



Ultimate Technical Guide to Tablet Presses & Tooling

- **Increase Tablet Quality by Checking these 7 Inspection Points**
- **8 Ways to Reduce Tablet Manufacturing Costs**
- **First Impressions: Tablet Shape Can Impact Patient Acceptance**
- **The Key to Tableting Success: How to Choose the Right Tooling**
- **Buffing vs. Drag Finishing**
- **Prevention and Repair of J-hook**
- **Quality of Steel**
- **Why You Should Be Using Ultrasonic Cleaning**
- **How Crucial is Compaction Dwell Time**
- **Detailed Formulation Development Helps Avoid Production Problems**



YOU DEMAND. WE DELIVER.



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CHAPTER 1:

INCREASE TABLET QUALITY BY CHECKING THESE 7 INSPECTION POINTS

Inspecting tooling and press components for wear or defects could be the most important step in improving tablet quality. There are certain inspection points that are easy to overlook yet can cause significant tablet quality issues and limit tool life. Spend a little time checking the following items for wear or defects to quickly increase tablet quality and reduce tooling cost.

1. WORKING LENGTH

The most critical punch dimension when using a rotary press as it is responsible for consistency in tablet weight, hardness, and thickness. This should be measured directly and shouldn't exceed a variation of .002 inches across a set of upper or lower tools. Working length should be thoroughly inspected on in-process tooling and spot checked on new tools when they are received.

2. DIE BORE WEAR

This inspection point is often overlooked during in-process tool inspection because, until recently, a lack of effective and affordable technology prevented wear measurement. New machines such as a Tooling Condition Monitor allow tooling wear to be measured and tracked. Die bore wear can cause capping, laminating, and excessive tablet flashing.



3. PUNCH TIP AND CUP WEAR

Punch cups should be checked for a condition called “J-hook.” J-hook is characterized by the edge of the punch tip curling inward toward the punch face. This type of wear can cause picking during tablet production. Punch tips should also be inspected for excessive clearance as they correspond to die bore wear. Just as with die bore wear, this can be measured using a Tooling Condition Monitor or by using an optical comparator. A traditional micrometer cannot properly check tip wear.



TOOLING CONDITION MONITOR

4. PUNCH RETAINERS

A part of the tablet press, punch retainers can play an important role in tablet quality. Check the tips for excessive wear. If they are worn out, they should be replaced, as wear can cause variances in tablet weight.

5. PRESSURE ROLLS

Another inspection point on the tablet press, pressure rolls should be checked for “run-out,” also known as concentricity. It is recommended that run out be measured on the pressure roller as it can cause inconsistencies in tablet hardness and weight. Concentricity can be checked by using a dial indicator affixed to a metal pole and magnetic base. The measurement is taken and averaged to determine if pressure roll wear is within the tolerance range.

A dial indicator is used to check concentricity on a pressure roll.



6. CAM WEAR AND DEPTH OF FILL

Cams should be inspected for wear either visually on the machine, or more thoroughly after removal. Cams also should be inspected and selected for proper depth of fill. Improper depth of fill can lead to excessive product loss and weight variance in tablets.

7. EJECTION CAMS

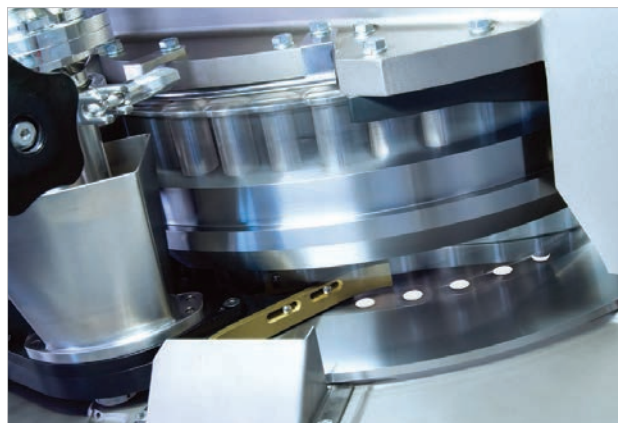
This inspection point should be checked with a straight edge. The edge should just meet the punch tip to ensure there is adequate clearance during tablet takeoff. Setting ejection cams to a proper height will reduce tablet chipping.

Checking the suggested inspection areas and correcting any wear issues or defects is a step that is well worth its time, as it will improve product quality and reduce tooling cost due to wear and breakage.

It's also important for written inspection procedures to be developed to ensure that best practices are followed. It is crucial for staff to thoroughly check that press parts and tooling are within their given tolerances, and in good condition.

Whatever your tableting needs, Natoli Engineering can provide a product or solution to meet them. We're the best in the industry at what we do. Contact one of our tablet tooling and press experts to receive a customized solution.

Check out our Accessories Catalog at natoli.com for items mentioned in this article.



CHAPTER 2:

8 WAYS TO REDUCE TABLET MANUFACTURING COSTS

It's no surprise that in today's economy, companies are facing budget cuts across the board. In an effort to help our customers address these challenges, we put together this list of 8 Ways to Reduce Tablet Manufacturing Costs.

1. LUBRICATE! LUBRICATE! LUBRICATE!

There's a reason we use the phrase "well-oiled machine" to describe something that performs at ultimate efficiency. A properly lubricated tablet press runs smoother and more efficiently with less wear over time, and significantly extends service life. Lubricating your tablet compression tooling reduces wear during use, and coating your tooling with protective oil during storage prevents rust.

2. MAINTAIN AND REPAIR YOUR CURRENT TOOLING WITH POLISHING EQUIPMENT & ACCESSORIES

Proper tooling maintenance goes a long way, and by using different polishing methods, you can buff out worn and eroded punch cup surfaces, remove burrs, and restore land to your punches. So before you decide to purchase a new set of tooling, check out the video below and contact one of our experts to learn how to rework your current set.



3. USE MULTI-TIP TOOLING WHENEVER POSSIBLE

The cost of an average set of multi-tip tooling is insignificant in comparison to the extensive costs of labor, tablet presses, and other tablet production expenses. Switching from traditional single-tip tooling to a 6-tip configuration increases tablet output by as much as 500%, which allows manufacturers to reduce the number of tablet presses and operators needed to achieve equal output, substantially reducing overall operating costs. Contact a Natoli tooling expert to determine whether multi-tip tooling is right for you and your product.

4. REGULARLY INSPECT YOUR TOOLING TO IMPROVE PRODUCT QUALITY & REDUCE WASTE

Regular tool inspection and management allows you to improve product quality and consistency, resulting in a reduction of “reject” tablets and wasted product. Combine the Natoli Laser Vision System (LVS) punch inspection device with the Tool Management II (TM-II) database software module to get the most powerful tool control system available. Visit natoli.com for additional information, photo galleries and video, schedule a free webinar, and download a free trial of the software.

5. PURCHASE REPLACEMENT PARTS & GET MORE LIFE FROM YOUR TABLET PRESS

A new tablet press can cost more than a million dollars, so before you take the plunge and buy new, check to see if purchasing replacement parts for your current press is a better option for you. We carry over 300,000 replacement parts (including turrets) for most major makes and models of tablet presses, in-stock and available for next-day delivery! Not sure which part you need? Contact a Natoli representative today to help troubleshoot your specific issue and determine the parts you need.





6. REFURBISH YOUR OUTDATED TABLET PRESS

If simply replacing a few parts isn't enough, consider having your press refurbished. Our engineers will evaluate your press and help determine your needs, which can range from fixing minor issues to completely rebuilding your press in order to meet FDA regulations, add features such as automated touchscreen interfaces, and have it running better than new. The average cost of a complete rebuild can range between 25%-50% of the cost of a brand new press.

7. INVEST IN YOUR EMPLOYEES

Having a well-trained, knowledgeable staff is critical to the success of any business, especially in this industry. One mistake by an unqualified press operator can severely damage a set of tooling, the tablet press, or both, which could end up costing tens of thousands of dollars or more. By investing in employee training, you'll increase productivity, product quality, and employee retention. Natoli Engineering offers comprehensive tablet press and tooling training.

8. WORK WITH VENDORS YOU KNOW AND TRUST

Buying from smaller, less experienced vendors may get you cheaper pricing, but as the old adage goes, "you get what you pay for." What those vendors don't tell you is with cheap prices come cheap products and poor service. At Natoli, we pride ourselves on providing exceptional quality products with extraordinary service. Our experts have decades of industry experience and have authored technical articles for major industry publications, lectured at major universities and institutions around the world, and have provided personal service time and time again to satisfied customers when no other company could.

As a Natoli customer, you'll have direct access to the expert knowledge of our team. So whether you need tablet or tooling design services, have general questions or require in-depth troubleshooting, our experts are there for you when you need it. So take the first step towards a better vendor experience and call a Natoli representative today at 636.926.8900.



CHAPTER 3:

FIRST IMPRESSIONS: TABLET SHAPE CAN IMPACT PATIENT ACCEPTANCE

{ First impressions are everything. This is especially true for pharmaceutical, nutritional and confectionery tablets. Discriminating consumers may decide if they will be repeat customers based on a tablet's appearance and their experience with it. This article discusses the limitations of the flat faced bevel edge and the benefits of a flat faced radius edge tablet design.

A tablet's size, shape, color, and perceived ease of use are quickly determined by the consumer from their first encounter with the product. The tablet's appearance must impart the sense that the customer/patient can successfully and easily swallow it, without an undesirable taste.

A tablet manufacturer can influence customer acceptance by producing tablets that appear simple to utilize. Tablet design drives much of the visual impact of a tablet, and design features such as a smooth tablet shape improve product appeal and influences consumer preference.

Because a tablet's design can so strongly influence consumer acceptance, a company's marketing department often provides significant input as design and coating decisions are made. However, it is highly advised to include the production department in these decisions as it is their responsibility to deliver the final product. The production department's experience and expertise can greatly reduce production costs and issues as some tablet designs present higher tooling costs and suboptimal physical properties of the tablets.



“ A good tablet design can help a company gain market share, consumer confidence and higher profits, whereas a bad design can cost literally thousands, if not millions, of dollars in lost sales, revenues and additional operating expenses.”



DALE NATOLI
President
Natoli Engineering Company

Tablet designs that have been developed to improve tablet quality and reduce production costs, include the **flat faced bevel edge (FFBE)** tablet design. FFBE became popular early in the development of tablet manufacturing using rotary tablet presses because it offered significant improvement to the flat faced design. The flat faced tablet design suffered from weak tablet edges because of powder leakage at the punch tip die wall interface. Weak edges were prone to chipping and excessive friability. Adding a beveled edge to the tooling was very simple for the tooling machinist to do and allowed for the formulation powder to be pushed back to the center of the die-making for stronger tablet edges. Over decades, the FFBE configuration became a very popular design for the tableting industry. However, the FFBE design has limitations on the maximum compression force that can be used without risking tip damage due to over compression.

SMOOTHER EDGES, GREATER ACCEPTANCE

Based on clients' experiences and its own investigations, Natoli Engineering Company, Inc., a global leader in tablet compression products and services, recommends customers use the **flat faced radius edge (FFRE)** design rather than the FFBE design for their uncoated tablets.

“ Our recommendations are solely intended to benefit our clients. We will not financially benefit if our clients use FFRE rather than FFBE tablet designs.”



DALE NATOLI
President
Natoli Engineering Company

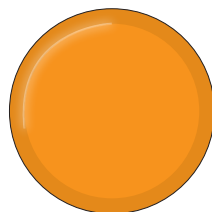
Finite element engineering analysis of the FFBE and FFRE designs for the same size tablet indicate a significant increase in the maximum compression force that can be utilized for tablet compression when using the FFRE design. This offers the manufacturer the option of using additional compression force, with no associated risk to the tablet press, to increase tablet breaking strength as opposed to changing the formulation to accommodate the desired increase in breaking strength. Tablets produced by high compression force are also less prone to edge erosion, sticking, and picking.

In the FFRE design, although they are sometimes visibly imperceptible, tablet edges are slightly smoother. Because of this, customers' impression of the FFRE design is that of softer appearance and a pleasant mouth feel. Comfortable mouth feel can reduce the anxiety that elderly patients often experience with difficult to swallow tablets. These observations are important to providing the first impression appeal that is essential to establishing a successful product brand.

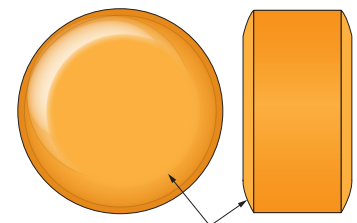
Natoli notes that a growing number of companies are adopting FFRE rather than FFBE for the manufacture of their uncoated flat faced tablets. This trend warrants consideration by companies seeking to produce quality tablets with greater consumer acceptance.

FFBE VS FFRE

The FFRE design features smoother edges than the FFBE.

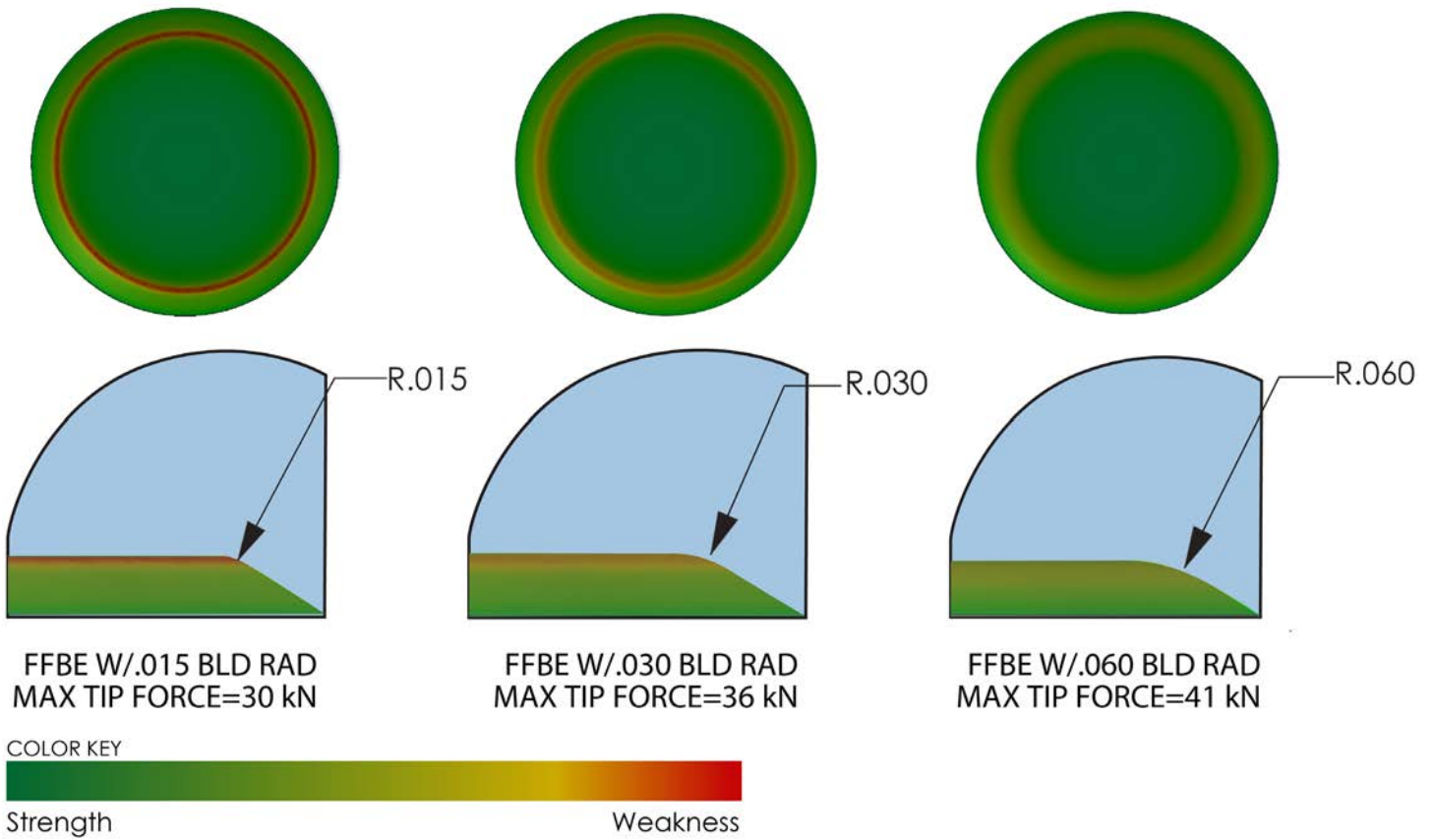


FLAT FACE BEVEL EDGE



FLAT FACE RADIUS EDGE

INCREASE STRENGTH BY INCREASING BEVEL TO FLAT RADIUS



CHAPTER 4:

**THE KEY TO TABLETING SUCCESS:
HOW TO CHOOSE THE RIGHT TOOLING**

{ Choosing the right tooling can increase tablet output, decrease waste and ultimately determine the success of a product launch.

CONSIDER PRODUCTION LIMITATIONS FROM THE START

Generally, a tablet starts as a concept in a company's marketing department without serious consideration of how it will be manufactured. If the marketing staff does not understand what's feasible in actual production and propose a complicated or impractical tablet design, the tablet could make it all the way to the production floor before someone discovers it will fail.

In order to avoid this costly mistake, organize a meeting with an experienced tool manufacturer and include people from marketing, product development, engineering, and production. Doing this at the start of the project allows everyone to share their ideas and concerns, and utilizes the resources and expertise of an experienced tool manufacturer who can help you avoid common problems by avoiding designs that have proved troublesome or impractical for others in the past.





ASK THE RIGHT QUESTIONS

After assembling your “dream team” from marketing, product development, engineering, and production, it’s time to meet with your tooling vendor. Here are some critical questions to ask before making any decisions on tablet design:

1. Given the intended tablet shape and size, what tooling configuration will the product require?
2. How will the tooling configuration of the cup affect the compression force required to compress the tablet?
3. Is the product prone to sticking and picking?
4. Is the product sensitive to the heat of standard operating temperatures?
5. Is the product abrasive or corrosive?

Failure to answer these questions in the early stages of product development will likely cause major problems when the product reaches the production floor. Every detail counts — so be sure to provide your tooling vendor with as much information as possible. Preventative measures taken early in the process will lead to increased tablet consistency and longer life from your tooling and other processing equipment.

STEEL SELECTION

Steel selection is one of the most important factors to consider when choosing your tablet compression tooling. General-purpose steels, such as S1 and S7 for punches and D3 for dies, provide a good combination of wear-resistance and toughness. If your product is abrasive, you may want to consider using A2, D2 or DC53 grades, or in extreme cases, consider punch tips and dies lined with tungsten carbide. For severely corrosive formulations, 440C or M340 high chromium steels are good options. When using premium tool steel, the punch must have a strong cup design in order to avoid tip fractures.





When choosing tool steels, you should always consider both the formulation characteristics and the tool design in order to determine the best solution. Your tooling vendor is your best resource for information and guidance, so be sure to take advantage of their knowledge and expertise.

CONCLUSION

Always remember that every formulation is different. There are no two products that are exactly alike. They don't run the same. They don't perform the same under compression and decompression forces. Likewise, when choosing tooling for tablet presses, tablet manufacturers need to know that one size does not fit all.

There are standards for tooling, but you can't always expect the standard tool configuration to be the optimum configuration for your product. Don't be afraid to ask your tooling vendor questions — and do it early. They should have the knowledge and experience to assist you with product development.



CHAPTER 5:

BUFFING VS. DRAG FINISHING

One of the surest and most inexpensive ways to maintain tablet quality and reduce tooling and operating cost is to correctly refurbish and polish your punches. Maintaining the quality of your punches helps to eliminate tablet defects such as picking, sticking, capping, lamination etc. Learning how to properly polish your punches can help to solve all of these issues while significantly reducing costs by increasing tool life, in many cases up to 80 percent.

PROPER POLISHING

Tablet tooling is a considerable investment for your company. Quality tooling and a proper maintenance program is also integral to producing high-quality tablets efficiently. Over time, tooling loses its luster and can develop nicks, scratches and/or a wear pattern commonly called J-hook. These imperfections can cause quality issues such as tablet capping, laminating, sticking, picking, and unnecessary down time in production.

It's not just polishing, but refurbishing, that permits tools being put back into service, and extending tool life while maintaining tablet quality.

Although there are numerous ways to polish and refurbish punches, the best method is to use a large unsewn cotton buff wheel. A 400 grit stone can be used for restoring land and removing nicks from the punch cup if the wear condition is severe. Restoring land is one of the most important procedures in tool refurbishing. Once a procedure is adapted to routinely refurbish land, you will immediately recognize an increase in tooling life and appreciate the cost savings compared to other common methods such as drag finishing.





DAVE PERRY
Assistant Plant Manager &
Polishing Expert
Natoli Engineering Company

“ Polishing can smooth out nicks and bring shine back to punch cups. A clean, smooth surface will release product better, produce better finished tablets, and reduce problems during production.”

J-HOOK

A common punch tip wear pattern called J-hook routinely causes lamination and capping. When J-hook forms, if the tools are not properly refurbished, they must be discarded and replaced. This is unfortunate as the procedure to restore the punch tip to remove the J-hook takes merely seconds per punch and at the same time polishes the cup to a mirror luster.

There are other common methods of polishing tools, such as using a drag finisher. Although drag finishing is considered an automated polishing process, you often won't receive the results you need compared to polishing using the unsewn cotton wheel—in fact, you can cause damage to your tooling if you aren't conservative with your use of a drag finisher which can result in tool binding, excessive cam wear and tablet discoloration. Using a drag finisher also will not restore land to the punch, nor will it help the tool perform as new. Although drag finishing is considered an “automated” process, it doesn't restore punch tip land therefore will not correct issues such as capping and laminating. An experienced technician can polish tools as quickly and more thoroughly than a drag finisher, in the same amount of time on a polishing station.

“ By restoring the punch tip land, you're extending the life to the tool. You're giving strength back to the cup, and you'll make better tablets.”



DAVE PERRY
Assistant Plant Manager &
Polishing Expert
Natoli Engineering Company



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Assistant Plant Manager &
Polishing Expert
Natoli Engineering Company

“ Press operators need to communicate any production difficulties or observations to tooling maintenance personnel so they can address any problems. If your tablets are sticking, you should visually inspect your tools for nicks and other signs of damage. If you see small nicks or reduced luster, you should remove the tooling and refurbish so you can get back up and running in a productive and efficient manner.”

Each organization should develop a Standard Operating Procedure to determine when to polish tools. Tools in more intense production situations may need refurbishing more often. Communication is very important, as well as teamwork.

If there are no concerns related to tablet finish, capping, laminating or sticking during a batch run, then the suggested practice to justify tool refurbishing is to visually inspect if refurbishing is required. Refurbish if necessary, then oil and properly store the tooling if they will not be immediately put back in service. Don't refurbish tools if it is not clearly indicated understanding polishing is a form of controlled wear. Unneeded refurbishing can adversely affect the life of the punches.

Proper training is the key to successful tool refurbishing. An experienced, well-trained technician can reduce cost by quickly putting tools that would normally be discarded back in service.

Although refurbishing tooling on site saves downtime, shipping, and the cost of paying someone else to refurbish your tooling, it must be understood that not all tool wear conditions are repairable. It's best to check with your tooling manufacturer if you experience tool damage that your trained polishing expert is unsure of repairing.

**SHARP
TIP O.D.**



**SHARP
RELIEF**



BRAND NEW PUNCH

**ROUNDED
TIP O.D.**



**ROUNDED
RELIEF**



NEW PUNCH DRAG FINISHED



DAVE PERRY
Assistant Plant Manager &
Polishing Expert
Natoli Engineering Company

“ Hands-on training is essential. You have to get a feel for the amount of pressure that’s required. Without proper training, you can destroy your tools pretty quickly.”

The benefits are clear - if you want to receive better performance from your tools, increased tooling life, reduce downtime which equates to better output, and maintained tablet quality then consider refurbishing tools on site. With proper training, you will be able to extend tool life and receive a higher quality tablet. You’ll also save money by reworking tools rather than purchasing new.

Natoli offers in-depth, hands-on training and has all the most popular polishing products available for purchase in our accessories catalog – including a CE compliant polishing station, all types of polishing compounds, and hard to find support products. Contact us to learn more!



BUFFING VS. DRAG FINISHING

	Buffing	Drag Finishing
Refurbishes punch cup	Yes	No
Polishes entire punch	Yes	Yes
Eliminates capping due to tip wear	Yes	No
Requires training	Yes	No
Extends punch life	Yes	No

CHAPTER 6:

PREVENTION & REPAIR OF J-HOOK

Anyone who has experienced capping or lamination during tablet production knows the frustration that comes from trying to diagnose the issue. In this article, we discuss a possible cause and several solutions.

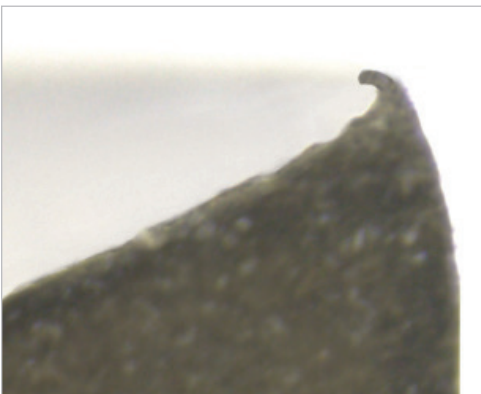
J-hooks are the distinctive wear patterns on punch tips that are a cause of such tablet defects as capping and lamination. If detected early, J-hooks can be easily and quickly repaired, thereby eliminating the need to purchase replacement tools.

By emphasizing tool maintenance as a standard operating procedure, tablet manufacturers can:

- Increase the life of their tools as much as 80 percent, thereby protecting the company's considerable investment in the purchase of these instruments.
- Eliminate need for press downtime to repair or replace punches with J-hooks.
- Reduce tooling and operating costs.
- Minimize the manufacture of defective tablets and thereby boost productivity.

WHAT IS J-HOOK?

A punch tip wear pattern that is a leading cause of tablet capping, lamination and poor friability.



A manufacturer whose SOPs require routine cleaning, inspection, repair, lubrication, as well as careful handling and storage of punches will discover that these maintenance practices are an inexpensive way to ensure the consistent production of high quality tablets and thus improve the company's bottom-line.

The following are J-hook basics for press operators and other tablet manufacturing staff.

WEAR CAUSES J-HOOKS

Over time punches and other compression tools lose their luster and develop nicks, scratches, and/or J-hooks. Wear from abrasive products and even the smallest contact between the upper punch tip and the die during entry can create J-hook on punches.

“ Typically the first area of the punch to wear is the land, the flat and narrow area at the tip’s perimeter. With wear, the tip becomes very thin and is more susceptible to damage.”



BILL TURNER
Technical Service Manager
Natoli Engineering Company

Tooling wear and J-hook can result from worn punch guides. The same type of wear can also be the result of improper die installation. Tools such as die driving rods, a die insertion tool, and present torque wrenches are all great instruments to prolong die pocket wear which will increase tool life and maintain tablet quality.

When the land erodes away, the upper punch is very susceptible to the formation of J-hook. However, J-hooks can form on both the upper and lower tips if the conditions are right. Inspection of upper and lower punch tips is essential.

REGULAR INSPECTION AND MAINTENANCE CAN HELP PREVENT AND MINIMIZE J-HOOKS

Like all manufacturing tools, compression tools should be inspected on a defined schedule. Visual inspection for deteriorated outer tip edge and/or J-hook is important. An inspector can simply drag their fingernail from the inside of the cup out to the outer edge and if a J-hook is present, his or her nail will catch on the hook.



DAVE PERRY
Assistant Plant Manager
Natoli Engineering Company

“ A clean, smooth surface will release product better, produce better finished tablets, and reduce problems during production.”

If the J-hook is light, it can be removed by polishing. In addition, polishing restores the cup's mirror luster.

A factory-trained staff member should be given the responsibility of repairing and refurbishing punches with J-hooks.



DAVE PERRY
Assistant Plant Manager
Natoli Engineering Company

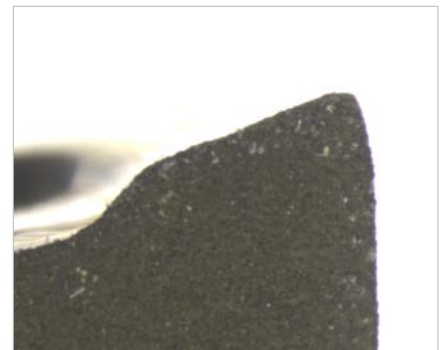
“ Proper hands-on training is essential, you have to get a feel for the amount of pressure that's required.”

Natoli recommends the large unsewn cotton buff wheel, rather than the drag finisher, as the best method to polish punches. Using a drag finisher will not effectively or efficiently restore land to the punch, nor will it help the tool perform as new. And as it doesn't restore land, it will not correct issues such as capping and laminating.

A large unsewn cotton buff wheel effectively eliminates J-hook and restores land to punch.



BEFORE



AFTER

CHAPTER 7:

QUALITY OF STEEL

{ Steel quality is the summation of how well a steel meets its specified chemistry, the cleanliness of the steel or degree to which it is free of impurities or inclusion, homogeneity of the microstructure, grain/carbide size and in some instances if it meets the mechanical requirements for that particular steel. In the design and manufacture of tablet compression tooling, nothing is more important than the quality of the materials being used. The best manufacturing principals maintaining the tightest tolerances will result in tool failure if the initial material quality is poor. Material quality is the fundamental building block upon which all successive value added steps are laid. The majority of all tablet compression tooling is produced from steel and steel quality is the subject of this article.

Quality of steel should be seen as an inherently quantifiable attribute that is used to determine a steel's ability to perform its designed function without limitation due to internal flaws or large variances in microstructure or homogeneity. Process control in all areas of steel production and refinement will determine a steel's quality. Heat treatment, while not a determinate in the initial quality of steel, must be carried out properly to ensure success; a quality steel poorly heat treated is also doomed to failure.

Typically, all non-powder metal steels are produced in the same way, with material charges added to a furnace and melted; the melted metal is called **A HEAT**. Chemistry of the heat is checked and adjustments (alloy additions) are made to ensure that the chemistry falls within the specified range. Once the chemistry is correct, the heat is tapped, slag is removed and the heat is poured; eventually to be rolled into a bar or plate for use in the production of tooling.



Powdered metals, on the other hand, are produced by compacting very fine powdered metal and densification of that powder using high temperature and pressure. After densification the resulting product is a fully dense billet that is then rolled in to bar or plate. There is very little physical distinction between a powder metal bar and a traditionally cast bar, except the microstructure of the powder metal is typically of a finer grain structure and more homogenous. This control over carbides and grain size enhances the mechanical properties of the steel and allows some unique chemistries not available to traditional casting. Due to the manufacturing process requirements, powder metals are more expensive than equivalent steels traditionally cast.

Additional steps can be taken before and after the initial pouring of steel, prior to rolling, to increase the cleanliness of the traditionally cast steels.

VACUUM INDUCTION MELTING (VIM) melts the “material charge” in a vacuum before pouring; this process reduces the partial pressures of gas in the melt, preventing the formation of some oxides and producing cleaner steel.

ELECTROSLAG REMELTING (ESR) takes a cast ingot, prior to rolling, and places it into a chamber with reactive molten slag that has high current electricity passed through it, melting the ingot. As the ingot melts, the liquid metal passes through the reactive slag, impurities are removed and solidification takes place where the liquid metal is chilled by the chamber wall. The solidification rate is much higher than the casting process, and the amount of segregation is reduced. The process continues until the entire ingot has passed through the slag and re-solidified on the opposite side. ESR produces very clean homogenous steel with a refined cast structure.

VACUUM ARC RE-MELTING (VAR) is similar in result to ESR, but the ingot is melted by an arc under vacuum. The vacuum lowers the partial pressure, removing any gases within the ingot leaving a cleaner ingot, with a homogenous microstructure and little segregation due to the higher solidification rates.





During rolling, the steel ingot is reduced in cross section and elongated to produce the wrought bars used to manufacture tablet compression tooling. This reduction helps to reduce segregation and refine carbide and grain size. Steel with a fine grain size and small, well dispersed carbides will perform better than steel with larger grains and course carbides; the larger the reduction the greater the refinement. Tight control over the temperature and amount of reduction, per pass, must be maintained during the rolling process to ensure that voids or cracks do not “open up” during rolling.

Analysis of the bar’s chemistry and microstructure after rolling provides assurance that the bars were produced within tolerance; the steel mill will provide a certification for that heat. End users of these finished bars should perform their due diligence by randomly having sampling bars tested and analyzed by an independent lab to ensure they meet the specification. During this quality assurance, at the mill or the end user, we quantify the cleanliness of the steel through image analysis; either comparatively with representative standards or with software designed to sort and classify inclusions. Several standards exist worldwide (ASTM, DIN, JIS, ISO) to make sure steel cleanliness and quality measurements are consistent and defined.

Because steel quality is something that can be quantified and compared between vendors it should be the basis for making informed judgments about the tools you purchase. *Don’t allow a salesman to tell you about the quality of their steel; ask them to show you!*

Natoli Engineering requires all steel to be Electroslag Refined (ESR) to ensure cleanliness and adhere to a strict internal carbide size and distribution standard. In addition to seeking the highest quality steel, we quarantine all incoming material until an outside laboratory verifies that all specifications and standards were met; ASTM A681-06 or manufacturers specifications for chemistry and ASTM E45 Method D (Low Inclusion Content) to quantify cleanliness. Natoli wishes to provide our customers with the best tooling available. While we can tell you about our quality, we would rather show you.





NATOLI STEEL & COATINGS CHART

Steel Type	Steel Grade	Tooling Type		Hardness Rockwell C	Nominal Chemical Composition											Benefits										
		Punch	Die		C	Cr	Mn	Mo	Ni	P	S	Si	V	W	WR	IT	CR	CS								
408	Standard	•	–	53 - 55	0.50%	7.5%	0.50%	–	3.00%	0.04%	–	0.30%	–	–	–	–	–	–	–	–	–	–	–	–	–	
S-1	Standard	•	–	56 - 58	0.50%	1.40%	0.25%	0.25%	0.15%	0.03%	0.03%	0.03%	0.70%	0.20%	2.25%	–	–	–	–	–	–	–	–	–	–	–
S-7	Standard	•	–	56 - 58	0.50%	3.25%	0.55%	1.50%	–	0.03%	0.03%	0.03%	0.60%	0.2-3%	–	–	–	–	–	–	–	–	–	–	–	–
D-2	Premium	•	•	58 - 60	1.50%	12.00%	0.30%	.95%	0.15%	0.03%	0.03%	0.30%	1.00%	–	–	–	–	–	–	–	–	–	–	–	–	–
DC-53	Premium	•	•	59 - 61	1.00%	8.00%	–	2.00%	–	–	–	–	0.25%	–	–	–	–	–	–	–	–	–	–	–	–	–
K-340	Premium	•	•	58 - 60	1.10%	8.20%	0.40%	2.10%	–	–	–	0.70%	0.50%	–	–	–	–	–	–	–	–	–	–	–	–	–
D-3	Premium	–	–	59 - 61	2.20%	12.25%	0.30%	–	–	0.03%	0.03%	0.30%	0.50%	0.50%	0.50%	–	–	–	–	–	–	–	–	–	–	–
440C	Premium	•	•	54 - 56	1.10%	17.00%	0.75%	0.40%	–	–	–	0.50%	–	–	–	–	–	–	–	–	–	–	–	–	–	–
M-340	Premium	•	•	56 - 58	0.54%	17.30%	0.40%	1.10%	–	–	–	0.45%	0.10%	–	–	–	–	–	–	–	–	–	–	–	–	–
A-2	Premium	•	•	58 - 60	1.00%	5.10%	0.50%	1.15%	0.15%	0.03%	0.03%	0.25%	0.35%	–	–	–	–	–	–	–	–	–	–	–	–	–
M-2	Premium	•	•	58 - 60	0.80%	4.10%	0.25%	5.00%	0.15%	0.03%	0.03%	0.30%	6.20%	–	–	–	–	–	–	–	–	–	–	–	–	–
PM-15V	Powdered Metal	–	•	58 - 60	3.40%	5.25%	0.50%	1.30%	–	–	–	0.90%	14.50%	–	–	–	–	–	–	–	–	–	–	–	–	–
PM-9V	Powdered Metal	•	•	53 - 55	1.90%	5.25%	0.50%	1.30%	–	–	–	0.90%	9.10%	–	–	–	–	–	–	–	–	–	–	–	–	–
PM-3V	Powdered Metal	•	•	56 - 58	0.80%	7.50%	0.30%	1.30%	–	–	–	1.00%	2.75%	–	–	–	–	–	–	–	–	–	–	–	–	–
PM-10V	Powdered Metal	•	•	58 - 60	2.45%	5.25%	0.50%	1.30%	–	–	–	0.90%	9.75%	–	–	–	–	–	–	–	–	–	–	–	–	–
PM-M2	Powdered Metal	•	•	58 - 60	0.80%	4.10%	0.25%	5.00%	0.15%	0.03%	0.03%	0.30%	2.00%	6.20%	–	–	–	–	–	–	–	–	–	–	–	–
PM-M4	Powdered Metal	•	•	58 - 60	1.42%	4.00%	0.30%	5.25%	0.15%	0.03%	0.03%	0.30%	4.00%	5.50%	–	–	–	–	–	–	–	–	–	–	–	–
PMS-90V	Powdered Metal	•	•	56 - 58	2.30%	14.00%	–	1.00%	–	–	–	–	9.00%	–	–	–	–	–	–	–	–	–	–	–	–	–
Hastelloy	Powdered Metal	•	•	–	0.01%	22.00%	0.50%	13.00%	56.00%	–	–	0.08%	0.35%	3.00%	–	–	–	–	–	–	–	–	–	–	–	–
Carbide Dies	Specialty	–	•	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Carbide Tip Punches	Specialty	•	•	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Ceramic Dies	Specialty	•	•	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Sleipner	Die Segment Plate	–	–	61 - 63	0.90%	7.80%	0.50%	2.50%	–	–	–	0.90%	0.50%	–	–	–	–	–	–	–	–	–	–	–	–	–
M-390	Die Segment Plate	–	–	58 - 60	1.90%	20.00%	0.30%	1.00%	–	–	–	0.70%	4.00%	0.60%	–	–	–	–	–	–	–	–	–	–	–	–

The ASTM E45 International Steel Testing Procedure is the test method used to determine the quality and cleanliness of tool steel. **Natoli Engineering's value is less than 1.5.**

Element Symbols

- C = Carbon
 - Cr = Chromium
 - Mn = Manganese
 - Mo = Molybdenum
 - Ni = Nickel
 - P = Phosphorous
 - S = Sulfur
 - Si = Silicon
 - Ti = Titanium
 - V = Vanadium
 - W = Tungsten
- Benefit Codes**
 WR = Wear Resistant
 IT = Improved Toughness
 CR = Corrosion Resistant
 CS = Compressive Strength
 RF = Reduced Friction
 RS = Reduced Sticking

Natoli Coating Specification Chart

Coating	Characteristics			Tooling Type											Benefits											
	Hardness	Thickness	Color	Punch	Die	S	P	PM	SPC	RF	RS	WR	CR	CS												
Hard Chrome Plating	950-1200 HV	3-6 microns	Silver	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Natoli Ultracoat	1200 HV	5-10 microns	Silver	•	–	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Chromium Nitride (CrN)	2300 HV	~ 3 microns	Metallic Grey	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Titanium Nitride (TiN)	2300 HV	~ 3 microns	Metallic Gold	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Diamond Like Carbon (DLC)	2500 HV	1-2 microns	Black	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Nickel/Fluoropolymer	–	20-50 microns	Gold	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Teflon	–	20-50 microns	White	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Plasma Nitriding	1000 HV	75-100 microns	Black	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Boron Carbide	3400 HV	1-2 microns	Black	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Diamond Like Carbon (DLC) 40/41	2000-2800 HV	~ 5 microns	Black	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

CHAPTER 8:

WHY YOU SHOULD BE USING ULTRASONIC CLEANING

{ Clean punches and dies are essential to maintaining the integrity and efficiency of your tooling investment, as well as the quality of your product. Ultrasonic cleaning has long been considered the most effective, nondestructive way to clean tools – from medical instruments to tablet tooling. The Tableting Specification Manual (TSM) states, “An ultrasonic bath is ideal for cleaning tooling.” This high-tech cleaning process also saves time, reduces cost and is better for the environment.

WHY CLEANING IS IMPORTANT

Dirty tools can cause tool binding, which can result in damage to the tooling and the tablet press. Keeping tools clean will decrease the chance of premature tool wear, allow lubrication to be more effective, and the machine to run more efficiently – which will increase product yield.

HOW IT WORKS

Ultrasonic cleaners use high frequency pressure waves to cause cavitation to agitate a liquid (usually cleaning solution and/or water, which in turn creates tiny bubbles that loosen and remove debris. This action is highly effective for removing all traces of product

Natoli Engineering offers an Ultrasonic Cleaning System with wash, rinse and dry units, as well as a tabletop model.



and/or contaminants from tooling. The ultrasonic waves penetrate all surfaces of the tool, including hard to clean areas such as key slots, cups, and die bores, and cause debris such as oil, grease, and biological residue to break up and disperse. In addition to using an ultrasonic wash unit, it's also critical that tools are rinsed and dried properly because any residue left from cleaning solution or water can cause corrosion or discoloration of the tooling. Thorough drying is extremely important to the cleaning process. The TSM states, "After cleaning, tooling must be handled carefully to prevent moisture from the operator's fingers remaining on the tooling and causing rust."

BENEFITS

MORE EFFECTIVE CLEANING

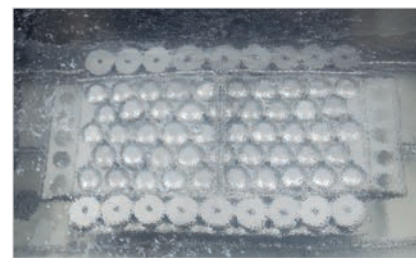
Ultrasonics clean more effectively and thoroughly than manual scrubbing, which can be ineffective on heavily soiled tooling and can cause damage to delicate surfaces. Using ultrasonic waves to clean will remove material even tightly adhered to surfaces.

REDUCED COST

Not only does ultrasonic cleaning save labor cost, it also completes the cleaning cycle in less time. A typical cleaning cycle for moderately soiled tools can last 10 minutes or less and requires little supervision, which frees up staff to spend time completing other tasks.



Proper drying prevents rust, which can severely damage your tooling.



Ultrasonic cleaning quickly and easily provides a safe, thorough cleaning of your punches and dies.

As mentioned, the most important cost savings may be reduced wear and tear on tools. Ultrasonic cleaners provide superior cleaning without using abrasives to remove grime, and they don't create friction or wear during the cleaning process. This means tools receive a better cleaning through a more delicate delivery than with manual processes.

ENVIRONMENTALLY FRIENDLY

Ultrasonic cleaning offers multiple environmental benefits. New-generation models require much less energy and are more efficient to run than older models. The machines also require less water to clean more tools than manual cleaning, and the FDA-approved cleaning solution is environmentally friendly and non-ozone depleting.

A BETTER CLEANING SOLUTION

Punches and dies are a big investment that should be protected by careful handling and thorough cleaning. Ultrasonic cleaners truly offer a better cleaning solution than other methods. In addition to saving time and reducing costs, they deliver the safest, most efficient cleaning process.



BEFORE



AFTER

CHAPTER 9:

HOW CRUCIAL IS COMPACTION DWELL TIME?

Transitioning product from one tablet press to another during scale-up has been an ongoing challenge in the industry for many decades. There are many different approaches and aspects that must be considered including the tablet press and punch design, and powder characteristics.

When developing a new formulation scientists are equipped with a small scale tablet press to study and understand their product's tableability. These small scale systems are very useful at the research level but do not always successfully transfer to the larger scale manufacturing machines. Ideally, developing the product on a manufacturing press would eliminate the transfer challenges, but the amount of powder required to operate such a machine is very high and not cost effective.

There are many stages that occur during tablet production on the rotary tablet press and a full understanding of their functions is crucial to the success of producing a quality tablet.

Stages include:

- Powder filling from the hopper into the feed system
- Powder filling from the feed system into the die cavity
- Proper fill cam and dosing cam settings
- Centrifugal acceleration and the need for a pull-down cam
- Pre-compression – is it needed and how much force?
- Main compression consolidation time and rate
- Main compression dwell time
- Main compression decompression event
- Ejection force and rate
- Tablet take off – sticking and picking adherence removal



Figure 1. – Turret Pitch Circle Diameter

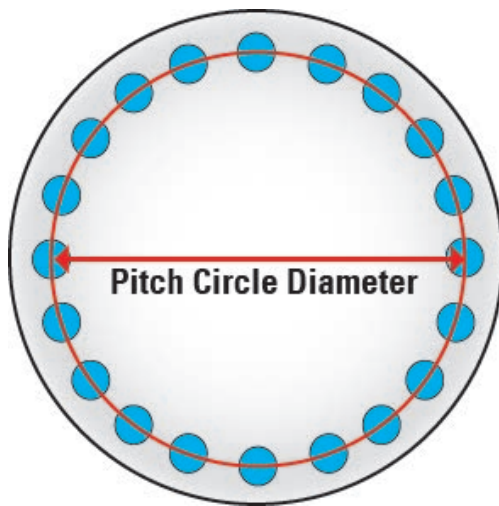
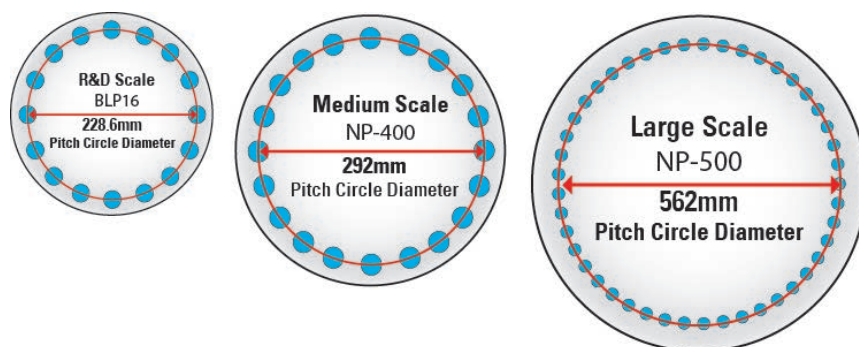


Figure 2. – Examples of Different Pitch Circle Diameters



Every step in the tablet press process merits a full discussion but this article will focus on the compression dwell time and how the tablet press and punch head design's impact this process.

DISCUSSION

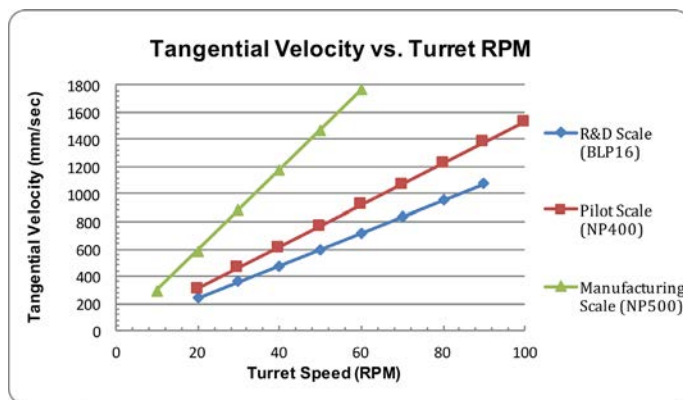
Dwell time expressed in milliseconds is the time in which the punches achieve maximum penetration in the die under the main compression rollers and the punches are no longer moving vertically. In other words, dwell time occurs when the compression rollers are in contact with the punch head flat. Dwell time is a contributing factor to the tablet strength and a means for product transfer from one tablet press to another. Although turret RPM or tablets-per-minute are a common language for the turret speed, it doesn't allow a true comparison for tablet presses with different turret sizes but the turret velocity is a normalization of turret size and the dwell time is a normalization of the turret size and punch head flat. It is important to understand the turret velocity before we can discuss dwell time.

TURRET VELOCITY

When comparing press speed, the tangential velocity or TV expressed in mm/sec allows for a true comparison. The TV is a function of the turret RPM and pitch circle diameter or PCD, which is the measurement of the turret from center of the die to the opposite die center. (See Figure 1.) The PCD is critical, as this is where the compression event occurs.

At a particular turret RPM the TV is dependent on the PCD, which varies depending on the number of stations on a turret. Figure 3. depicts examples of different sized machines and the relationship between turret RPM and TV.

Figure 3. – Tangential Velocity for Different Sized Presses



As the turret PCD increases the required turret RPM is reduced to match a particular TV. A representable manufacturing velocity is above 1,000mm/sec. At 1,000mm/sec, the larger scale NP-500 press will operate at a turret speed of 34-RPM, where the medium scale NP-400 operates at 65-RPM and the smaller scale BLP-16 at 84-RPM. Running at 84-RPM turret speed can pose some challenges with powder flow into the die cavity, inhibiting the ability to evaluate tablet attributes. In fact, some industry small-scale tablet presses are not able to generate manufacturing velocities due to their smaller PCD or limited turret RPM. This is where the punch head flat can be designed to provide this gap for scale-up matching.

HEAD FLAT AND DWELL TIME

Compression tooling heads are designed with a flat, providing a constant strain to the powder bed while under the compression rollers. The longer the head flat the longer the dwell time and depending on your powder deformation characteristics and strain rate sensitivity, a longer dwell time may be needed to produce a robust tablet. Slowing the turret speed can also increase the dwell time but slowing the turret speed will also decrease production rates.

There are many different types of tools used in the industry that have different head configurations. Some are designed specifically to increase dwell time, while others are designed to reduce premature



Figure 4. – “B” Type Tooling Dwell Time Comparison

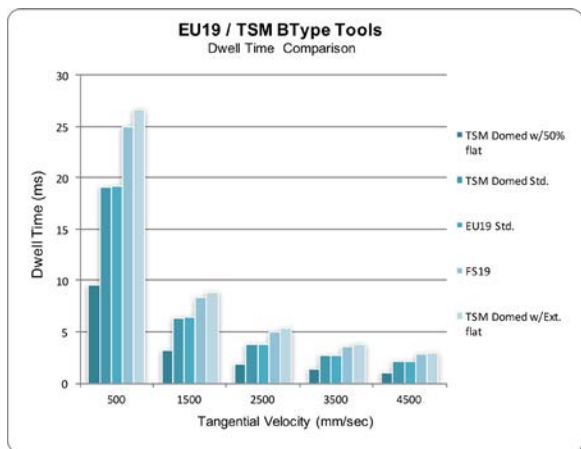


Figure 5. – “D” Type Tooling Dwell Time

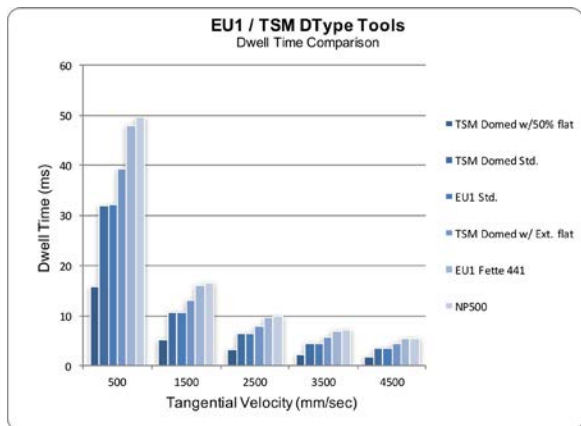
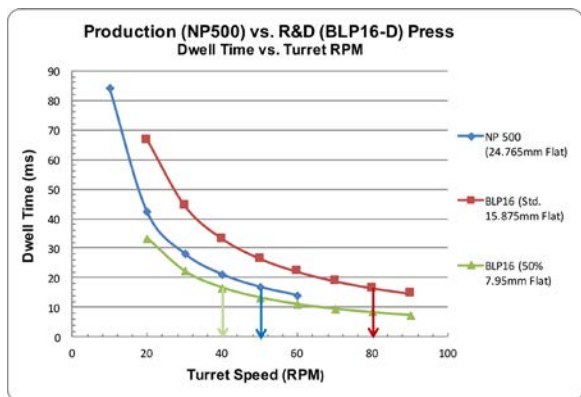


Figure 6. – Production Press vs. R&D “D” Tablet Presses



wear. The two most recognized tool configurations are the European ISO standard and the American TSM. These standards are provided to allow tablet press tool interchangeability, consistent quality between tooling vendors, simplified inspection processes and inventory. Within both configurations, the “B” and “D” type tools are the most common. “B” tooling is designed with a smaller body allowing a higher population of punches in a turret which is favorable for high tablet output, where the “D” tooling is designed with a larger body, allowing for larger tablets approaching up to one inch. As a “D” tool is larger the head profile and flat for a standard configuration is also larger, providing a longer dwell time. Figures 4. and 5. provide a chart of different head designs and their respective dwell times for a given TV. Notice that the TSM Domed Std. and EU 19 Std. are almost identical as their head profiles are very similar. Also notice that the dwell time is less sensitive at the higher turret rates.

Dwell time can be calculated by taking the punch head flat dimension divided by the turret tangential velocity. This simple calculation is helpful when transferring product to a different size press. And in the case of the large gap between TV as discussed previously with smaller R&D machines and larger scale machines, the tooling head flat can be designed by your tool manufacturer to match, or closely match, dwell times. The flexibility you have on your flat dimension is dependent on the punch neck diameter. To ensure the robustness and integrity of the punch, the neck diameter should be larger than the head flat and with some safety margin.

Figure 6. is an example of comparing the dwell time of a production press (NP-500) and an R&D tablet press (BLP16-D). The NP-500 is a high-speed, 45-station, double-sided production tablet press with extended head flat tooling, and the BLP16-D is a 16-station, “D” tooled development press. The NP-500 running at 80% of its maximum speed reaches 50RPM and 17m

Figure 7. – Production Press vs. R&D “B” Tablet Presses

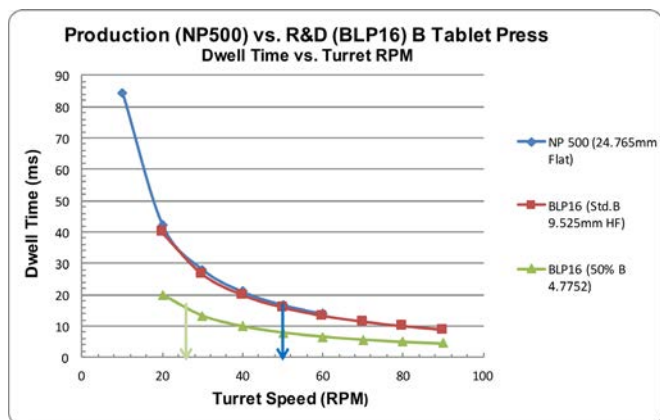
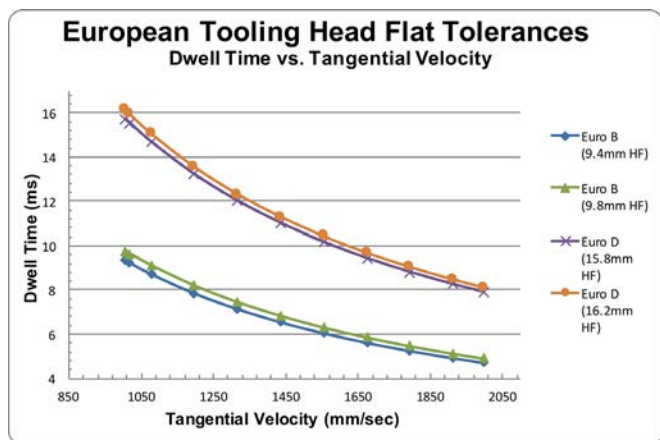


Figure 9. – European Punch Head Tolerances & Impact to Dwell Time



of dwell time. With standard TSM domed heads the BLP16-D must reach 80RPM turret speed to match 17ms. It can be challenging to maintain consistent tablet weights at such a high speed. When using the reduced head flat of 7.95mm on the BLP16-D, the required turret speed is now only 40-RPM, which is a more manageable speed for tablet weight consistency and helps reduce powder wastes.

Another challenge that can be resolved with head flat designs is transferring product from a “B” tooled machine to a “D” tooled machine or visa versa.

Figure 7. is an example of matching dwell time from an NP-500 to a BLP-16 utilizing “B” tooling. The standard “B” tooling matches dwell time of the NP-500 at similar turret speeds. When using the 50% of standard “B” head, the turret speed is reduced to 25-RPM, which again, at slower speeds, helps reduce powder wastes.

As previously discussed the European ISO standard and American TSM are the references for tooling specifications. They provide the acceptable tolerances to ensure proper installation, alignment and tablet consistency. The punch head flat also specifies an acceptable tolerance of +/- 0.2mm for the Euro standard and +0.00 / -0.76mm for the TSM standard. At common production rates the extreme difference is less than 1ms and as low as 0.2ms at higher production rates. Figure 9. depicts the small dwell time differences for the European tolerances. To accurately measure your punch head dimension a Horizontal Optical Comparator can be used.

CONCLUSION

Tooling designs and dwell time are one of many important parameters that play a role in tablet quality. Tooling head flats can be designed to achieve your desired dwell to assist in product transfer scalability processes or tablet robustness issues. Normalizing for turret size, speeds and tooling allows for a clearer understanding and comparison of different size tablet presses.

CHAPTER 10:

DETAILED FORMULATION DEVELOPMENT HELPS AVOID PRODUCTION PROBLEMS

Compression tooling and tablet press manufacturers are faced with ongoing challenges in the tablet manufacturing environments. Providing support in all aspects of the tablet compression process should be expected from your tooling and tablet press partner. These services should include: press operator training, maintenance/calibration services, quick delivery of replacement parts, tooling, tablet design and powder formulation support.

If changes to compression conditions do not address tablet quality problems, then changes to the formulation may be needed to remediate the problems. These changes can be time consuming and costly; in addition scale-up and post approval change (SUPAC) guidelines must be followed. It is important to perform compaction studies during the formulation development process, before final regulatory submission. This ensures formulation performance and will minimize the risk of post approval changes. The following examples of formulation performance evaluation were performed at the Natoli Institute for Industrial Pharmacy Research and Development at the Arnold and Marie Schwartz College of Pharmacy and Health Sciences on the Brooklyn New York campus of Long Island University.

DISCUSSION

Developing a robust tablet formulation that can be scaled into product manufacturing without any issues can be a difficult challenge. Formulators and research professionals alike are tasked with the development process and must have an understanding of the science involved with powder compaction. Formulators must also maintain proper communication with the scale-up or manufacturing group, which can accelerate the time to achieve a marketed product with a higher return on investment.



SINGLE-STATION TABLET PRESSES

Single-station tablet presses offer many advantages during early development. These machines require a very limited amount of material to characterize a potential formulation. The die-filling process can be performed manually, allowing the use of only a few grams of formulation. Characterizing just the active pharmaceutical ingredient (API) can also be performed on these machines allowing the scientist to select the appropriate excipients using the results of the compacted API to guide their selection.

Figure 1.

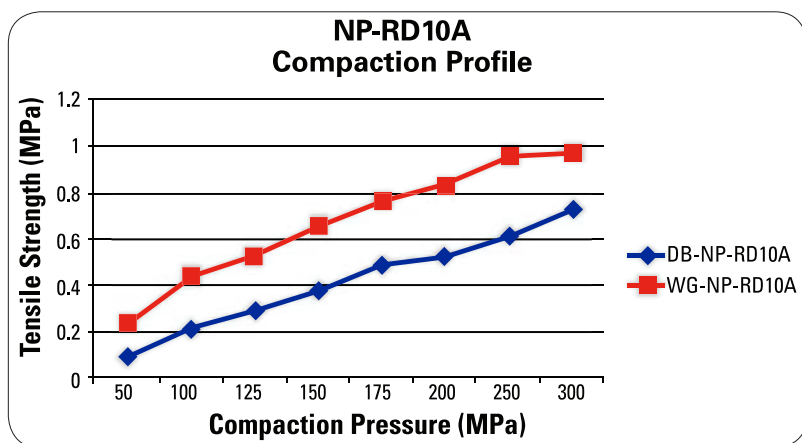


Figure 1. describes a tableability profile performed on the Natoli NP-RD10A single-station tablet press. This example is of an evaluation of a high drug load directly compressible APAP (acetaminophen) formulation (DB) versus a wet granulated APAP formulation (WG).

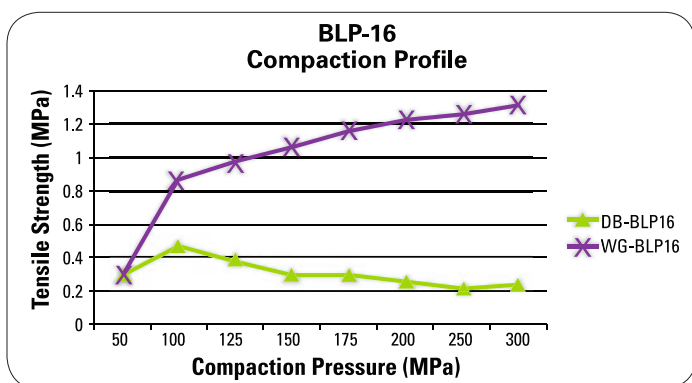
There is an advantage to normalize the compression force for the punch tip face area and thus utilize compaction pressure instead of analyzing the data using the compression force (kN) values. With any

new formulation, the compression force required is determined by the material properties and the tablet's diameter and thickness. Performing a compaction study from 50MPa – 300MPa covers the typical pressure ranges for compressing pharmaceutical tablets of all sizes. Furthermore, by utilizing the tablets diameter and thickness, the tablet's required breaking force is normalized for the tablet geometry. Tablet breaking force values (kilopond or Newton's) are determined by post-compression testing. The values for breaking force are normalized by the tablet geometry yielding tablet tensile strength. Target tablet tensile strengths in the range of 1 to 2MPa are representative values for a robust tablet that will withstand normal handling and the coating operation.

Figure 2. depicts the tableability profile performed on the BLP-16 rotary tablet press at 20-RPM turret speed for the dry blend and wet granulated formulations. The BLP-16 rotary tablet press is a 16-station, "B" tool machine that is capable of running at variable turret speeds.

Although there is a cost advantage with directly compressible blends, as the equipment investment costs and process times are much lower, the profile (Figure 2.) clearly shows that the wet granulation blend yields stronger tablets than the directly compressible blend throughout the compaction pressure ranges.

Figure 2.



It is clear that the profiles shown in Figure 2. illustrate different results as compared to the Natoli RD-10A single-station tablet press data shown in Figure 1. This data is representative of what can be expected at the manufacturing level, since the manufacturing machines utilize the rotary press design with upper and lower compression rollers. Due to the rotary press design, the upper and lower punches are moving horizontally across the rollers in addition to moving vertically to compress the powder.

Single station tooling can only move vertically for non-eccentric tablet designs in the tablet press. The movement difference changes the dynamics of the compression event and has an impact to the final tablet attributes as shown in Figure 2.

Compaction profiles for the dry blend formulation and wet granulated formulation on both the Natoli NP-RD10A single-station and the BLP-16 rotary press are depicted in Figure 3. The wet granulated

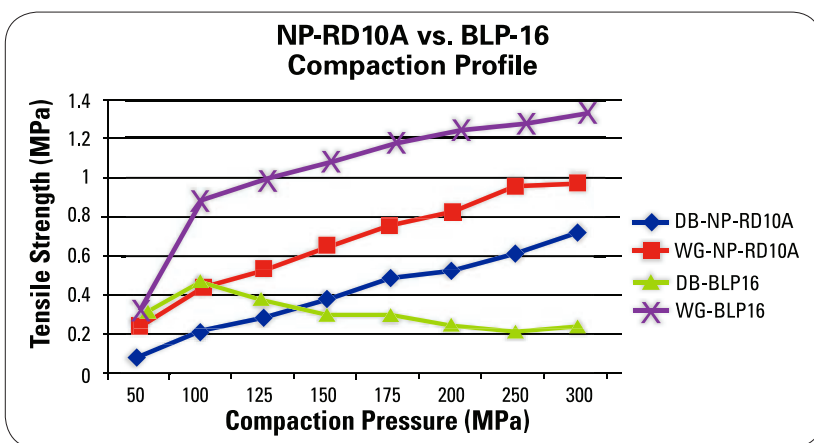
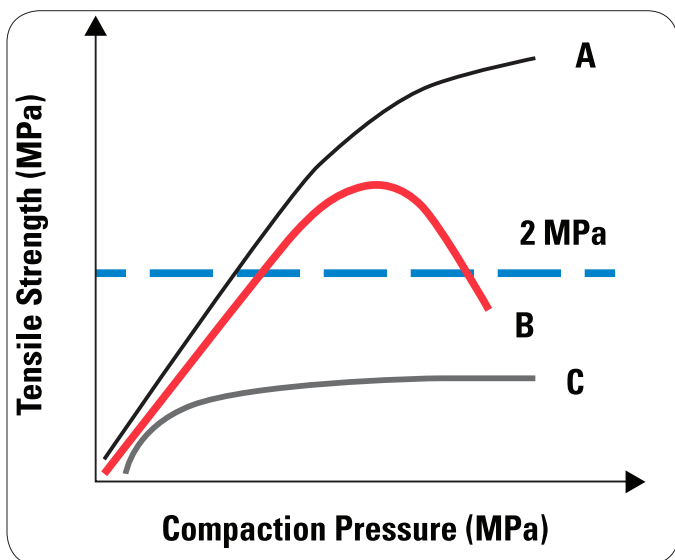


Figure 3.

formulation run on the BLP-16 yields robust tablets above 1MPa tensile strength at a reasonable compaction pressure. In this range the addition of more compression force yields tablets with higher tensile strength, whereas the dry blend formulation exhibits capping above 100MPa of compaction pressure. It is clear that the wet granulated blend is the choice formulation and that the dry blend will likely fail on a larger scale rotary press.

Many factors can impact the tableability curve including the powder deformation characteristics, particle size, shape, moisture content and proportion of powder fines. Variation in formulation performance is

Figure 4.



often traceable to changes in the properties of the API and excipients from batch to batch. It is crucial that your product has a robust tableability profile as illustrated by profile A in Figure 4. Figure 4. is an illustration of typical compaction profiles for various formulations.

Profile B is an example of where your tablet attributes might be acceptable at the research level or even scale-up level due to lower compaction rates but fail at the higher levels of the manufacturing process. Operating too close to the peak of the curve or on the descending side does not give any flexibility to the press operator when issues are found, which is crucial due to the previously described variables. The use of pre compression can improve your tableability profile as it de-aerates and consolidates the material before

the main compression event but it is wise to save this tool as a back up when issues arise at the manufacturing level. Profile C indicates a poor tableability profile and would not be acceptable tablet attributes. Developing a robust formulation will allow the manufacturing press operators to make press adjustments to solve these issues.

Another study that is valuable in the formulation development process is a strain rate study, where the compaction pressure is held constant. In this case we selected 150MPa since tablets were robust at this level, the turret speed was incrementally increased, and tablet attributes were evaluated.

Instead of evaluating tablet tensile strengths at different turret speeds, it is a more scalable approach to normalize for the turret pitch circle diameter, punch head flat diameter and evaluate the tablet tensile strengths as a function of dwell time (the time formulation is under maximum compression force in the die or when the punches are no longer moving vertically). Another important parameter to consider for press scalability is the punch vertical velocity or loading rate and the decompression event.

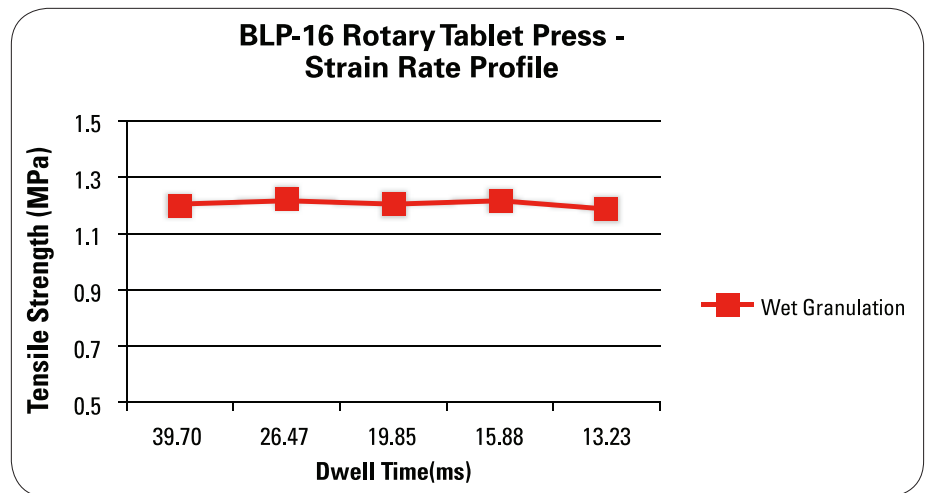


Figure 5.

In figure 5. we can conclude that the wet granulated formulation is not strain rate sensitive at dwell times as low as 13 milliseconds. Ultimately the product will be produced on a high-speed manufacturing press and the dwell times can be calculated with further studies being performed at full scale. As most research presses are designed with smaller diameter turrets, reaching similar velocities as the manufacturing machines cannot be achieved, so your tooling head profile can be designed to simulate similar dwell times. (For further explanation see *EPM* November/ December 2015 "Pressing Points" by Natoli Engineering Company.)

With the many challenges in the pharmaceutical manufacturing world today, tooling and press manufacturers are your key partners in the support of delivering a quality product. Tablet manufacturing issues arise from many variables including operator training, maintenance/ calibration of equipment, and the formulation that is compressed.

CONCLUSION

Speed to market is important when developing and delivering a branded or generic medicine to the market. Despite the need to minimize drug product development time, the time invested in ensuring that your product and process are capable of not only clinical supply, but also full market supply has lasting value. It is crucial in the development process to optimize the formulation and evaluate tablet robustness from tableability and scalability studies. This will help minimize the challenges faced at the manufacturing level and will allow the press operators to make press adjustments if there is a change in suppliers resulting in API or excipients with unexpected variability in their physical properties. Natoli Engineering Company offers hands-on training opportunities for formulation development and scale up to the tablet manufacturing process. For further information visit www.natoli.com.





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