A test of quality

Measuring a powder’s flow characteristics is key to establishing Quality-by-Design in powder-handling facilities. Mark Copley, of Copley Scientific, reviews current methods for powder flowability testing.

Powders are the starting point for many processes in the pharmaceutical industry, including capsules, granules, inhaled products and tablets, and their flow characteristics are critical-to-quality parameters in the production process.

Current regulatory thinking (European Medicines Agency and the US Food & Drug Administration) is based on the concept of Quality-by-Design (QbD) and places heavy emphasis on the application of Process Analytical Technology (PAT) during manufacturing. The exact nature of the PAT techniques to be used is normally determined during the pharmaceutical development process through the use of ‘Design of Experiments’.

Historically, a variety of methods have been used to test powders, and in an effort to rationalise the situation the Pharmacopoeias recently introduced a new harmonised chapter on Powder Flow. This gives recommended procedures for four simple methods, which are examined here.

Success or failure in many pharmaceutical operations can be linked directly to the flow properties of the powder being processed. Flowability is clearly important when assessing how material moves around the plant, particularly from storage bins and hoppers.

Much work has gone into developing links between powder properties and discharge behaviour, to provide design methods that reduce the likelihood of problems such as flooding and ratholing. Ratholes and arches form within a hopper when the strength that the powder bed develops is sufficient to form a stable structure that prevents further flow. Flooding, the uncontrolled flow of material, occurs with powders that flow too easily once mobile.

Other process steps affected by flow properties include blending and tableting. Manufacturing pharmaceuticals often involves mixing a relatively small amount of active ingredient into a much larger excipient bulk. Homogeneity in the final formulation is essential and easier to achieve if the powders have appropriate flow characteristics. Research has shown a direct correlation between both the rate and degree of mixing and flowability.

Tablet making provides a good example of the many ways in which flowability can influence process performance. The goal is to produce a consistent dosage form that always behaves the same in vivo. A high degree of powder flowability ensures:

- Smooth powder flow into the press. This discourages the formation of air pockets in the die for improved weight consistency and tablet stability.
- Accurate filling of the dosage chamber. This decreases weight variability and creates even pressure during compression, lessening wear on machine parts.
- Improved reproducibility of feed parameters. This results in more consistent tablet hardness, friability, dissolution rates, and ultimately blood drug levels.
- Rapid air release during compression. Free-flowing powders tend to be highly permeable so air is readily released during the compression step, reducing problems such as capping and splitting.
- High production speeds. Throughput has increased with the maturation.
of tabletting technology; however, very fast production rates demand excellent flow characteristics.

It is clear then that the pharmaceutical industry needs the ability to develop formulations with tailored flow properties, and the first step is identifying suitable techniques for powder characterisation.

Many factors influence the flow behaviour of powders, making characterisation a significant challenge. These factors can be grouped under three general headings:

- physical properties of the particle
- properties of the bulk powder
- processing environment.

This dependence on so many different variables explains why the powder characterisation community is still a long way from being able to predict processing behaviour from particle descriptors. It also highlights the difficulties inherent in trying to develop a single test that will accurately define a powder. In fact, no single test can adequately characterise the flow properties of powders, so most scientists advocate using multiple standardised test methods.

Over many years an array of testing techniques has been developed. Some, such as angle of repose and compressibility index, are relatively simple and well-established within the pharmaceutical industry. Their advantages and limitations are understood and there is much experience linking results with aspects of manufacturing practice. More recent techniques, such as powder rheometry and avalanche testing, bring new capabilities that complement traditional methods. All are valuable in providing information about different aspects of powder behaviour.

The new harmonised pharmacopoeia chapter on the testing of powder flow and flowability, is a move towards standardisation. It reviews four of the most commonly used techniques – angle of repose, compressibility index/Hausner ratio, flow through an orifice and shear cell analysis – recommending instrumentation and methodologies for each. Organic growth of characterisation techniques has produced many variants of similar tests and the new guidance outlines best practice with the aim of improving consistency of approach.

pharmacopoeial methods

In developing guidance, the pharmacopoeial bodies have extensively reviewed literature relating to each of the four powder flowability tests covered and assessed the impact of variations in method. Equipment manufacturers have responded by developing instruments that provide testing in accordance with the new advice. The powder flowability tester model BEP 2 from Copley Scientific, for example, provides flow through an orifice, angle of repose and shear cell in a single instrument.

angle of repose

Angle of repose is ‘the constant three-dimensional angle assumed by a cone-like pile of material’ formed as powders flows onto a surface. It is a function of the strength of interparticle forces, flatter cones being formed when these are weak. The more acute the angle of repose, the better the flowability of the material (see table 1). The literature suggests that formulations with an angle of repose as high as 40 - 50° will process satisfactorily but above this level flow will be problematic.

The pharmacopoeia chapter recommends that testing is carried out using a common fixed base with a retaining lip. This avoids the variability introduced by using different surfaces and by allowing the powder to spread in an uncontrolled way. A similar method is also described in an ISO standard dating back to 1977.

compressibility index

Compressibility Index and Hausner ratio are closely related: both are based on the comparison of ‘as poured’ and tapped bulk density. These techniques have existed for some time and are well-established. Both the US and European Pharmacopoeia already have separate monographs that define methods for determining Bulk Density and Tapped Density. Compressibility Index is defined as the percentage change in volume induced by tapping a sample of fixed mass. Hausner ratio is simply the unsettled volume divided by the tapped volume.

\[
\text{Compressibility Index} = \frac{100 \times (V^* - V_f)}{V_f}
\]

Where \(V^*\) = unsettled volume and \(V_f\) = tapped volume.

\[
\text{Hausner ratio} = \frac{V^*}{V_f}
\]

These two parameters are influenced by variables such as particle size and shape, and cohesivity, since they essentially reflect the impact of tapping on the particle packing. These are primary factors in determining flow behaviour that can therefore be inferred directly from values of Compressibility Index.

The impact of Quality by Design

The FDA’s Guidance for Industry Q8 Pharmaceutical Development emphasises the importance of product and process knowledge for the implementation of Quality by Design (QbD). The basic premise of QbD is that quality should be designed into the product and manufacturing process rather than simply tested for prior to release. It demands the identification of critical-to-quality variables – those that directly affect product performance – and the development of a robust manufacturing process that effectively controls these parameters.

The realisation of QbD requires enhanced knowledge of product performance over a range of material attributes, manufacturing process options and process parameters. The guidance emphasises the importance of building scientific understanding to support the establishment of the ‘design space’, specifications and manufacturing controls that define operating conditions for the production of material that meets the defined specification. Changes within the design space are not subject to further regulatory approval, providing a strong incentive for developers to ensure that it is optimally defined.

QbD is not compulsory but its adoption ultimately offers manufacturers greater flexibility with respect to regulation than has previously been afforded. The concept is therefore generating significant interest within the industry. Since powder flowability is frequently a critical process parameter, the focus on greater process knowledge is likely to increase the need for testing. The pharmacopoeias release of new guidance relating to powder flow is, therefore, timely since it highlights the most widely used characterisation techniques and the best ways of implementing them.

Table 1: The relationship between angle of repose and flowability

<table>
<thead>
<tr>
<th>Flow property</th>
<th>Angle of repose (degrees)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>25-30</td>
</tr>
<tr>
<td>Good</td>
<td>31-35</td>
</tr>
<tr>
<td>Fair – aid not needed</td>
<td>36-40</td>
</tr>
<tr>
<td>Passable – may hang up</td>
<td>41-45</td>
</tr>
<tr>
<td>Poor – must agitate, vibrate</td>
<td>46-55</td>
</tr>
<tr>
<td>Very poor</td>
<td>56-65</td>
</tr>
<tr>
<td>Very, very poor</td>
<td>&gt;66</td>
</tr>
</tbody>
</table>

Table 2: The relationship between Compressibility Index/Hausner ratio and flowability

<table>
<thead>
<tr>
<th>Compressibility Index (%)</th>
<th>Flow character</th>
<th>Hausner ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>Excellent</td>
<td>1.00-1.11</td>
</tr>
<tr>
<td>11-15</td>
<td>Good</td>
<td>1.12-1.18</td>
</tr>
<tr>
<td>16-20</td>
<td>Fair</td>
<td>1.19-1.25</td>
</tr>
<tr>
<td>21-25</td>
<td>Passable</td>
<td>1.26-1.34</td>
</tr>
<tr>
<td>26-31</td>
<td>Poor</td>
<td>1.35-1.45</td>
</tr>
<tr>
<td>32-37</td>
<td>Very poor</td>
<td>1.46-1.59</td>
</tr>
<tr>
<td>&gt;38</td>
<td>Very, very poor</td>
<td>&gt;1.60</td>
</tr>
</tbody>
</table>
and Hausner Ratio (see table 2). In general, powders that are less affected by tapping have better flow properties.

The pharmacopoeias recommend 100g sample in a 250ml volumetric cylinder for this test and point out that both rotation of the sample during tapping and the number of taps will affect results. Sample should be tapped until there are no further changes in volume. Scott Bulk Density testers and Tapped Density testers are widely used for this test, appearing in ASTM standards dating back as far as 1958, originally produced for the metal powder manufacturing industries.10

**powder flow**

Assessing how a powder flows through an orifice is an intuitively sensible way of investigating flowability and is a popular test for basic assessment. However, there is no established scale that allows behaviour to be inferred from results because there is such variability in the way tests are performed. Results depend on diameter and shape of the orifice; wall friction of the container material; and diameter and height of the powder bed.

The technique’s main value is for comparative study, although it also allows direct observation of flow behaviour. Pulsating flow patterns and changes in flow rate induced by changing the bed height are two phenomena most frequently detected. Only free-flowing powders can be studied.

Tests are conducted using either a cylinder or hopper as the powder container. Cylinders have advantages because particle-wall interactions are minimised, so the results are less dependent on the construction material of the instrument. However, a hopper may more closely simulate production conditions. Conventionally shaped funnels are not recommended because flow rate will be dictated by the length and size of the stem, and by particle stem material interactions.

Orifice shape and the method of measuring powder flow rate (in particular whether mass or volume is recorded) are additional test variables. In an effort to create a degree of standardisation, the European Pharmacopoeia had previously generated a precisely defined funnel arrangement, through the creation of a dedicated powdery flowability monograph.11 Equipment based around this funnel arrangement, with three nozzle sizes (10, 15 and 25mm), is now widely used. The powder flowability tester model BEP 2 from Copley Scientific is such an example.

To account for the wide range of methods already in existence, the new harmonised pharmacopoeia chapter2,3 simply recommends using an orifice with a diameter six times greater than that of the particles and a cylinder with a diameter twice that of the opening. While a circular orifice is preferred, other geometries are acceptable. The availability of orifices of different diameter allows testing to be carried out on the basis of the minimum orifice through which a powder will flow satisfactorily, and also facilitates optimal tailoring of the instrument to the test material.

**shear test**

Shear cell testing involves applying force to a powder sample to shear it across a plane. The methodology is more involved and time-consuming than the test described above, but the close control of degree of consolidation and environmental conditions permits a more precise and detailed investigation of flow behaviour. Shear cell testing closely defines the cohesive nature of powders, generating parameters such as the angle of internal friction, unfomed yield strength, tensile strength, flow factor and flowability indices. These data can be used directly in design methods for hoppers and bins. Shear cells can be annular, vertical or plate – each offers benefits and disadvantages. The new guidance offers no specific recommendations but endorses the value of the technique.

**References**

1 ICH Q8 (Pharmaceutical Development) – Manufacturing Process Development (2.3)
2 European Pharmacopoeia Chapter 2.9.36. Powder Flow
3 US Pharmacopoeia Chapter <1174> Powder Flow
5 ‘Developments in powder flow testing’ M Ros Pharmaceutical Technology Feb 2006
6 ISO 4324:1977 Surface Active Agents – Powders and Granules – Measurement of the Angle of Repose
7 US Pharmacopoeia Chapter <616> Bulk Density and Tapped Density
8 European Pharmacopoeia Chapter 2.9.15. Apparent Volume
10 ASTM B 527 – 06 Standard Test Method for Determination of Tap Density of Metallic Powders and Compounds
11 European Pharmacopoeia Chapter 2.9.17. Powder Flowability