

# QbD vs Troubleshooting

A science-based approach to shorten tablets development time



Reducing “time to market” is the ultimate goal for every pharmaceutical lab. Being the first on the market brings a competitive advantage for prescription, over-the-counter, or generic-drug manufacturers. **Applying quality-by-design (QbD) principles at the formulation phase can prevent tablet defects at an early stage and**

**R**educing “Time to market” is the ultimate goal for every pharmaceutical lab. Being the first on the market brings a competitive advantage for prescription drugs manufacturer, Over-the-counter (OTC) or generic drug manufacturers.

Applying the Quality by Design (QbD) principles at the formulation phase can prevent tablet defects at early stages and hereby drastically reduce time during the complex and troublesome phase of “scale-up”.

The determination of the right material and quality attributes (lubrication, elasticity, cohesiveness, weight variation etc.) can help developing a robust formulation. An extensive characterization of a formulated blend can also prevent capping, sticking or even die binding on a commercial-size rotary tablet press.

Instead of waiting until the “production size phase” later in development which then forces the scientists to solve formulation issues at pilot level or even worse in the actual production only, a QbD approach secures the scale-up to production with maximum safety right from the beginning.

New tools available make these investigations steps much less painful than in the past. Major Contract Development and Manufacturing Organisation (CDMOs) are using the QbD approach in combination with tableting instruments to secure their formulation by in-depth material characterization, by direct scale-up thanks to high speed press mimicking.

## LAMINATION OR CAPPING?

Lamination and capping are common tablet defects occurring in tablet manufacturing. Both terms are used to describe cracks on the side of the tablet. Lamination is a defect exhibiting cracks on the cylindrical part of the tablets (the “belly band”. See figure #1). Capping is a defect occurring at the junction between the cylindrical part and the convex part of the tablet (see figure #2). Even though lamination and capping look more or less the same, some of their causes can be different.

**Lamination.** This air-entrapment can also come from a tight clearance of the compression tooling. Every manufacturer has

its own mechanical tolerance between the punch tip and the die bore. However, a very tight tolerance is not recommended as the air will have a hard time to escape from the powder bed, and will thus create air bubbles. Reversely a too large tolerance creates powder loss mainly on the lower punch. In a study performed with one of our clients the same blend was compacted on a high-speed single punch tableting instrument with identical process parameters. The only difference was the supplier of the compression tooling. Mimicking a Kikusui rotary tablet press at high speed, the tablets made with the punch set #1 had no lamination. The tablets made with the punch set #2 although all the process parameters being identical, revealed lamination. The cause of lamination was attributed to the difference of mechanical tolerances between the punch tip and the die bore. In this case, the tableting instrument was used to troubleshoot manufacturing issues and pin-point the parameter to be adjusted (i.e. change punch supplier). Nevertheless, studying the effect of the mechanical tolerances at the formulation phase is something formulation scientist could take into account. Only less than one hour is necessary to test these parameters and the cost is limited to one set of punch and die.

It's really worth the effort to validate such process parameters in the first steps of QbD.

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**Capping.** Capping has its origin in the chemical nature of the excipients and active pharmaceutical ingredients (API), the tablet shape and process parameters, such as the turret speed, compression/edge thickness (and the resulting compression force) or insertion depth (penetration depth). Capping is ingloriously famous because it generally occurs during scale-up, either at the clinical manufacturing stage, or worse, during scale-up on a commercial-size rotary press. If tablet capping is discovered at a late stage, then re-formulation is most likely not an option anymore. The first process parameter that can be adjusted is the convexity of the tablet by modifying the radius of the punch tip to reduce capping tendency. Computer simulation [ ] using Finite Element Modelling has shown that a radial (shear) stress appears on the tablet cap when the upper punch tip is moving away from the tablet surface. The upper punch is losing contact first at the land (the little flat portion surrounding the punch tip). This creates stress on the radial direction, explaining why capping occurs in the land region. Some experienced tableting experts know that the higher the curvature (ie the lower the radius), the higher the risk of capping tendency. Thus curvature becomes another process parameter simple to evaluate in a QbD approach.

However, “flattening” the tablet has its limits, especially when the tablets have to be film coated. Trying to coat flat-face tablets generally result in a defect known as “twins”, where two tablets are glued together.



Figure 1 - Lamination



Figure 2 - Capping

The second process parameter that can be adjusted after the tooling shape is the pre-compression. This will remove excessive air inside the powder bed and most likely enhance the cohesion of the tablets. This additional cohesion should most likely counterbalance the shear stress inherent to the tablet shape and avoid capping.

The third process parameters is the insertion depth, also called upper punch penetration. By compacting deeper into the die, the applied pressure becomes symmetrical, thus densifying and creating cohesion equally on both sides of the tablet. Likewise the pre-compression, the additional cohesion on the upper part of the tablet might be enough to prevent capping.

A fourth process parameters is very efficient on reducing capping: The compression/edge thickness. By increasing the compression thickness, the compression force will be mechanically decreased and capping will rapidly disappear. However the tablet breaking force (cohesion) will also drop and it will most likely change the disintegration time and dissolution profiles as well. This process parameter needs to be assessed carefully.

Adjusting all these parameters using a commercial-size press is time-consuming and requires large quantities of blend. A dilemma for most formulators which forced them to rely on their past pragmatic experiences. However, it is possible to evaluate capping by using single punch presses with high strain rate capabilities. Those presses are sometimes named “compaction simulator”, even though there is no computer simulation implicated. Being able to modify the strain rate (ie the linear vertical punch velocity), those premium tableting instruments can mimic the dynamics of a rotary tablets running at full speed. The experiments described above can be performed on such tools to troubleshoot the tablet defects with small quantities of blend in a timely manner.

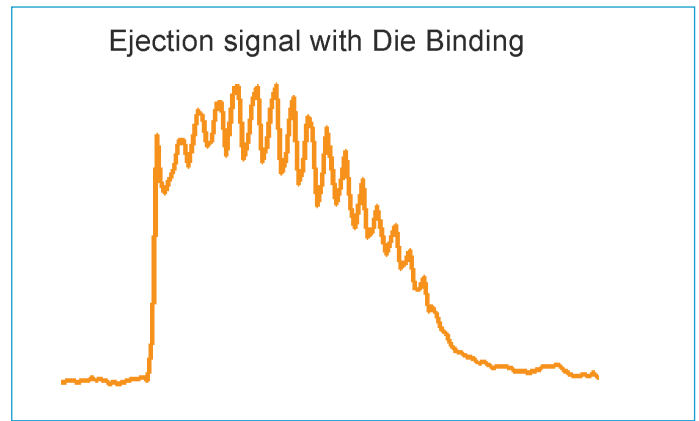
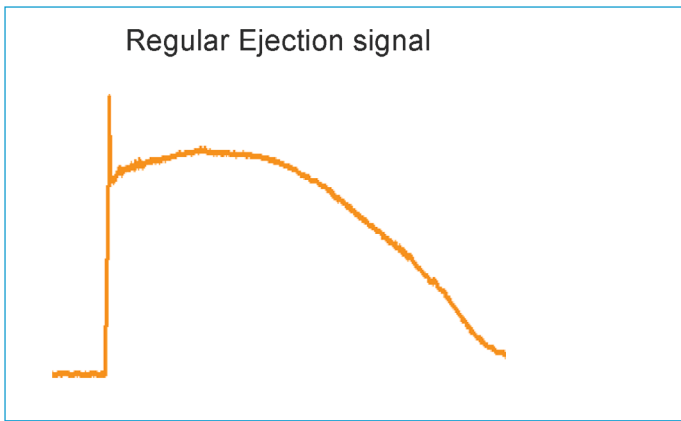


Figure 3 - Ejection signals - Die Binding vs Regular

## QBD APPLIED FOR TABLET FORMULATION

Formulators can use QbD to optimize a formulation in the early development stage, before scaleup. Based on the Quality Target Product Profiles (QTPP) and the process flow chart (wet/dry granulation, tableting, coating), formulation scientists will have to list the Material Attributes (MA), Quality Attributes (QA) and Process Parameters (PP) that are required to achieve the QTPP. This risk assessment, based on the scientist's process understanding and experience, shall then pin-point the critical attributes and parameters and assess them with the compaction simulator.

As described earlier on capping and lamination, the process parameters studied to troubleshoot the defects can be evaluated during formulation to determine the process space to produce good tablets without capping or lamination.

## ASSESSING TABLETABILITY

Material Attributes of the Active Pharmaceutical Ingredient (API) and Excipients generally include physico-chemical attributes, such as assay, impurities, particle size distribution, flow indexes, water content, .... However, the compactibility of the ingredients is not always taken into account for a simple reason: Excipients have to comply with the monographs listed in the Pharmacopoeias and these monographs do not contain any functionally-related specifications. Surprisingly an excipient designed for direct compression does not have any specifications on its ability to form bonds, which is what should be expected from a binder! A scientist getting an USP / Ph. Eur. compendial excipient shall only rely on the supplier's brochure on its performance in tableting. This is the same for an API for which it could be possible to test its ability to form bonds under pressure.

Generic drug manufacturers generally intend to source an API from different drug substances suppliers. In addition to the chemical purity criteria and other common physical characterization, such a flow and particle size distribution, it is wise to make a tabletability profile on an instrumented tablet press. Due to the poor flowability of APIs and small quantity of available API at this stage, the loading of the die would most likely be carried out manually (external lubrication with a dry lubricant on the die bore and punches is often necessary to avoid sticking and die binding). If the API is able to form bonds, it's then possible to plot the Tensile Strength vs Axial Pressure. This tabletability profile can be considered as a Material Attribute and comparing them from the different grade of API, can help choosing the

right grade for the drug product. This approach can definitely be performed the same way on neat excipients.

Another Material Attribute that is highly recommended to assess, is the requirement for lubrication. It is widely known that a quantity of 0.5% to 1% of lubricant is necessary into the tablet formulation. But is this correct? The obvious Quality Attribute to look at is the ejection force. However, there are other QA that can be studied. First, the ejection force is only the peak of the complete ejection force signal. By taking a close look at the signal, it is possible to see oscillations on the signal just after the peak (see figure #3). Even if the peak of the ejection force is still fairly low, this is a sign that die binding (also known as die tightness) is occurring. A less common approach is to consider also the transmission coefficient [ ], defined as the ratio of the upper and lower punch force. To measure those forces, an R&D press will have to be equipped with force sensors on both punches and be able to operate the punch in a non-symmetrical way.

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Old common technologies such as eccentric R&D presses can do the trick if they are well instrumented. The compression force recorded by the lower punch will be systematically lower than the force recorded by the upper punch. The powder densification occurs first at the upper side of the powder bed. The energy provided to the system will be partially lost due to frictions between particles and between particles and the die bore. This will result in a measurement of a lower punch force. The target of the transmission coefficient should be between 90% and 100%. Low transmission ratio such as 70% might be linked to a non-effective lubrication. By looking at the peak of the ejection signal, the oscillations of the ejection signal and the transmission ratio, the quantity of lubricant and its associated blending process can now be optimized. Different grades of magnesium stearate, a well known lubricant, featuring different specific surface area, can give very different lubrication.



## ELASTIC RECOVERY

Elastic recovery is another Material Attribute seldom assessed. Acquiring this data requires the tablet press to be instrumented with position sensors. The elastic recovery is the difference between the tablet thickness measured out-of-die, with a caliper for instance, and the in-die tablet thickness measured by the sensors at the peak of compression. Elastic recovery is often linked to lamination as it can create micro-fractures within the tablets. Interparticular cohesion is therefore reduced and lamination can occur. As an example, calcium phosphate excipient exhibits an elastic recovery around 4%. But some sustained release polymer can be as high as 20%. Generally speaking, it is recommended to associate ingredients having similar mechanical properties, especially when formulating bi-layer tablets where an elastic layer could induce a layer separation.

## COMPRESSION FORCE, A PROCESS PARAMETER? A NEVER DYING MYTH?

The compression force is quite often considered as a process parameter. Actually it is in the first place a Quality Attribute.

On a basic rotary tablet press, an operator can adjust the dosage height (and its corresponding Quality Attribute “tablet weight”) and the compression/edge thickness. The compression force is then measured by strain gauges located on the pressure rolls. Decreasing the compression thickness will result in increasing the compression force and vice versa. That is the main reason why many people think that this compression thickness knob is controlling the compression force. Now, when the operator increases the dosage height, the compression force will also increase. Therefore compression force cannot be a Process Parameter and is in fact a Quality Attribute.

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On the other side, any modern rotary tablet presses are equipped with “weight control loop”. This control loop will basically rely on the relation that exists between the tablet weight and the compression force. The Belgian manufacturer GEA, former Courtoy, has to be considered as an exception using the relation between tablet weight and tablet thickness. The strain gauges measuring the compression force are the indicators to monitor the tablet weight. Any variation of the compression force will be an indication of a variation of tablet weight, most likely due to a non-uniform blend density and flowability between the beginning and end of the batch. A control loop will then electronically change the dosage height to maintain the compression force within the target values (set point). A production press is mechanically designed to compress the powder bed to a given volume, ensuring that similar force indicates similar weight. Therefore the particular set point for compression force is a Process Parameter. Depending on the context, compression force is both a QA and a PP.

When considering compression force has a QA, how does it help a formulator in speeding up tablet development? Well, simply by plotting the relation between the compression force and the tablet weight. To do that, the PP “dosage height” has to be modified to mimic a change in powder density during the process. For example, if the nominal tablet weight is 850mg, the dosage height shall be adjusted to reach respectively 850mg + 5% and 850mg – 5% (tablet weights within this range are compliant with Uniformity of Mass test as set forth by European Pharmacopeia). The scientist can now plot the compression force versus tablet weights (figure 4). This graph will be of a critical help to set-up the ejection and tolerance set points on the commercial-size rotary tablet press during scale-up. A big time and especially material-saving technique. In addition, other Quality Attributes, such a tablet breaking force (also known as “hardness”), disintegration time or even some key dissolution times can be plotted versus tablet weight. All these graphs will guide the formulator in the determination of the Design Space.

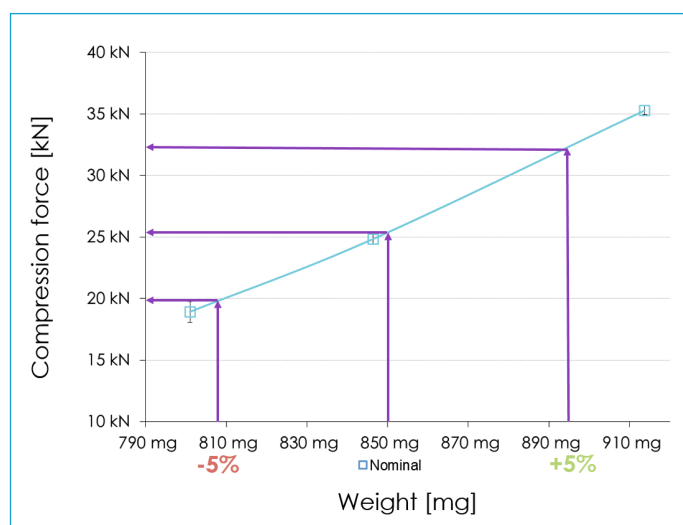


Figure 4- Force vs weight variation

This full QbD approach has been implemented for complex oral solid dosage forms, such as multi-layer tablets or tab-in-tab, at several CDMOs. The company Skyepharma has made it their motto: “Right First Time Approach”. Using a tableting instrument with high speed rotary press mimicking features, so-called compaction simulator, robust formulations are quickly designed. But most importantly, this ensures a smooth scale-up and reduces risks and costs. Ultimately, it accelerates the time to market.

[1.] Mazel, V., V. Busignies, H. Diarra, and P. Tchoreloff. “Lamination of Pharmaceutical Tablets Due to Air Entrapment: Direct Visualization and Influence of the Compact Thickness.” *International Journal of Pharmaceutics* 478, no. 2 (January 30, 2015): 702-4.

[2.] Mazel, V., H. Diarra, V. Busignies, and P. Tchoreloff. “Shear Strength of Pharmaceutical Tablets: Theoretical Considerations, Evaluation and Relation with the Capping Tendency of Biconvex Tablets.” *International Journal of Pharmaceutics* 532, no. 1 (October 30, 2017): 421-26.

[3.] T. Ménard, L. Pisarik. «New but also “forgotten” ideas to quickly solve compression problems”. *STP Pharma Pratiques*. VOL 25 n°6 (Nov-Dec 2016)