear) results in larger, denser, more adhesive granules.
- This means that more water and more work input results in higher flow energy as granules are harder to move (denser, larger, stickier and less compressible).

![Flowability Energy of 50/50 Lactose/MCC with Increasing Water Addition](chart)

- **Wet mass (50:50 lactose/MCC blend)**

  - 20% water w/w
  - 40% water w/w
Continuous Manufacturing and Tableting Study

GEA ConsiGma™ 1 Continuous High Shear Wet Granulator and Drying System

- **Process Variables (Granulator)**
  - Water Content
  - Screw Speed
  - Powder Feed Rate
  - Barrel Temperature

- **Process Variables (Dryer)**
  - Time
  - Air Velocity
  - Air Temperature

- Can also measure on-line NIR using Lighthouse Probe.

(photocourtesy of GEA Pharma Systems)
Continuous Manufacturing and Tableting Study

**Formulation**
- Two types of formulation considered in this study:
  - APAP – 90% API
  - DCP – 90% API

**Process Variables**
- Water content varied to provide granules with different properties, from under-granulated to over-granulated (determined visually).
- Screw speed varied to investigate its influence on granule properties. Settings chosen: 450, 600 and 750rpm.
- Feed rate of dry powder feeder also varied for a limited number of samples. Settings reduced from 25kg/hr (standard, equivalent to ConsiGma 25), to 20 and 15kg/hr.
Measuring Granule Properties

Changes in Bulk Material Flow Properties of Wet Granules as a function of Water Content & Screw Speed
Measuring Granule Properties

Data for wet granules of DCP formulation showing how granules of similar properties can be manufactured using different process settings.
### Measuring Granule Properties

<table>
<thead>
<tr>
<th>Condition</th>
<th>Screw Speed (rpm)</th>
<th>Powder Feed Rate (kg/hr)</th>
<th>Liquid Feed Rate (g/min)</th>
<th>Moisture (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>450</td>
<td>11.25</td>
<td>15.0</td>
<td>8.0</td>
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<tr>
<td>2</td>
<td>750</td>
<td>20.0</td>
<td>36.7</td>
<td>11.0</td>
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<td>450</td>
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<td>20.0</td>
<td>20.0</td>
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<tr>
<td>4</td>
<td>750</td>
<td>9.0</td>
<td>30.0</td>
<td>20.0</td>
</tr>
</tbody>
</table>

### Granule properties

<table>
<thead>
<tr>
<th>Condition</th>
<th>BFE – Wet Mass (mJ)</th>
<th>BFE – Dry Granules (mJ)</th>
<th>BFE – Milled Granules (mJ)</th>
<th>BFE – Lubricated Granules (mJ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2217</td>
<td>1623</td>
<td>1283</td>
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<td>4</td>
<td>3342</td>
<td>4140</td>
<td>1951</td>
<td>1795</td>
</tr>
</tbody>
</table>

Data showing how the flow properties of granules from each “Condition” change as they move through the process (wet, dry, milled, lubricated)
**Tableting and Critical Quality Attributes**

- **GEA Modul™ S Tablet Press**
  - Tooling: 7mm Round
  - Pre-Compression
    - Upper Position: 2.15mm
    - Lower Position: 4.82mm
  - Compression
    - Upper Position: 2.29mm
    - Lower Position: 4.29mm

- **Tablet Hardness Tester**

*(photo courtesy of GEA Pharma Systems)*
**Correlating Granule Properties with Process Data**

Data showing the strong relationship between granule properties and a critical quality attribute of the tablet (hardness) for each type of granule (wet, dry, milled, lubricated).
Conclusions

1. Powders (wet or dry) are complex materials.

2. The multiple process steps involved in tablet production, subject raw materials and intermediates to a range of different variables.

3. Each process operation provides the opportunity to adjust settings in order to improve process efficiency and / or to alter the properties of the material leaving that stage of the process.

4. With sufficient understanding of the relevant material properties and critical process parameters, it is possible to employ a QbD approach to tablet manufacture, ensuring the Critical Quality Attributes (CQA) of the tablets are met.

5. Full characterisation of powder flowability and other bulk and particle properties ensures the necessary information for QbD is available.

6. The FT4 Powder Rheometer from Freeman Technology has proven to be a uniquely valuable instrument in these applications and has been widely adopted across most powder processing industries worldwide.
Thank you for your attention

Thanks also to

Andrew Birkmire (GEA Pharma Systems)

For further information, please visit us at

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