

CHAPTER 1:

R&D TO PRODUCT: HOW TO REDUCE COSTLY SCALE-UP PROBLEMS

When scaling a new drug formulation from the development side of R&D into manufacturing, there is often a reality check with respect to process scale-up and performance of the formulation at production levels. Problems with capping/lamination and sticking/picking are often first realized when a formulation is introduced to a level of compression required to supply market demand.

Manufacturers of compression tools are often asked to proffer a reason why tooling that is causing a formulation to generate tablets with obvious and unacceptable defects. Despite having approved the tablet design, the manufacturing manager is faced with a fix that will not involve discussions with regulatory authorities – internal or external. Often the technicians in the compression suites will have taken the liberty to manipulate the compression conditions, in every possible combination, attempting to solve the problem. After trying every possible mixture of pre-compression, final compression, feeder speed, and turret speed, the obvious failure in the process must be the tooling.

The issue with this thought is compression tools have many additional variables that are not often considered and certainly not tested before scale-up is studied. These tooling variables typically come under scrutiny only when there is a problem like sticking. The unfortunate reality is that drug product formulation should be evaluated through a series of simple experiments to determine whether potential problems should be



**Natoli's NP-400
Tablet Press**

addressed before regulatory registration of the drug product recipe. Rushing a product to market can yield some expensive and painful lessons if the formulation fails to meet manufacturing expectations of capacity and yield.

To screen formulations for scale-up problems, the following simple experiments should be considered to fully characterize formulation performance: compaction profile and strain rate sensitivity. A compaction profile offers insight into the performance of the powder under compression. The simplest test is compression of the powder at different forces and testing the tablet breaking strength of the resulting tablets. An alternative approach is to normalize for the punch tip pressure as opposed to using just the compression force. A study of the powder using a range of pressure typical to the pharmaceutical industry of 50 MPa - 300 MPa allows a simple comparison of tablets of all sizes using the same formulation. A typical profile is shown in Figure 1 for a pair of formulations that have been compressed on a single station tablet press. The formulations contain a high drug load. One formulation is a direct blend recipe while the other is a wet granulated powder. A robust tablet will typically have a tensile strength of 1 to 2 MPa. Neither of the two blends tested yields a tablet that would be acceptable.

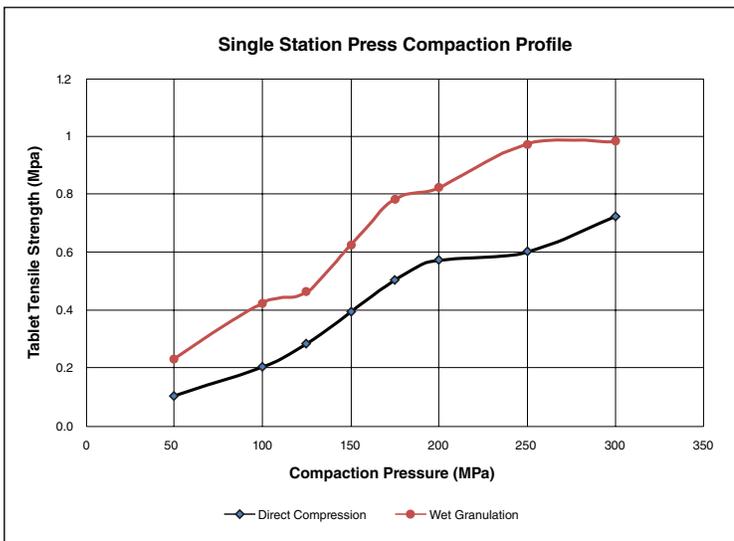


Figure 1. Profiles a pair of formulations that have been compressed on a single station tablet press.

Moving the compression process to a rotary tablet press yields a different result. As shown in Figure 2, the wet granulation formulation yields a tablet that increases in tensile strength with additional compression force. Once the compression force reaches 150 MPa, a robust tablet is formed. The direct compression blend will not compress into a tablet of sufficient strength and in fact yields a tablet that exhibits capping behavior at higher pressures. While uncommon,

the race to register has participants that will proceed directly to direct compression formulas. With data indicating that the single station presses will provide a tablet with acceptable hardness, disintegration and dissolution, the jump to registration will be in motion before testing on the rotary tablet press is accomplished using material from the first step of the scale-up process. The majority of formulations do not bypass the required rigor of testing during scale-up; however, many do make assumptions regarding the capability of their formulation at the scale required to meet the demands of the patient population. Moving to a large rotary tablet press with 40 to 70 tooling stations significantly changes the dynamics of the powder compaction process as a result of changes in the overall speed of the compaction process. As larger tablet presses are utilized to meet tablet demands, the pitch circle diameter of the turret increases, the resulting punch vertical velocity increases and the compression dwell time decreases. Figure 3 illustrates the results of a simple strain rate study. To generate the proper data, the compression force is fixed and the tablet press is run at different speeds. For this illustration, the velocity of the tablet press pitch circle and the size of the compression tool head flat have been used to calculate the dwell time for compression and is shown with the units of milliseconds on the X axis. For the purposes of this discussion, the dwell time is defined at the time during which the upper and lower punches have no vertical movement.

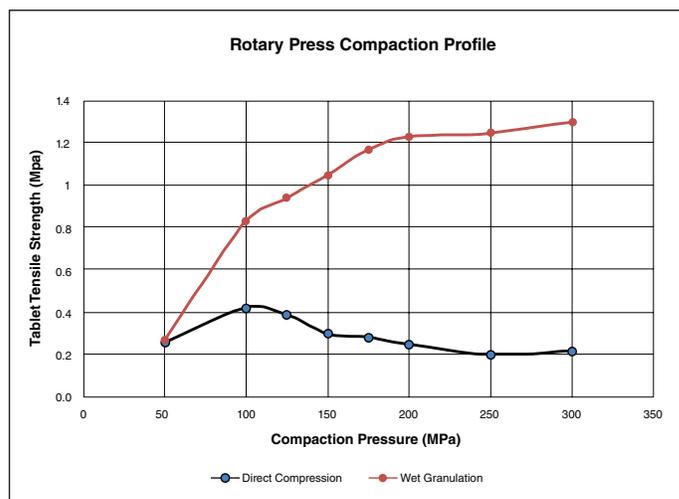


Figure 2. The wet granulation formulation yields a tablet that increases in tensile strength with additional compression force.

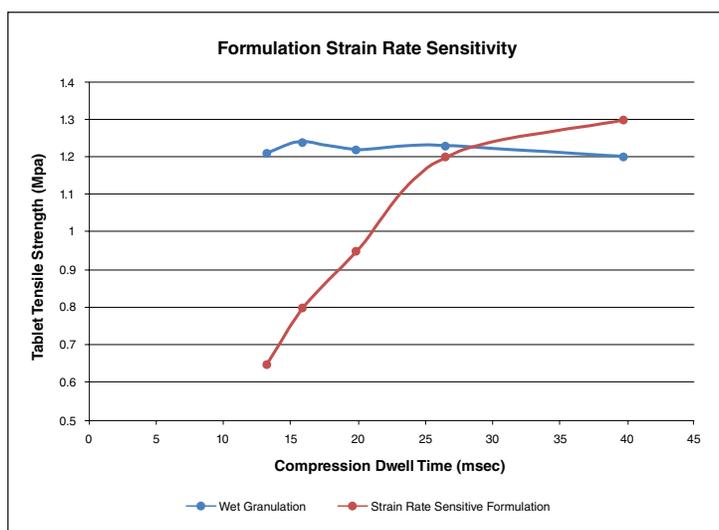


Figure 3. The results of a simple strain rate study.

The wet granulation is capable of generating acceptable tablets at all of the turret speeds while the strain rate sensitive formulation requires a slower turret speed to make acceptable tablets. This is a problem as the strain rate sensitive formulation will not be able to produce as many tablets per hour as the wet granulation.



FORMULATION STICKING TO THE PUNCH TIP.

While these tests may be easy to do, they are time consuming and costly with respect to API costs. So what is a production manager to do when caught up with the need to satisfy the demands of management and an underperforming drug product formulation? Discuss your options with the company that provides your compression tools. They can offer tooling modification that may be capable of solving, or at least minimizing, the problem.

When strain rate sensitivity is a problem and requires a slower production rate to produce acceptable tablets, then tools with extended head flats can be considered. TSM-B and TSM-D type tools can be modified to increase the head flat size and provide a longer dwell time at the same turret speed. This can provide improvement in the tablet production rate or elimination of minor defects that are linked to a lack of powder consolidation time.

Sometimes a drug product formulation performs well; however, after several hours there will be problems with material sticking to the punch cup or die bore. There are various root causes to these problems. Sticking may be temperature-related and relief for that problem

may require testing a coating for the punch cup to reduce powder adhesion. Heat generation can be caused by fine particles sifting past the punch cup into the die bore and there causing excess friction and an increase in temperature. The number of fines sifting past the lower punch can be decreased by reducing the clearance between the punch tip and die wall. In addition, a narrow tip width can help reduce the generation of friction and a deeper sharp relief for the lower tip can be more effective at scraping excess powder away from the die bore wall.

Picking is a condition that refers to formulation becoming stuck in the letter or numbers of the tablet logo or identifier. Picking problems can often be addressed by modifications to the embossing letters or utilizing compound cup configurations to improve compression in the deepest areas of the punch cup. Pre-picking letter or numeral islands and isolated areas as well as tapering the engraving cuts for some letters will often alleviate picking problems. Consider running a full-scale performance lot, including tooling stations with different pre-pick and taper, to identify potential picking and sticking problems before they appear. Sometimes these problems arise courtesy of small changes in environmental factors or variability in the supply chain for excipients. Running a performance lot can provide more process understanding and knowledge about the design space for a product's formulation.

Picking in a tablet identifier.



Another problem occasionally encountered is the appearance of tablet defects when a process is moved to production and the new tablet press has pre-compression capability while the research and development machine did not. The proper adjustment of pre-compression should be studied in detail prior to writing the final tablet compression ticket. For a drug product formulation that has a high loading of API improper pre-compression setup can be a path to tablet quality problems. Active pharmaceutical ingredients are typically organic crystals that compact via a brittle fracture mechanism. Excess pre-compression force followed by final compression can result in the generation of a significant population of very small crystals that will not consolidate the same as when minimal or no pre-compression force is utilized. The function of pre-compression is to remove as much air as possible from the powder before final compression. In conjunction with tapered dies, this will minimize problems with tablet capping.

Running a performance lot can provide more process understanding and knowledge about the design space for a product's formulation.

Proper setting of pre-compression requires the press mechanic to remove all pre- and main compression. Fill the press with powder and manually rotate the press while adding pre-compression force. Add this force until a tablet is ejected from the die. This tablet should look like a tablet but fall apart when grasped. At this point the pre-compression is set and final compression added until the desired tablet hardness is realized.

The use of the proper fill cam is often overlooked during scale-up of the tableting process. Often a tablet press is utilized with whatever fill cam is installed. If conditions can be set to hit the desired weight and

hardness targets, all is good. This works until operators start to see excess powder accumulating on the die table because of too much powder being pushed out by the dosing cam. Recycled powder re-enters the feeder and is blended once again with virgin material. Depending on the particle size distribution and the propensity of the API crystals to fracture, a fraction of the blend is now smaller and may adversely affect the quality of the tablets. The smaller particles can change the die fill dynamics, as well as contribute to the loss of small particles to the space between the punch tip and die bore. Very small particles ($<10\ \mu\text{m}$) can start to accumulate in scratches and digs in the punch cup surface, leading to film formation in the cup, which is a first step toward sticking. Improper fill cam also can affect the variability in fill weight and tablet hardness as different press speeds are utilized. Different press speeds will require adjustments to the feeder speed to meet tablet physical property targets. Studies performed as part of a scale-up performance lot, and done with an improperly selected fill cam, can be compromised if the fill cam is changed at some point down the road. As well, feeder speed adjustments may not be as intuitive as expected. If modified feeder paddles were utilized during development to address problems with die filling of a formulation that is cohesive in nature, the same type of feeder paddles will be needed for full-scale production. Excess powder recycle, courtesy of an incorrect fill cam, can affect variability of tablet weight control and blend uniformity at different press and feed frame speeds. Proper fill cam selection is a simple step, often ignored, that can stave off problems in the future.





For drug product developers that would prefer to minimize the steps from concept to registered dosage form, the previous suggestions likely describe undesirable diversions of time and resources. These recommendations should prove valuable for those that want to minimize the steps from development to a state of controlled manufacture with minimum deviations. For a perfect system work is independent of path, but not necessarily independent of regulatory pain.