

# From the Formulator to the Tablet Manufacturing Floor

## Desiderata and Troubleshooting

Fred A. Rowley



In pharmaceutical tablet manufacturing processes, the same problems and oversights occur all too frequently. Many companies forget critical basic concepts or established practices that could dramatically improve their production and their products. In this article the author shares some observations, along with suggestions of how to avoid these common mistakes.

Unfortunately a number of misunderstandings and omissions are still fairly common in the pharmaceutical and nutritional supplement industries regardless of the level of technical expertise present in the various departments or the managerial philosophy surrounding them. This article reviews some of these observations in the various operations with the hope that the reader may benefit from the author's experience.

### Formulation

Several basic issues appear on the production floor far from the formulator and long after the final formula has been set. The common cry from both technical service and line management personnel is that "the formula or process is now set and cannot change; why didn't they think of this earlier?" Indeed, in some cases the response from the formulator has been, "I knew about this, but there were trade-offs required to move this formula forward." Both points are well taken. Below are a few of the items to consider.

**Too many fines.** As a general class, formulations of pharmaceuticals for human use contain too many fines. Tablet presses are high-speed, precision machines engineered to successfully compress a wide variety of powders. With the addition of the precompressing station and the punch entry control, many formulas that have an unusually high number of fine particles are compressed every day. But sometimes we collectively seem to miss the point.

With ever-mounting pressure to minimize cost and maximize output, formulas must be engineered for compression at the highest possible speed. This simply cannot be accomplished when the total quantity of fines exceeds 30% of the formula. This does not imply that the formula cannot be compressed, but rather that the formula can never run successfully at high speed, even with the use of precompressing and punch entry controls. Too many fines also directly contribute to capping with the most common response being a reduction in press speed.

**Insufficient lubricant.** Research and clinical formulas are frequently compressed with new or slightly used tooling that does not necessarily represent what the formula will come in contact with later on the production floor. Traditional practice dic-

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tates that tooling should be routinely inspected, polished, and replaced as it falls out of established tolerances, but this is not necessarily the whole story. One simple example demonstrates the point: Each time a set of punches are pulled off a machine for tip cleaning and polishing during a batch compression, is it considered a process failure? Is someone tracking the number of times a particular set of punches fails in this way? What is the root cause of the failure — the tooling or the formula? If tooling is well maintained as described above, why does it still fail? Is it really tooling or is it lubricant levels?

This issue is particularly relevant for embossed tooling, which may have markings that are very different from the original research or clinical work. Unfortunately, quite often it is exactly during this time when lubrication levels are designed and then set.

**Sensitivity of lubricant.** The care with which the lubricant should be stored, screened, added, and blended is greatly underestimated in the production department. Lubricants are one of the cheapest components added to the formula, yet the sensitivity of the lubricant is oftentimes taken for granted. Although the supplier is qualified and the lab test is performed and passed, lubricant performance will be optimized only if the storage conditions, method of screening, avoidance of static charge buildup during addition, and reproducible blending sequences are strictly controlled.

## Milling

Milling also is taken for granted; it is viewed as a boring operation in which little goes wrong. In fact, many companies introduce new operators to the tablet manufacturing process by placing them in this operation, where it is assumed they will gain basic knowledge with minimal negative impact to the larger organization. Some items commonly overlooked are discussed below.

**Belt maintenance.** Proper belt maintenance is critical yet minimized. Many mills have multiple belts oriented along a common track. Although the standard operating procedure (SOP) will likely address the correct number of belts, there are other items to consider. Are one or more of the belts stretched and larger than the others? Are operators required to report obviously stretched belts before use?

**Belt tension.** Another consideration that is greatly underestimated in the production department is the effect of proper belt tension on particle size. Most mill manuals specifically point out that belt tension must be checked before use, and many provide tables outlining recommended settings and checks. Yet SOPs and cleaning procedures frequently omit a reference to belt tension. For example, if a major cleanup requires the disassembly and reassembly of the pulley system, this should automatically trigger a tension review.

**Batch failure.** Any batch failure investigation involving a shift in particle size traditionally will review the mill speed or screen size as a possible root cause. It is important, however, to realize that loose or worn belts will alter the actual rpm used, as will the failure to properly adjust belt tension. This becomes critical when the batch record simply calls for low, medium, or high speed, and the mill used has no tachometer. There is in fact no

## An optimization checklist

To improve production, manufacturers should ensure that the following key processes involved in tablet manufacturing are optimized:

- **Formulation:** Decrease the number of fines, maintain adequate lubricant levels, carefully store all lubricants.
- **Milling:** Maintain all belts by ensuring proper use and tension.
- **Granulation:** Minimize power consumption, ensure filter bags are used properly, install dehumidification equipment on fluid-bed granulators and driers, quickly reduce roll chatter.
- **Compression:** Define overload events, including their cause, and determine the overload set point; specify machine set points for the precompression station; ensure proper use of the upper punch entry system; maintain proper use of the slide gate in the powder hopper; reconsider the need for embossed lettering on tablets; examine all root causes of tablet capping; replace worn punches.
- **Aqueous coating:** Check gun geometry settings throughout the coating process, optimize pan speed, set pan pressure to slightly negative settings (in most cases, do not exceed  $-0.5$  in. water), optimize spray rates (not too fast as to compromise tablet elegance).
- **Tablet printing:** Monitor ink storage and replace water or solvents to maintain viscosity, maintain rubber rolls.

way to link the two requirements without understanding the proper use and tension of belts.

## Granulation

“Good tablets are made in the granulating department” is a long-established statement that illustrates a key point. Although direct blending does not alter the powders being mixed, all wet and dry granulating operations essentially create a granule. How those operations proceed directly affects how the tablet compresses and ultimately performs in the human body.

**Power consumption.** As a reliable means of determining the end point, power consumption is frequently overlooked with high-energy (shear) granulators. These granulators are used to convert fine powders that have poor flow characteristics into free-flowing, reproducible granules. The rate of solution addition and the end point of the process determine how many granules are formed and their morphology. The process end point may be determined in a variety of ways such as postaddition mix time, loss on drying, a combination of both, or the total power consumed during the process.

Although power consumption may be difficult to measure with low- or medium-energy (shear) granulators, its use on a high-energy granulator is critical for producing consistent granulate. Overgranulating, or the excessive use of power after the end point has been reached, is a basic root cause of disintegration or dissolution failure and may go unnoticed or unrecognized without the use of power-monitoring equipment.

**The filter bag.** The role of the filter bag in the fluidized-bed granulator is not clearly understood. The primary use of the filter bag is to collect particles and prevent them from leaving the vessel; however, the manner of its use may be very different during the three processing cycles. For example, the bag may not even require shaking during the premix cycle, but the frequency and duration of bag shaking during the spray and dry cycles has a profound effect on the final quantity and mor-

phology of granules formed. Many companies do not seem to understand this fact or choose to ignore it.

**Dehumidification.** Another widely overlooked consequence is the direct effect of failing to install dehumidification equipment on a fluidized-bed granulator-drier. Dehumidification systems for the air used to process granulations are expensive to purchase and maintain. Facing this investment, a company may tend to minimize the potential effects of humidity variations, place extraordinary pressure on its staff to justify a dehumidification package purchase, and generally take a head-in-the-sand approach to the link between such process variations and potential batch failures. After enduring significant variations in drying and cooling cycle times associated with seasonal change, and in many cases multiple batch failures, the same company will spend significant amounts to retrofit the original equipment.

**Roll chatter.** In dry granulation (also called Chilsonation or roll compaction), a condition known as roll chatter and its effect on tablet compressing often is not understood. When powder is compressed between two rolls at high pressure, a number of critical parameters must be satisfied to achieve success. One parameter, the vertical screw speed, determines the rate of powder addition to the nip area of the pressure rolls. Any significant variation of this feed rate may cause roll chatter. This sometimes loud noise sounds much like a pinging noise in a combustion motor. Roll chatter results in underoptimized granule formation. Operators tend to ignore or react slowly to significant periods of roll chatter when simply modifying the vertical screw speed would alleviate the condition.

## Compression

Tablet compression is the heart of the solid dosage production cycle. There are at least seven different areas in this unit of operation in which a significant amount of misunderstanding or variation on a single idea exists. The reader may want to review his or her concept of the compressing cycle before reading this section.

**The overload set point.** The overload set point is a number fed into a compressing machine to protect the tooling in case of an overpressure situation. It is not related in any way to tablet attributes or machine speed. It is the relief valve on the pressure cooker. Yet its role is sometimes misunderstood by operators and management alike. For example, many believe that it is the pressure used to compress the tablet; others believe that a change in the setting will affect tablet attributes.

It is also important for both operators and supervisors to understand what an overload event is and what causes it. Further, what happens to the tablet once an overload event occurs will vary greatly depending upon the control system surrounding it.

**The precompressing station.** Often improperly used, the precompressing station is designed to remove air from the granulation. It is not used to compress the tablet, and it was not engineered to be a duplicate compressing station. In fact, the overcompressing of a tablet at the precompressing station is just as serious as overcompressing at the final station. Both can cause capping. Sometimes companies go to great lengths to specify machine set points for the final or main compressing station but specify few or none for the precompressing station.

**The punch entry system.** The proper use of the upper punch entry control is widely ignored, and recommended settings are infrequently mentioned on the master batch document. The punch entry system also was invented primarily to relieve air entrapment during high-speed tableting. Modern presses may have punch entry controls for both the precompressing and final compressing stations. This vital tool alone may allow a tablet manufacturer to increase tablet hardness without altering either tablet weight or thickness. Yet the proper use of the punch entry system is not well understood or regularly challenged for proper setting. Again, many master batch records are silent on the proper setting or give essentially incorrect ranges for proper application.

**The slide gate.** The use of the slide gate in the powder hopper assembly is also underoptimized. The slide gate is used to restrict powder flow into the feeder; that is, to restrict that occasional granulation that flows too well. The proper position for the slide gate is fully open until conditions indicate that it should be used. The primary reason that powder recirculation systems fail is a lack of basic understanding of the slide gate and its effect on powder flow.

**Embossing.** The long-term negative effect on the bottom line of using embossed lettering on tablets is underestimated. In the long run, embossing tablets may be more expensive than printing on them. Before the cost accountants object to this statement, they should review the frequency and duration of downtime associated with embossing. Although the root cause of a production problem may be a lack of lubrication, improper blending of lubrication, or too much moisture in the granulation, the outcome is always the same: embossing brings trouble to the production floor.

**Tablet capping.** The problem of tablet capping commonly is attributed to two or three root causes when in fact there are many others. Most companies recognize that capping can be caused by excessive press speed or pressure, but there are at least seven other root causes, including compressing too deeply in the die, excessive paddle speed in the force-feeding system, excessive pressure at the precompressing station, damaged tooling, dies used past their expected lifetime, an outright bad formulation, and too many fines. The failure to consider all the root causes of capping may lead an investigator in the wrong direction.

**Worn punches.** Worn upper and lower punches produce different defects, but all worn punches must be replaced. If they are missed during an inspection, their effect on the batch will depend upon what kind of punch they happen to be. A worn upper punch may produce a thicker, softer tablet with a constant weight while a worn lower punch will produce a heavier tablet with constant thickness and hardness. It is important to recognize and react to each situation accordingly.

## Aqueous coating

**Gun geometry.** Proper gun geometry is taken for granted and rarely checked. Because many gun assembly installations come with a fixed or semifixed gun system, operators and managers sometimes wrongly assume that spray patterns are safe from alteration. This is not true. All settings must be checked before

and periodically throughout a coating campaign. To further complicate the issue, batch records do not discuss gun geometry in detail. Five basic settings are collected conveniently under the title of Gun Geometry, yet not more than two are ever discussed in a formal manner.

**Pan speed.** Pan speed usually is not optimized. Many master batch documents specify a single pan speed throughout a run. Although using a single speed is not incorrect, it fails to consider the potential value-added aspect of this important unit of operation. The coating process is in reality two separate and distinct suboperations: the tablet protection process and the appearance improvement process. Current practice emphasizes the tablet protection process. The second part of the coating process begins once the tablet has been protected. During this portion of the process using higher pan speeds will improve appearance with no loss of tablet integrity.

**Pan pressure.** Pan pressure is generally too negative. Pan pressure draws the coating suspension into a bed of tablets. A slight negative condition is desirable because it directs solution toward the tablet bed while keeping it off the pan sides and other surfaces and maximizes tablet exposure to the suspension stream. Therefore, it is unnecessary in most cases to have a pan pressure in excess of  $-0.5$  in.  $H_2O$ , and in many cases excellent results are obtained using even less pressure. Pressures greater than  $-0.5$  in.  $H_2O$  may waste significant quantities of suspension. In cases of extreme pressure, tablet defects are caused when the tablet edges become impinged in the perforated portion of the pan.

**Unoptimized coating process.** Most companies believe their coating process is optimized, but they rarely challenge it. While process changes, based on good science, are not hard to make under the new SUPAC guidelines, coating processes tend to remain as filed. Companies frankly would rather modify an operation to optimize yields, improve press speeds, or minimize process variation than improve the one step in the manufacturing train that best exemplifies their attitude about quality.

**Spray rates.** Fast spray rates compromise potential elegance. Experienced and professional though they are, coating equipment manufacturers are neither formulators nor process engineers. In many cases, they do not know your product as well as you do. They can and do sometimes recommend a generic spray rate that is highly acceptable for minimizing tablet damage but is not optimized for tablet elegance. Further, it is the author's observation that success in tablet coating is frequently expressed as an acceptable-quality-level result (or worse yet, just a pass) rather than as equal to or better than the highest standard possible.

## Tablet printing

**Ink standardization.** Not often mentioned in development documentation, ink standardization is misunderstood or outright ignored on the production floor. Although ink manufacturers are committed to producing the best possible product available, they cannot control ambient conditions during the shipment and storage of ink. Ink used to print tablets intended for human consumption is normally supplied in quart bottles, and large batches may require numerous bottles of ink.

Manufacturing firms should realize that each bottle of printing ink is a discrete entity whose viscosity may shift with time and conditions, and therefore it should be evaluated on-line before use. Further, it is very important to recognize that ambient conditions in the printing room have a much greater influence on the printing process than on any other unit operation in tablet manufacturing. For this reason, ink must be closely monitored and solvents or water replaced as necessary to maintain correct viscosity.

**Roll maintenance.** The importance of rubber roll maintenance and timely replacement is underestimated. Rubber rolls take a preformed impression from the gravure roll and transfer the image to the tablet surface. These rolls are wear parts and are subject to damage if used incorrectly. Unfortunately, an inadequate check system sometimes causes rubber rolls to be used past their prime. They should be checked each time they are removed and cleaned and should be treated as critical components of a larger system.

## Summary

In solid dosage manufacturing there remain today many conditions, practices, and parameters that are not optimized and in some cases not recognized. A review of the items presented in this article will enable the reader to better audit and understand items in the major unit operations that are commonly overlooked. **PT**

## FYI

### Sabbatical fellowship

The Pharmaceutical Research and Manufacturers of America (PhRMA) Foundation is offering sabbatical fellowships to provide stipends to individuals in a research training program that creates or extends their pharmaceuticals credentials.

The fellowships provide as much as \$40,000 per person and are designed to enable faculty members with active research programs to work outside of their home institution for a period of six months to one year. Eligible applicants must possess a PhD in pharmaceuticals from a school of pharmacy accredited by the American Council on Pharmaceutical Education, a faculty appointment that allows a sabbatical leave, and an institution-approved plan that includes a partial salary matching the PhRMA stipend.

Awards may be activated beginning 1 January 2002 or on the first day of any month thereafter until 1 December 2002.

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