The importance of normalisation when comparing tablet properties

Tablet quality definition

The properties of a tablet, both during manufacturing and in vivo, are determined by the properties of the materials used to make it; and the manufacturing conditions used to prepare the powder blend and compress the tablet. Understanding the impact of starting material properties and manufacturing conditions on the tablet at the development stage is of paramount importance. Some material and tablet characteristics may not matter but others can have a dramatic effect on processing and in vivo behaviour. These physical and chemical properties are known as Critical Quality Attributes, and they must be established for starting materials, in-process materials, and the finished tablet.

To assess the impact of starting materials and manufacturing conditions, it is important to ensure that the correct tablet properties are used when making comparisons with tablets made from different formulations or on different pieces of equipment. It is actually very difficult to make scientifically robust comparisons between formulations and processes. This whitepaper explains the importance of the most commonly reported physical measurements—“tablet hardness” and “compression force”—and how they should be modified in order to make valid comparisons.

Tablet hardness and compression force

Tablet hardness, or breaking strength, is an important and widely used parameter to control the tablet manufacturing process. In many cases it is used a surrogate measure for compression force during manufacture, often because the tablet machine is unable to measure compression force. It is a very important control parameter because compression affects every tablet property including disintegration, dissolution and friability. In some cases stability is also affected.

However, tablet hardness (or breaking force) comparisons are applicable to one tablet size and shape only. If you materially change the size, shape or thickness of a tablet then all tablet hardness comparisons become incorrect. It is intuitively obvious that it is more difficult for a small tablet to withstand a given load than a larger tablet to do so, and in engineering terms this indeed proves to be the case.

In fact there are two factors at work here. One is the effect of the cross sectional area across which a tablet breaking force is applied. Again it is intuitively obvious that the strength of the tablet is proportional to the cross sectional area across which the force is distributed and this is indeed the case.

The second factor is that if the same force is applied to (say) a 6mm tablet and a 3mm tablet, the force per unit area on the small tablet is four times the force per unit area on the large tablet. This is because area is proportional to the square of the diameter of a circle. So the material in the 3mm tablet will experience a pressure four times that of the 6mm tablet at the same load.

It is essential that these factors are taken into account when making comparisons between tablets. Instead of comparing breaking loads (measured in Newtons or Kilograms), tablets should be compared using breaking “pressure”, which in engineering terms is called the “tensile fracture stress”. And instead of comparing compaction force we should compare compaction pressure. When we do this, results make much more sense as can be seen below.
In Figure 1, 3mm and 6mm tablets appear to have similar breaking strengths implying the tablets are similar. However this takes no account of the differences in tablet thickness, nor the effect of differences in the compaction pressure. Only the applied compression force is quoted which does not take into account the punch diameter and hence the area over which the force is applied.

Making the correct comparison

Figures 1 and 2 show that making comparisons using only compression force and hardness does not reveal all of the information available in the data. This is particularly important for comparing formulations which have been compacted on different equipment. To make the proper comparison the tablet punch diameter, thickness of the tablet, and the compression force must also be taken into account so that a graph of tensile fracture stress (TFS) vs compaction pressure can be prepared.
The differences in tablet thickness, diameter and compression force for circular tablets can easily be accounted for by calculating tablet tensile fracture strength, and tablet compaction pressure.

**Tablet Tensile Fracture Stress**

For round flat face tablets this can be calculated from the breaking force according to the following equation first used by Fell and Newton in 1970 (1):

\[
\sigma_t = \frac{2P}{\pi Dt} \quad (1)
\]

\(\sigma_t\) is the tensile fracture strength of the tablet, \(P\) is the fracture force (N), \(D\) is the tablet diameter, \(t\) is the overall thickness

The equation takes account of the breaking load, thickness and diameter of the tablet and effectively divides the breaking load by the area of the fracture surface. This formula is only correct for cylindrical tablets.

Pitt et al (2) has derived equations for a wide range of other shapes.

\[
\sigma_t = \frac{2}{3} \left( \frac{10P}{\pi D^2} \left( 2.84 \frac{t}{D} - 0.126 \frac{t}{W} + 3.15 \frac{W}{D} + 0.01 \right) \right) \quad (2)
\]

\(\sigma_t\) is the tensile strength, \(P\) is the fracture load (N), \(D\) is the length of the short axis, \(t\) is the overall thickness and \(W\) is the wall height of the tablet

If tablets of different shape are to be compared, these must be used for the comparison to be correct.

**Compaction pressure**

For a flat faced tablet, compaction pressure is calculated simply from the force applied divided by area (3)

\[
Cp = \frac{P}{A} \quad (3)
\]

\(Cp\) is the compaction pressure, \(A\) is the area of the punch tip
Figure 3: Variation of compaction pressure with punch diameter and compression force

As mentioned earlier at the same compression force, punch diameter has an exponential effect on compaction as shown in Fig 3. 400kg of compression force on a 3mm punch produces four times the pressure as 400kg on a 6mm punch.

For tablets which are not flat faced, the cross sectional area of the punch is still normally used, although this may introduce a small error.

**Tensile fracture stress/compaction pressure comparisons**

When the tensile fracture stress and compaction pressure for the tablets have been calculated, the data reveals its full value. By using the tensile strength for tablets and normalising the applied force with the punch diameter to give the compaction pressure we can see the impact of tablet size and compaction pressure on the key tablet property tensile fracture stress, and the effect of tablet size.
Figure 4: The tablet tensile strength comparison for 3mm and 6mm tablets made from Avicel

Figure 4 show that the higher the compaction pressure applied the larger the tablet tensile fracture stress. There is an area of overlap around 150MPa of compaction pressure when the tensile strength of a 6mm tablet is similar to the tensile strength of a 3mm tablet. Normalising the data in this way provides an objective way to measure tablet physical properties.

This shows that the behaviour of Avicel, when compressed into a 25mg tablet of 3mm diameter is completely scalable to the behaviour of 100mg tablet of 6mm diameter. We have in-house data to show that a 25mg tablet correctly predicts the compaction behaviour of an 800mg tablet of a completely different shape.

The advantage of tensile fracture stress measurement

Tensile fracture stress measurements become meaningful without regard to tablet size. A statement that a specific hardness is required to pass a friability test or survive a coating operation is not universally true and applies to one specific size only. Normalising the data will remove that barrier and help particularly in comparing formulations compressed on different equipment.
The Gamlen Tablet Press GTP-1 and tensile fracture stress measurement in formulation development

The Gamlen Tablet Press GTP-1 is the world’s first computer controlled bench-top tablet press and tablet hardness tester. Ideal for small scale formulation and pre-formulation studies, the Gamlen Tablet Press is simple and easy to use.

![Gamlen Tablet Press GTP-1](image)

**Figure 5:** The Gamlen Tablet Press GTP-1 (left) and dispensing powder with a powder pipette into the die of the GTP-1 (right)

Measurement of tensile fracture stress is easy on the Gamlen Tablet Press GTP-1 as the force applied is recorded and the GTP-1 can also record the breaking force for the tablet under test. Since the GTP-1 also uses flat face round punches, the compaction pressure is simple to calculate.

We have already used the GTP-1 for a number of applications in formulation development. We investigated the compressibility of various formulations of a well-known blood pressure medicine, comparing the existing wet granulated formulation with various substitutions of direct compression excipients. Tablets were formed at various compression forces - 100, 200, 300 and 400kg. 100mg of each material was compressed to form a 6mm round faced tablet. Data was collected on the compression profile, weight and thickness of the tablet formed. Some tablets were then subsequently crushed on the same instrument and the fracture profile recorded as well as peak fracture load. This was repeated for all formulations and a profile of the formulations compressibility and tensile fracture stress of subsequent tablets built up. Dissolution testing of the various intact tablets was also then carried out to determine the effect of excipient substitution on bioavailability.
The tensile fracture stress results (Figure 6) showed clear differences between the formulations. In particular we see how extra Avicel and agglomerated lactose 80 have a major effect on tensile strength of the tablet compared to the existing wet granulated material, whilst other formulations are worse.

The dissolution behaviour (Figure 7) of the various direct compression formulations also reveal considerable variation according to the excipient used. After 45 minutes the tablets made from agglomerated lactose 80 and spray dried lactose produced dissolution profiles comparable to the original wet granulated material. These are followed by the partially pregelatinised starch and then the microcrystalline cellulose with the lactose powder 200 and sieved lactose 80 exhibiting the slowest dissolution profiles for this drug. The agglomerated lactose 80 and spray dried lactose produced tablets with superior tensile strength compared to the wet granulate. Since the Pharmacopoeial test for dissolution is taken at 45 minutes, it is feasible that the existing wet granulation step in the manufacture of this particular drug could be replaced by use of either agglomerated or spray dried lactose as a direct compression ingredient. This would be of considerable benefit to the manufacturer, saving process time and cost resulting in a more efficient manufacturing process with associated economic benefits.
Conclusion

Without proper normalisation of tablet hardness and compression force data, misleading conclusions may be drawn on formulation behaviour particularly when using different equipment for tableting. We have shown how important the tablet thickness and punch diameter is to normalise the tablet hardness and compression force data to give meaningful comparative data.

Further information

For more information on the Gamlen Tablet Press and tensile fracture stress measurement go to ;

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