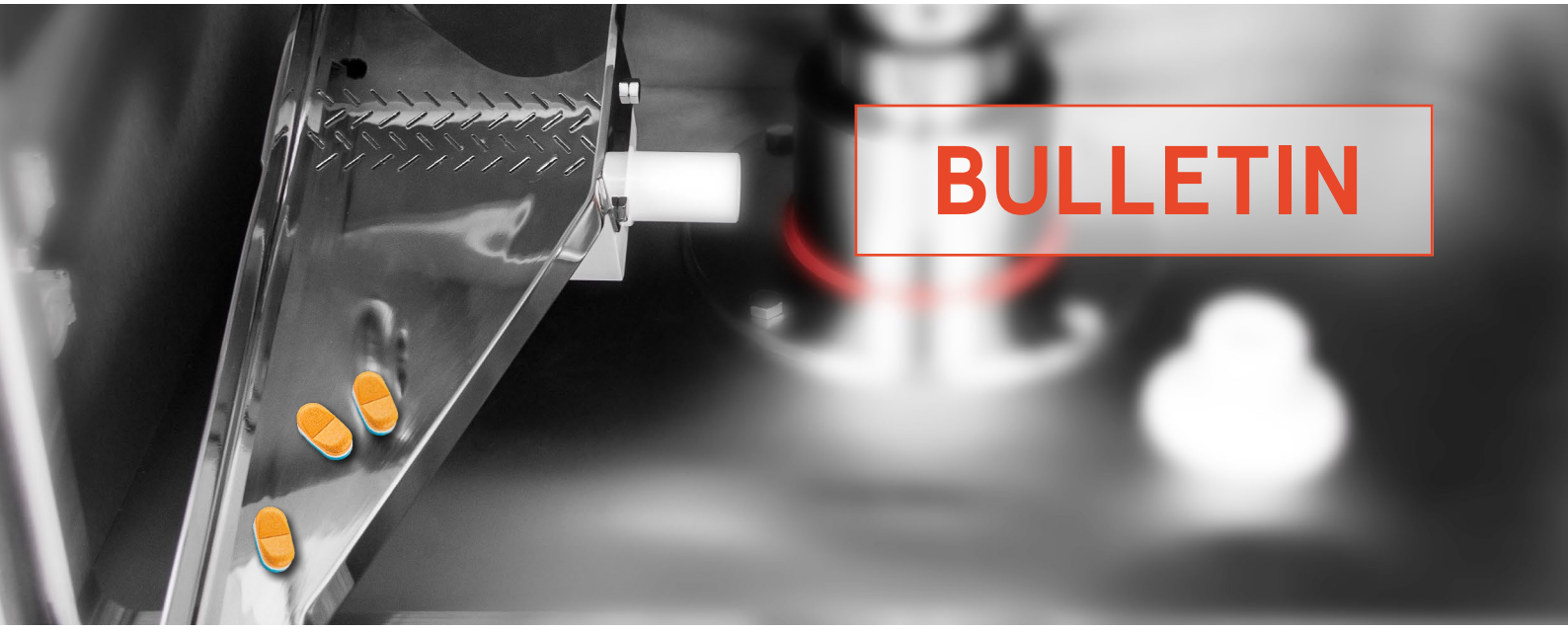
MEDELPHARM
the tableting instrument company



A FUNDAMENTAL STEP IN YOUR TABLET DEVELOPMENT

Formulation development and technical transfer from lab to production can be challenging and requires a deep knowledge of your formulation.

The integrated and intuitive data analysis features drive formulators and scientists in their decision-making process with build-in graphs and reports to develop robust and scalable formulations. Knowledge management based on data leads to avoid tablet defects in production and guarantee high production output. This can be undertaken right from the development stage thanks to STYL'One compaction simulators

Tensile strength: a better way to express tablet breaking force.

Tablet breaking force as a function of compression force are useful to assess formulations and to determine the critical process parameters of production rotary tablet presses. However, according to the USP <1062> monograph, this plot also known as manufacturability profile should be replaced by the tabletability profile which normalizes data and minimizes the impact of tablet dimension and weight on tableting behavior. This plot expresses the tablet tensile strength as a function of compression pressure

Working with compression pressure and tensile strength has several benefits. As the compression force is divided by the punch tip cross-section, it allows scientists to compare compression data from different tooling sizes and shapes.

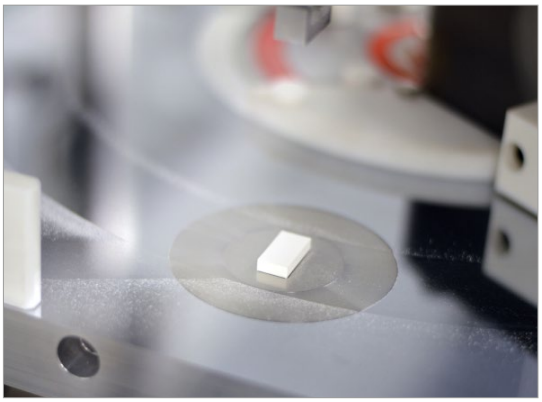
Compression stress for an ideal direct-compression material goes from 20 MPa to 125 MPa and should not exceed 300 MPa with a shaped tooling. In case of limited amount of material available, a single point pressure can be quickly performed to compare different products. At MEDELPHARM Science Lab, a pressure of 200 MPa is considered as a standard pressure to study pharmaceutical blends.

Tensile strength is calculated automatically thanks to different equations that depends on tablet geometry. Tensile strength at around 1 MPa should suffice for small batches where tablets are not subjected to significant mechanical stresses. A tensile strength of 1.7 MPa will ensure that a tablet is mechanically strong enough to withstand commercial manufacture, and packaging. When dealing with short material supply, scientists can compare tablet tensile strengths at the same solid fraction, i.e., a solid fraction of 0.85.

Fast experiment setup with limited amount of material

In this study, excipients were used as placebo materials, but the concept remains the same with formulations. Four well-known excipients have been compared on a STYL'One Evo compaction simulator: microcrystalline cellulose grade 102 (MCC 102), maize starch, di-calcium phosphate (DCP), and mannitol grade 200 SD. A six-point compression profile was made from 5kN to 30kN, using a standard EU-B 11.28mm round flat tooling and a V-shape research compression profile (also known as saw-tooth profile). V shape profile is often used for material characterization to ensure constant speed of the punch during the compaction process.

The STYL'One external lubrication box has been used with MgSt to assess the tableting behavior of neat material.



Tablet physical properties including weight, dimension and hardness were measured on a Sotax® ST50 and automatically retrieved by Analis, the piece of software that drives the STYL'One Evo and analyses the data generated. Analis then computes the data and generates standard and custom charts and reports, including the ones from the USP guidelines.

What to learn from a tabletability profile?

The tabletability plot (tensile strength vs pressure applied) can quickly reveal if target tensile strength is achieved or if either the formulation or the process parameters must be optimized. Generally, tensile strength increases with compression pressure. However, tabletability profiles differ from one product to another.

MCC 102 shows the best cohesiveness. Even though high tensile strength can be achieved at very low compression pressure, it can lead to other issues in production. For example, a small tablet weight variation will induce a small change in compression pressure that will have a significant impact on tablet tensile strength. It will be quite challenging to regulate the production press with narrow regulation and acceptance bands. Low production yield could be obtained with a high number of rejections, leading to an increase in manufacturing cost. This behavior is typically seen with plastic deforming material.

The mannitol grade exhibits good cohesiveness, but an inflexion point appears for a pressure around 250 MPa. This phenomenon is called over compression on the USP guidelines. Tablet defects including lamination or capping might appear above this pressure.

Maize starch and DCP are the least cohesive materials. High compression pressure will be required to achieve reasonable tensile strengths. Using such excipients at high concentration in a formulation will lead to a risk for poor tablet quality with tensile strength well below 1.7 MPa.

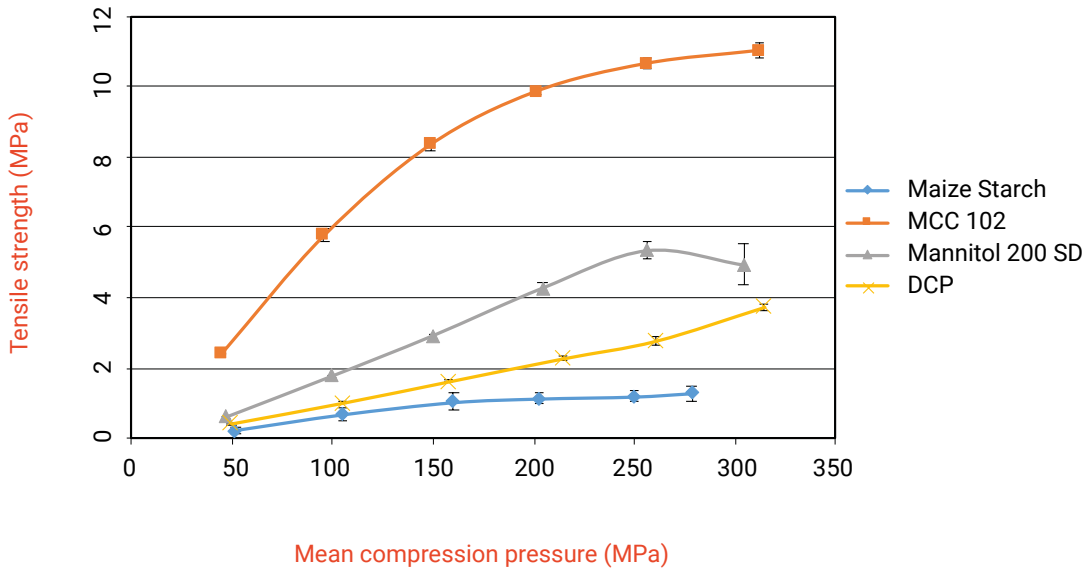


Figure 3

Tabletability profiles of four well-known excipients

To go further ...

The USP <1062> monograph describes the tabletability of pharmaceutical materials as the following equation:

log (Tensile Strength) = K log (compression pressure) + B

Where K and B are empirical constants

The K and B constants were retrieved with high correlation level during this experiment. The B-value is the y-intercept of the tabletability profile. It gives an information on the cohesiveness of the material at low pressure. Here, the MCC 102 has the highest B-value. The K-value is the slope of the tabletability profile.

For products with similar B values, it allows formulation scientists to compare their cohesiveness. Here, the K-values of Maize starch, DCP and Mannitol are in sorting order. However, it is important to bear in mind that the K and B values must be handled as a pair to appreciate the tabletability of a product. For example, just looking at the K value for the MCC 102 might be misleading.

Product	K	B	R^2
Maize Starch	**1,0146**	**-2,3007**	0,9661
MCC 102	**0,7932**	**-0,8659**	0,9728
Mannitol 200 SD	**1,2714**	**-2,3118**	0,9986
DCP	**1,1424**	**-2,2980**	0,9994

Conclusion

This case study highlighted how quickly excipients or powder blends can be compared thanks to tabletability profiles. In this example, tests were performed with neat excipients. In real tablet formulation development, it is critical to assess the tabletability of your final blends.

Similar experiments can be easily conducted on a STYL'One Evo during formulation development and optimization but also for troubleshooting. For example:

- Impact of compression speed on quality attributes
- Formulation optimization and influence on tablet properties
- Determination of the best lubricant grade
- Capping/lamination issue solving

STYL'One Evo key benefits

- Versatile
- Standard tooling
- Ideal for small amount of material
- Quick product and tooling changeover
- Easy to clean – easy to handle
- Simulation of any rotary tablet press
- User-friendly HMI for fast experiment setup and results with automatic studies

References:

• USP Monograph <1062>, current edition

• McCormick D. Evolutions in direct compression. Pharmaceutical Technology. 2005;29(4):52- 62.

• Leane, M., Pitt, K., Reynolds, G., & The Manufacturing Classification System (MCS) Working Group. A proposal for a drug product Manufacturing Classification System (MCS) for oral solid dosage forms. Pharmaceutical Development and Technology 20, 12–21 (2015).

• Hancock BC, Colvin JT, Mullarney MP, Zinchuk AV. The relative densities of pharmaceutical powders, blends, dry granulations and immediate-release tablets. Pharmaceutical Technology. 2003;April:64-80

• Pitt KG, Heasley MG. Determination of the tensile strength of elongated tablets. Powder Technol. 2013;238:169-75

Author
Adrien Pelloux
MEDELPHARM

AB-MKT-003-A (2021-SEP-30)