Good Form

New developments in laboratory instruments offer the prospect of taking single point measurements to determine tabletability properties of compression blends, bringing fresh insights to tablet manufacture.

Most tablet formulations are developed and manufactured on a large scale without any objective assessment of their ability to form tablets, or whether they are adequately lubricated. With the latest tablet presses measuring both of these parameters, as well as a third critical quality attribute (CQA) – punch sticking (or take-off) force – taking measurements on small amounts of material may start to offer improved process understanding and control.

Main Methods

The principal production methods for tablets are direct compression, dry granulation (DG) and wet granulation. The product control strategy (PCS) is based on understanding the links between the formula and process, CQAs and the certificate of a pharmaceutical product. Generating the data to support the PCS is therefore key to meeting the regulatory expectations of Quality by Design (QbD).

The development of the formulation and process is usually an iterative one, in which it is adjusted based on evaluation of intermediates and products. All of these are carefully evaluated to understand the impact of formulation and process changes on product quality, in addition to supporting QbD. The manufacturing scale used during formulation development largely depends on the amount of drug substance and the equipment available.

Change in Approach

Based on the work of JM Newton, measurement of tabletability is rapidly becoming accepted as a simple and effective way of measuring compaction properties.
In his pioneering paper of 1972 (1), Newton calculated tablet tensile fracture stress (TTFS) values using the formula:

$$\sigma_t = \frac{2P}{\pi Dt}$$

Here, $\sigma_t$ is the TTFS, $P$ the breaking load in Newtons, and $D$ and $t$ are the tablet diameter and thickness, respectively. When the TTFS of a number of size fractions and lactose grades was plotted – as a function of tablet compaction pressure, measured using an instrumented tablet press – a previously unrecognised linear relationship was found. This enabled materials compressed under widely differing conditions to be accurately compared, and was subsequently given the term ‘tabletability’. Evaluation of the tabletability of hundreds of materials has yet to uncover one which does not demonstrate this linearity, although not all TTFS plots pass through the origin.

Other important CQAs are compressibility – the relationship between TTFS and solid fraction (or relative density) – and compactibility – the relationship between solid fraction and TTFS. These parameters clearly correlate (see Figure 1).

**Direct Comparison**

The use of tabletability is the simplest and most sensitive way to evaluate materials, as it provides a measure of both formulation and process effects. Figure 2 shows data from a recent in-house study comparing paracetamol tablets prepared by direct compression, DG and wet granulation. The superiority of wet granulation is clearly seen, with little difference in product quality between DG and direct compression. As a result, standard tabletability of 2MPa, at a compaction pressure of 200MPa, has been proposed as a target for tabletted products for routine large-scale manufacture (2). Even the wet granulated product tested here barely reaches the required standard.

**Influence of Tablet Size**

The Gamlen Tablet Press (GTP) is a versatile powder compaction instrument that can be used throughout development – from the selection of the salt, through to formulation design, process implementation and routine quality control (QC). It permits small-scale compression under controlled conditions, with measurement of compaction, ejection and detachment force – all for the same event and in real-time, using simple software for the measurement of the CQAs of active pharmaceutical ingredients, excipients and intermediates. In addition, the fracture load of the tablet can be measured under the carefully...
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independent of tablet size and shape. Most research has been done in the 2-6mm size range, but recently this has been extended to a range of capsule-shaped tablets from 65-650mg in compression weight. As expected, the formulation or process with the best tabletability – that is, the material which produces the strongest tablet at a given pressure – will usually be the best. This is because they can be made at the lowest compaction pressure, making them easier to manufacture, and they will also have the lowest solid fraction/highest porosity of the formulations being compared. In addition, this usually corresponds to the material with the best dissolution behaviour, as was the case when the dissolution properties of the materials in Figure 3 were compared.

Single Point Determinations

It is highly desirable to improve the assessment of materials prior to compaction for a number of reasons. In the simplest case, developers measure all of the CQAs of a granule or compression blend, except the one which matters most – the ability to form a tablet. Measuring tabletability on a routine basis opens a new potential mechanism for feed-back or feed-forward control-based systems. If used properly, this can be used as a process control tool when related to process parameters such as moisture content. Many materials have a minimum moisture content below which compression becomes problematic (for example, starch-based products and paracetamol granulations). As a result, a check on tabletability can be used to ensure that all batches meet minimum standards. However, to achieve wide adoption, a single-point QC control test is highly desirable, as the generation of full tabletability profiling using a range of compaction pressures is too time-consuming for routine use.

A further opportunity involves using the ability to determine in-die tablet dimensions to measure the solid fraction of a tablet which is subsequently fractured. In this way, a full profile of compressibility, compactibility and tabletability on a single tablet sample can be generated. When used in conjunction with historical

controlled conditions needed to ensure a reproducible tensile failure.

During the same in-house study outlined earlier, the tabletability of wet granulation was compared using the GTP and the Fette 2090, running under production conditions using different tablet sizes (see Figure 3). The Fette tablet machine was fitted with capsule-shaped punches and dies, making an 800mg product. Meanwhile, the GTP was using an 80mg tablet compressed on 5mm punches and dies. Results showed that the linearity of the tabletability plot was very good, and the tabletability on the two machines was identical, indicating that both can predict production behaviour accurately.

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and development data, this technique has the potential to yield powerful insights into the compression properties of in-process materials.

An additional benefit of routine measurement of compaction properties in a QC setting is the ability to build up a database of historical data for analytical use. Again, when used in combination with measurements for compaction blend particles, moisture content and density, a substantial amount of knowledge will be gained.

**Materials Control**

DG is becoming an increasingly important process in the pharma industry. It offers a number of advantages over both wet granulation and direct compression. Benefits over wet granulation include the absence of the need to use solvents or water during manufacture, meaning it can be used for moisture- and heat-sensitive products. Its advantages over direct compression include the capability to work with low bulk density materials and use a higher proportion of drug substance in the formulation.

The limitation of DG is that materials are significantly less compressible the second time around, which can result in friable tablets and dissolution problems caused by over-lubrication and over-compression when using DG. This phenomenon has been attributed to pressure-related work-hardening of the plastic formulation components during the first compaction, which makes it important to control the properties of both the starting material and the dry granular intermediate.

The GTP has recently been used to study the impact of the first compression event of DG on tablet compressibility (3). In this work, a range of paracetamol grades were dry granulated to a range of solid fractions between 0.65 and 0.80. The granules were then lubricated and compressed a second time at a range of solid fractions between 0.8 and 0.95 (see Figure 4). Distinct differences between the compressibility profiles of the different grades were seen, but there was no impact of the compaction pressure applied at the DG stage on the compressibility of the final formulation. This indicates that paracetamol does not undergo work hardening during DG – a surprising and interesting result.

**New Insights**

The use of laboratory compression instruments for powder testing offers new insights and opportunities in the challenge to develop, register and manufacture tablets of the highest quality and reproducibility. Product and process development using these new techniques should result in better formulations processes, as well as reduced manufacturing variability.

**References**


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