

## WHITEPAPER

## DATA GATHERING AND ANALYSIS NECESSARY IN NEW TABLET DEVELOPMENT

A significant concern in tablet manufacturing is speed to market. Moving too quickly, however, may cause delayed production, lost product, and missed deadlines. To reduce potential headaches, companies are embracing the principles of Quality by Design (QbD) and utilizing automated data gathering and tablet analysis during research and development. This allows organizations to reduce product development and delivery stress and loss.

Even under ideal circumstances, tablet development will encounter unknown variables before a final product is realized. To reduce problems, performing several simple experiments and creating characteristic profiles enables R&D and production to accurately evaluate new drugs as oral solid dosages. Experimental data is used to characterize formulation performance with both patients and manufacturing organizations as ultimate customers. Understanding these compaction and compression characteristics is fundamental because they often drive changes in production requirements.

These anticipatory experiments result in less formulation changes prior to full-scale production. Changes to production-ready formulations are the costliest and most time-consuming because they must meet FDA SUPAC compliance or other regulatory guidelines. The pharmaceutical industry benefits from utilizing vendor partnerships for troubleshooting techniques and solutions. A quality tooling vendor can provide help to prevent tableting issues with information provided in compactability, tableability and compressibility profiles. The study completion and analysis outlined in this article also provide smoother transitions from R&D to full-scale production.



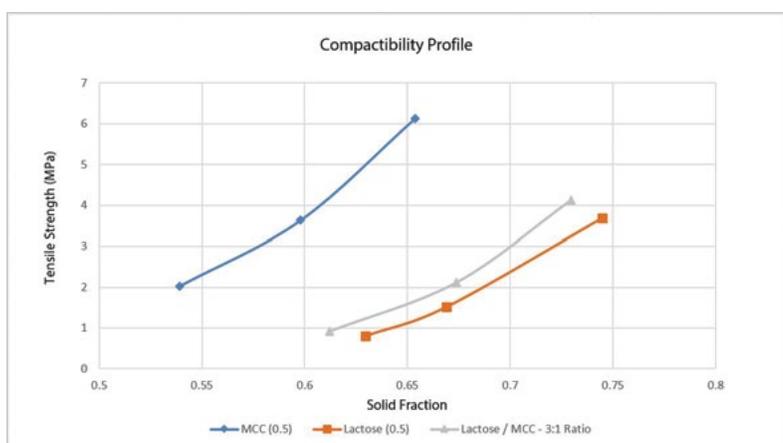
## GATHERING POWDER PERFORMANCE DATA WITH SINGLE-STATION PRESSES

Single-station tablet presses offer crucial advantages during new tablet early formulation and pre-clinical development. When utilizing a single-station press, operations that would otherwise occur automatically are performed manually, such as blending and the die filling process.

The advantage of a single-station press is it allows R&D scientists to perform tableting studies on the active pharmaceutical ingredient (API). Having these data can assist in excipient selection. Use of single-station tablet presses also makes performing formulation studies easier. Each study works harmoniously to provide data about a tablet's planned components and how well they consolidate and compress.

## COMPACTABILITY PROFILE

This profile illustrates how readily a material undergoes changes in volume when compressed. It is a measure of how a powder can be changed into a tablet and the resulting strength of the tablet. A simple plot of compression force against the resulting tablet's breaking strength is often referred to as a manufacturability plot. To compare various sized tablets, the compaction pressure is calculated by using applied force and punch cup area. A tablet's solid fraction is an important parameter because small changes in solid fraction can affect tablet properties. Figure 1 illustrates a compactability profile for two excipients and a blend of the two generated on a single-station tablet press. The three samples have a magnesium stearate level of 0.5% for lubrication.



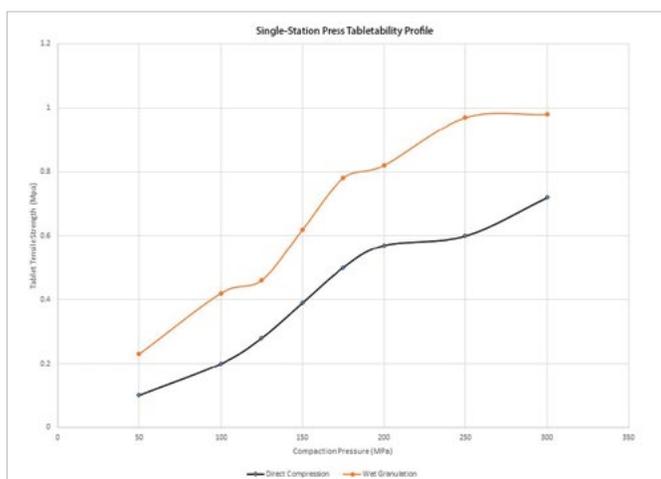
**Figure 1.** The compactability profile for two excipients and a blend of the two generated on a single-station tablet press.

## TABLETABILITY PROFILE

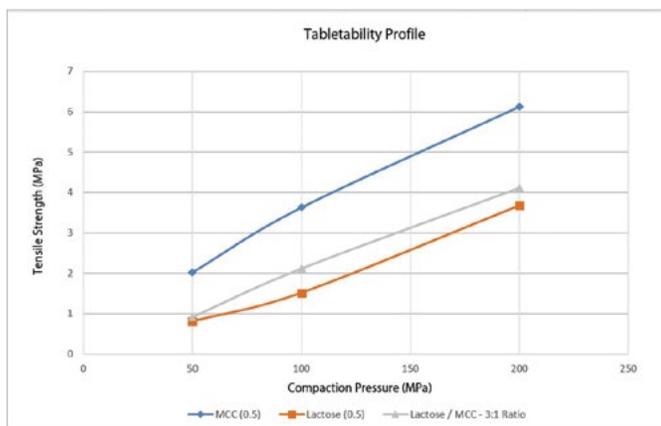
To better understand tablet tensile strength's relationship to force used in tablet compression, it is vital to plot the tablet tensile strength against compaction pressure. Both variables are normalized to the tablet area to facilitate comparison of tablets of different size or tablets compressed on other tablet presses.

In the tableability profile in Figure 2, we see a typical formulation profile compressed on a single-station press. Each formulation contains a high drug load; one is a direct blend recipe and the other a wet granulated drug product. Tablets with a tensile strength of greater than 2 MPa are desired, and as neither formulation is found to form a suitable compact at any pressure between 50 MPa and 300 MPa, further study should occur before expending efforts on a rotary tablet press.

Figure 3 illustrates the tableability of the three samples measured for Figure 1. It is clear that microcrystalline cellulose (MCC), with 0.5 percent magnesium stearate, provides the strongest compact. This is due to the MCC plastic deformation characteristics. The lactose monohydrate, with 0.5 percent magnesium stearate, also provides a robust tablet at reasonable compaction pressures. By blending the two excipients, it's possible to add functions to the formulation's performance, including plastic and brittle deformation characteristics. A 3-to-1 ratio of lactose-to-MCC provides a slightly stronger tablet than one made from pure lactose.



**Figure 2.** Typical formulation profile compressed on a single-station tablet press.



**Figure 3.** The tableability of the three samples measured for Figure 1.

## COMPRESSIBILITY PROFILE

The compressibility profile illustrates how readily a material undergoes volume changes when compressed, and affects tablet properties like dissolution, hardness, and friability. Analyzing tablet compressibility data will ensure the

tablet quality throughout the R&D and manufacturing processes. Figure 4 shows the compressibility profile of the same excipients as Figures 1 and 3.

### IMPORTANCE OF THE ROTARY TABLET PRESS IN R&D

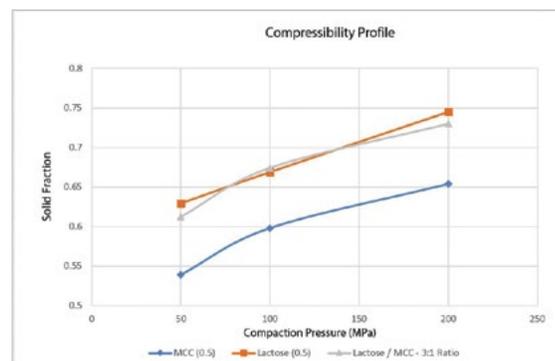


Figure 4.

The use of a rotary R&D press is the next step in planning tablet compression scale-up to meet client needs. Integrating this step into tableted product development allows additional study completion and provides data at larger-scale production that can be used for further scale-up and production considerations.

As previously shown in Figure 2, there is a stark contrast between compaction profiles of the direct compression blend compared to the wet granulation when completed on a single-station press versus a rotary press (as presented in Figure 5). The differences in moving to a large press with 30+ tooling stations will significantly change the compaction process even further. These changes can occur due to the pitch circle diameter of the tablet press turret, increases in the tangential punch velocity, and decreases in compression dwell time.

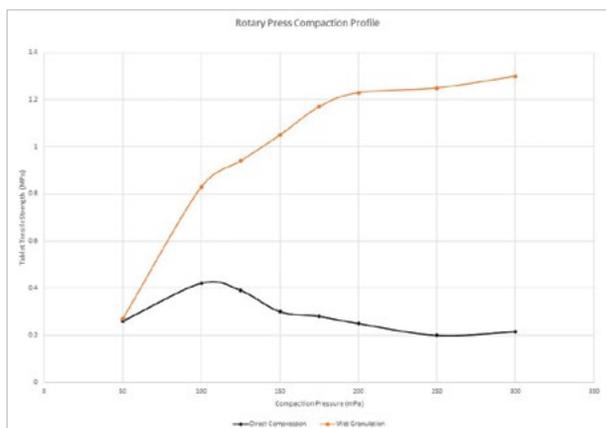
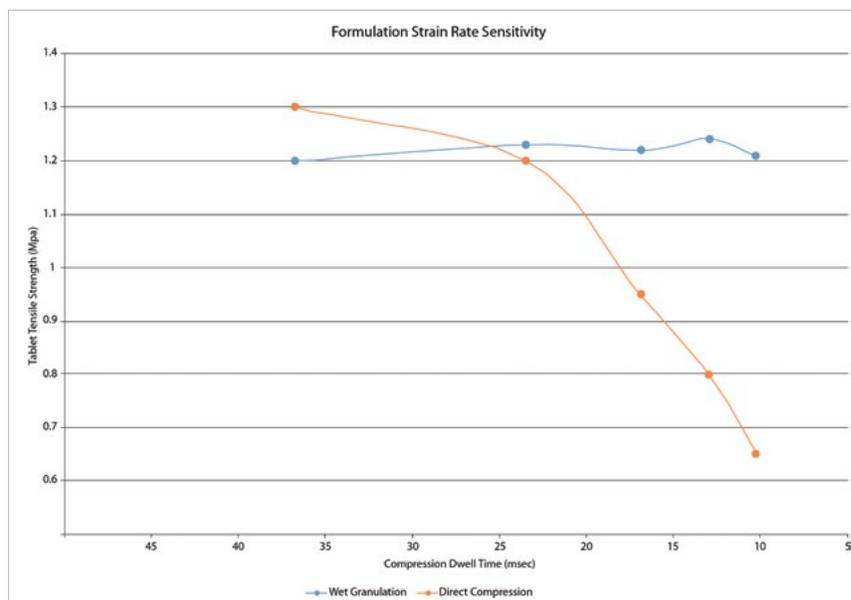


Figure 5.

A simple strain rate study helps determine whether a blend produces an acceptable tablet at various turret speeds and dwell times. Figure 6 reveals that the strain rate-sensitive formulation will need almost twice the dwell time to produce a quality tablet compared with the wet granulation. With respect to API, completing these tests can be costly, so what can be done to reduce costs? Discuss tablet compression tooling options with reputable vendors. Tooling manufacturers offer modifications that may reduce or solve the problem of reduced strain rate.

**Figure 6.**



## OTHER AREAS TO REVIEW: COMMUNICATION AND TOOLING

Gathering and analyzing data are important, but lack of communication between departments is often an additional cause of missed deadlines. Make sure your product development team communicates with colleagues in other departments on a regular basis. Strengthening communication and common goals relieves pressure from different areas to fix problems that may have gone otherwise unnoticed. Communication should remain open throughout the entire process—from R&D through final production. Strain rate studies may reveal potential issues with production departments' ability to manufacture the desired number of tablets due to formulation issues, which may need to be addressed via compression tooling modifications.

Tooling vendors are an excellent resource for troubleshooting formulation issues, so it is important to communicate issues as they occur. Formulation issues that cannot be changed due to regulatory implications may be resolved by a quality tooling vendor early in the process.



As some APIs are prone to initiate sticking and picking issues, a tooling vendor should have a strong working knowledge of different steel types. By carefully selecting tooling steel, sticking and picking issues may be alleviated without the use of expensive coatings. For example, tools with high concentrations of chromium in the alloy—16 to 18 percent—can enhance the release of tableted materials. Other specialty steels enhance performance needs like even wear, corrosion resistance, or better compressive strength. Tooling modifications also may be a viable option. For example, both TSM-B and TSM-D tools can be manufactured with an increase in head flat diameter to increase dwell time. This allows a tablet press speed increase, which increases production.

Formulations with a significant quantity of fine particles are prone to powder sifting between the punch tip and die bore. This results in excess heat generation, which can initiate sticking and picking as well as cause binding of the lower punch in the die. Fixes may include machining a narrow tip width and deeper sharp relief for lower punch tips, which can help scrape excess powder from the dies.

Many picking issues are preventable and may come from tablet design. Embossing design is a common culprit with problematic font selection, font size, location on the tablet surface, and engraving cut depth or angle. Compound cup configuration, utilizing practical font selection, incorporating pre-picking, and character tapering can reduce the probability of picking prior to a product run.

With the emergence of better information-gathering techniques, the inclusion of data analysis must become part of the process for acquiring QbD information. The tooling vendor remains the best resource to contact when problems are encountered that may be addressed by minor changes in tablet design or tool configuration. However, use of the tableting profiles mentioned will aid in building suitable drug product component profiles that comprise much of a company's tableted products. As the profiles stated in this article are generated, gathered, and cataloged, R&D scientists, production managers, and others involved in submitting new drugs for review will be better equipped to make tablet design and formulation decisions with less outside consultation.