Sticky Situation: How to Avoid Sticking and Picking

Sticking and picking problems are ubiquitous in tablet manufacturing. In the regulated world of drug-product manufacturing, there is often a sense of urgency to develop a new molecule. But this urgency can result in hasty decisions to enter clinical trials or submit for regulatory approval with a formulation that ultimately results in unanticipated compression scale-up problems.

The design process for an oral solid dosage form often overlooks some of the seemingly minor details of tablet design. This can result in tablet defects as manufacturing scales up from clinical to full patient-population supply. Pharmaceutical company marketing departments' desires for certain tablet shapes and logos to enhance brand recognition are a source of design constraints, often resulting in post-approval manufacturing complications. Compression tooling manufacturers can identify potential sticking and picking issues before tablet and tool designs have been finalised, reducing the challenge shared by the tablet manufacturer and the tooling vendor.

Sticking and picking issues generally arise from either formulation or tablet design inadequacies. Both emerge because of the differences in physical properties of the formulation excipients and drug substance.

Cohesive Forces: Forming a Solid Dose Tablet

Formation of a compact is the result of chemical dispersive and mechanical forces joining particles to form a solid of measurable density and porosity. The cohesive forces binding the particles can be assessed through a series of studies to determine whether problems with tablet compaction can be anticipated. Compaction profiles and strain rate studies are important to development projects. These studies ensure that the probability for successful scale-up and technical transfer is high. Therefore, market supply is not affected because technical due diligence was overlooked.

Tablet particles are bound by cohesive forces. However, during the compression process, the cohesive forces binding the particles are challenged by the adhesive forces of the punch cup and the embossing within the punch cup. The first stage of a sticking problem occurs when the adhesive force of the punch cup can pull even a single particle away from the tablet. A recent publication indicates this is principally caused by the physical properties of the active pharmaceutical ingredient (API), and the mechanism and kinetics can be successfully modelled.

The problem of formulation sticking in the letters and characters of punch embossing is typically referred to as picking. Picking is a type of sticking often rooted in an inferior tablet design. Picking issues can be resolved but are rarely predictable. They often are not detected until transferring product from research and development to production. Among the typical sources of picking issues are the selection of the proper font and the engraving cut design for character islands and character peninsulas.

Simple Considerations to Alleviate Sticking and Picking

Remediation of picking and sticking does not always mean changing the tools used for tablet manufacturing. When powder sticks in the embossed letters, one of the first things to check is the moisture level of the formulation. Excess formulation moisture or excessive humidity in the compression suite can initiate picking. Insufficient compression force is also a potential source of picking because the compaction of the powder is not complete. This means the adhesive forces can readily overcome the cohesive forces of the improperly compressed tablet.

Another potential solution is to try slightly increasing the amount of lubricant used in the formulation. This will impart greater release of the compressed tablet from the punch cup surface. Careful inspection of the punch cups is also essential to ensure there are no surface scratches to capture small particles of formulation. Scratches will lead to filming, a slow form of sticking, often due to excess moisture in the granulation. If surface scratches are identified, punches should be polished. A specialised polishing compound can be used to impart greater lubricity and better product release properties as well.

Reducing Picking with Font Selection

When simple fixes are not enough, a full tablet and tooling design review may be necessary. Font selection is often a battle of form versus function. An ornate or decorative font, while pleasing to the eye, will likely cause picking problems and tablet defects. Figure 1 illustrates an impractical font selection. The variation in engraving width, as well as the isolated and unnecessary peninsulas of the letters, are impediments to even powder compaction. This variation often leads to powder picking away from the compressed tablet core and remaining in the punch cup. Figure 2 illustrates the same embossing using a practical font that utilises increased engraving and corner radii. The font modification minimises picking opportunities, increases the opportunity for consistent powder compaction, and yields the best possible cohesive forces for the tablet.

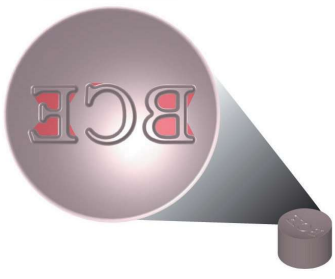


Figure 1. An impractical font selection

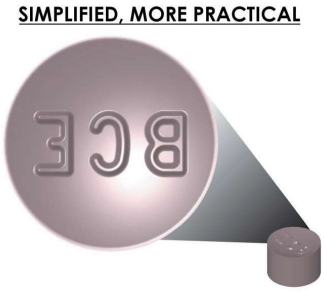


Figure 2. A simplified, more practical font selection

Changing the Engraving Cut

In addition to changes in the font selection, attention should be paid to the design of the engraving cut. Figure 3 illustrates a typical round tablet. The engraving of the "9" cut into the tablet is illustrated with typical engraving cut width, depth, and angle of 35 degrees. Most product formulations should be readily compressed into tablets using tools with this engraving design. However, many formulations are not typical, and problems can still occur.

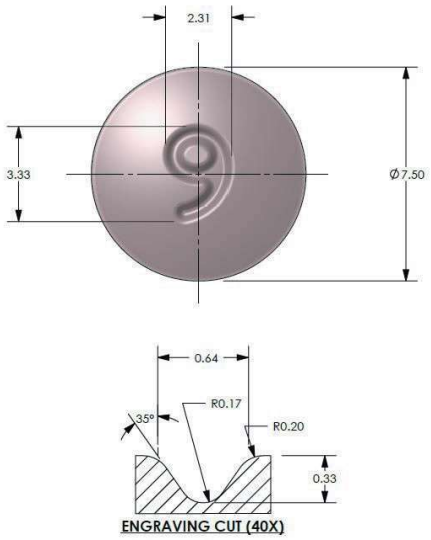


Figure 3. A typical round tablet with a "9" engraving cut

To reduce or eliminate problems with material picking in the centre island of the "9" (Figure 4) pre-picking can be incorporated in the design. This is illustrated in Figure 4, where the depth for the island is reduced from 0.33 mm to 0.17 mm. This reduction is defined as a 50 per cent pre-pick. The amount of reduction can range between 10 and 100 per cent, depending on the extent of the picking problem. For branding or aesthetic purposes, consideration must be taken for tablets being coated post-compression, as excessive pre-pick will significantly reduce the clarity of the logo. The partial pre-pick concept is applicable to any letter or numeral with fully enclosed areas called "islands" or "pads."

Many other somewhat complex characters that do not have fully enclosed areas are also prone to picking. Letters like E, S, K, and M and numerals like 2, 3, and 5 all contain these partially enclosed areas that are described as peninsulas. For these areas, we employ a feature called "tapering" or "ramping" to prevent picking. Starting on the tablet surface at the open end of the peninsula, this feature tapers downward toward the enclosed end of the peninsula by a percentage of the engraving depth. Peninsulas usually are tapered between 10 and 50 per cent of engraving depth, with 30 per cent the most common. An example of a 50 per cent taper is illustrated on the right side of Figure 5.

Materials of Tooling Construction

If sticking and picking have been discovered during the research and development stage, or if it is time to order the next set of punches for a product with known sticking and picking issues, another consideration is to have the punches made from a speciality steel. It is widely accepted that punch steel with a high concentration of chromium in the alloy, usually between 16 and 18 per cent, enhances release of the compressed product. A reputable tool vendor will have multiple grades of high-chrome steel available to manufacture the punches. Several other speciality steels are available to enhance the performance and service life of the punches and dies for compressive strength and wear resistance.

As an alternative to using a speciality steel, some may choose to have a coating applied to their standard steel punches to enhance the

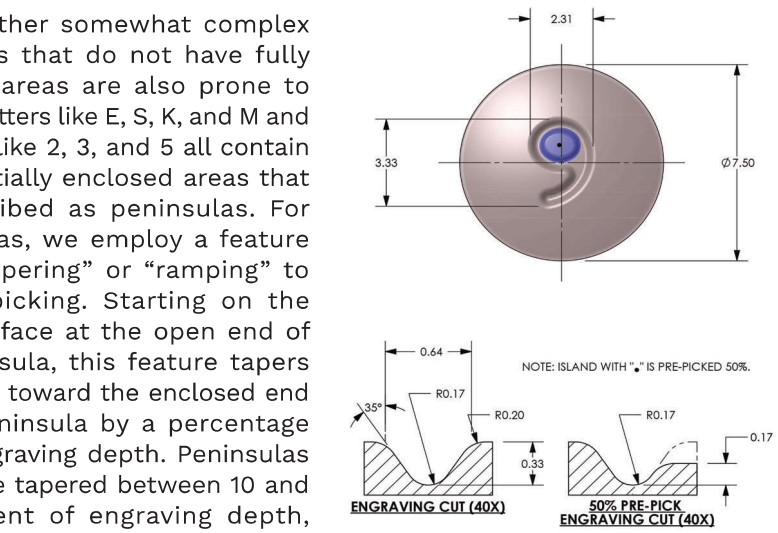
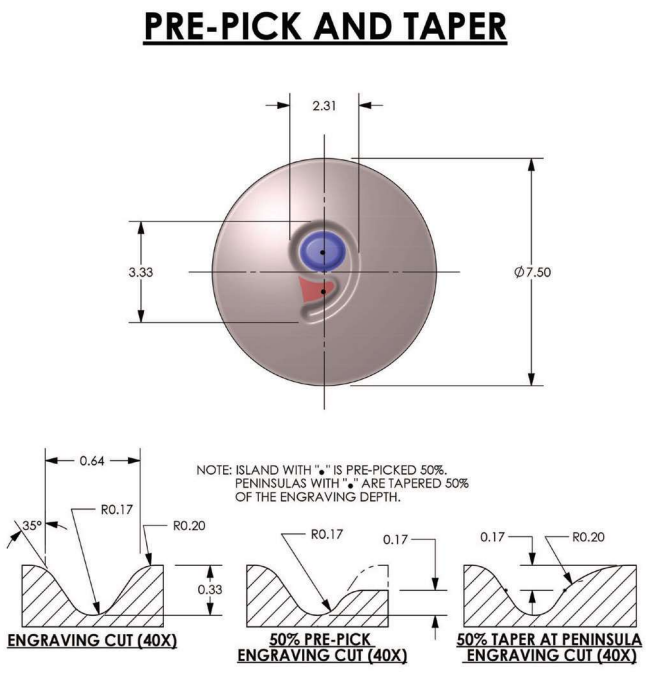


Figure 4. The depth of the island is reduced from 0.33 mm to 0.17 mm



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release characteristics of the punch faces. The most common coatings are hard chrome (Cr) and chromium nitride (CrN). Several other coatings are available as well, depending on the unique characteristics of the blend to be compressed. However, it should be noted that the thin chrome coating layer could wear off over time, due to the abrasion of the formulation and polishing. Thus, the better choice may be a high-chrome steel, without coating, for a long-term solution.

Discuss these issues with your tooling vendor early in the process to help reduce production issues and additional costs. Your tooling vendor should be able to explain the unique properties and advantages of the various steels and coatings available for your tooling.

In Conclusion

Ultimately, several remedies can help speed a new drug to market, ranging from slight formulation changes to major tablet design and tooling modifications. When developing a to-market strategy, it is often best to consult with your tooling vendor early. Their insights will benefit the final product and assist in creating a tablet that is accepted by both the manufacturer and the consumer. Discussing all unique physical properties with your tool vendor during the tablet design phase can eliminate sticking and picking issues before they occur.

Jonathan Gaik

Jonathan Gaik is Director of Natoli Scientific. He has worked in solid oral dosage formulation and process development in the pharmaceutical and food industries. Mr Gaik has various patent applications for his work combating the opioid crisis via abuse-deterrent dosage forms. His current interest is driving the development of continuous manufacturing and first principles sources of solid oral dosage formulation-related issues during processing.

Product News

Sartorius Stedim Biotech launches new ambr® 250 high throughput bioreactor system for perfusion culture

- **Unique, single-use perfusion system offers a fast-track to intensified cell culture process development**

Sartorius Stedim Biotech (SSB), a leading international supplier for the biopharmaceutical industry announced the launch of the ambr® 250 high throughput (ht) perfusion, a new automated parallel bioreactor system. It has been specially designed for rapid cell culture perfusion process development to optimize production of therapeutic antibodies.

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The ambr 250ht perfusion system has been developed in collaboration with major biopharma companies. It combines 12 or 24 single-use perfusion mini bioreactors (100–250 mL working volume) with associated single-use perfusion components, all controlled by one automated workstation. The combination of this multi-parallel processing capacity and fully single-use perfusion vessel enables scientists to perform more perfusion culture experiments in a fraction of the time and cost of using traditional perfusion-enabled bench top bioreactors. This new innovation supports a range of hollow fiber perfusion applications, enabling Design of Experiments (DoE) studies for high cell density process development in a Quality by Design (QbD) approach.

Central to the system is the novel perfusion bioreactor assembly, which is based on the established and award-winning ambr® 250 bioreactor design. Intensified cell culture processing is enabled via new components such as high efficiency spargers, perfusion pump chambers and an industry standard hollow fibre for cell retention filter. The geometrical similarity of the mini perfusion bioreactor design to BIOSTAT STR® pilot and manufacturing scale bioreactors, enables rapid scale-up f optimized perfusion processes, and shorter development time-lines.

The ambr 250ht perfusion system is simple to set up and use, due to the fully assembled and irradiated perfusion bioreactors which include all the essential components. This includes single-use sensors to continuously monitor pressure at the culture fluid inlet and permeate outlet, enabling online monitoring of transmembrane pressure, as well as standard parameters such as pH and DO.

Dr Barney Zoro, ambr Product Manager at Sartorius Stedim Biotech, explains: “By introducing our new ambr 250ht perfusion system, we are offering our customers an important enabling technology for early-stage development of intensified cell culture processes. Transitioning from fed-batch to perfusion culture offers the potential to reduce capital intensive risk by using 1–2000L single-use bioreactors instead of 10,000L production volumes in stainless steel. ambr 250ht perfusion is a predictive process development tool that could lower the cost of goods of antibody production, as well as significantly shortening development timelines.”

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