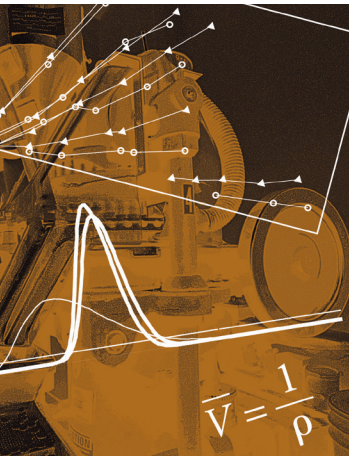
Fundamentals of Tablet Compression

Armin H. Gerhardt



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"Pharmaceutical Processes" discusses scientific and technical principles associated with pharmaceutical unit operations useful to practitioners in compliance and validation. We intend this column to be a useful resource for daily work applications. The primary objective for this column: Useful information.

Reader comments, questions, and suggestions are needed to help us fulfill our objectives. Please send your comments and suggestions to column coordinator Armin Gerhardt at arminhg@comcast.net or to journal coordinating editor Susan Haigney at shaigney@advanstar.com.

KEY POINTS

The following key points are discussed in this article:

- Tablet compressing is an established manufacturing process with multiple applications in pharmaceutical, dietary supplement, food, cosmetic, diagnostic, and other industries
- The most important performance characteristics of tablet dosage forms are identified
- Actual tablet compressing may be subdivided into four stages: Filling, metering, compression, and ejection
- Characteristics of an efficient compression operation are identified. These include machine assembly and operation, powder flow, machine operating parameters for specific products, and others.
- Formulation components and manufacturing processes conducted prior to compressing have significant impact on the compressing process
- Specific considerations for which compliance professionals should exercise the greatest vigilance are identified. These include obvious changes such as new suppliers of primary ingredients as well as subtle less visible changes. A strong change control program is key to management of change.
- Annual product reviews give a broad overview of product performance. Compliance professionals should also monitor compressing performance indicators such as low yields, frequent stoppages, frequent machine adjustments, and punch breakage. Technical personnel should address these problems when their frequency becomes excessive.

INTRODUCTION

Compressing a small quantity of powder to form a tablet has been performed trillions of times by myriad pharmaceutical companies. Technical innovations to tablet compression machinery have improved production rates to the point where more than 500,000 tablets per hour are possible. Specialty tablets have been crafted for sublingual, buccal, rectal, and vaginal therapeutic use. Release of the active drug component may range from a few seconds for rapidly disintegrating tablets to approximately 24 hours for controlled or sustained release products as they transit the entire length of the gastrointestinal system. In addition, compressed tablets may be intended for use in analytical or diagnostic applications, or dissolved in liquids prior to ingestion.

As we strive to deliver optimal quality compressed tablet products, consideration may be focused on activities performed prior to the compression step, during the compression operation itself, and also on the performance characteristics required of the tablets after their creation. Rather than discuss the activities in order of occurrence, we will identify the target goals, discuss the final results intended, and then work backward to establish the intermediate steps needed to finish with the goals intended.

PERFORMANCE CHARACTERISTICS

Table I lists the important characteristics of tablet dosage forms. Taken together, these attributes of tablets have propelled this dosage form to become the most commonly taken by patients, accounting for the majority of all dosage units consumed.

Consistent Release Rate

Tablets are always required to release the active drug component at a consistent rate and a consistent dose. The release rate may vary widely and is linked to the therapeutic effect intended. Among the techniques employed to assess the consistency of release are the dissolution rate or disintegration rate. Extensive focus has been placed on specifications for conducting these tests and on the analytical test methods that measure these rates.

TABLE I: Tablet performance characteristics.

Consistent release rate
Consistent dose content
Consistent stability throughout the expiry period
Sufficient durability until the time of ingestion
Show product identification marking
Facilitate swallowing or ease of administration for patient use
Minimize production costs

Consistent Dose Content

In terms of consistent dose, the pharmacopeial requirements must be met for the quantity of drug claimed by the product label until the expiry date is reached. Effectively the range allowed for drug potency at the time of production is much smaller than pharmacopeial stipulations. This is due to potential drug degradation or instability during the expiry period, limitations on potency assay variability, and variation of tablet weight. Typical high performance liquid chromatography (HPLC) potency assay relative standard deviations are 1-2%, as is the relative standard deviation of tablet weight (1-2%, or perhaps larger when relatively small [less than 150mg] tablets are being produced). If there is a 5% potency decline during a 24-month shelf life, then the tablets must be within roughly 98-102% of label claim at the time of initial release.

Each and every tablet released is required to meet specifications. Thus it is necessary to focus particular attention on those points during a commercial lot compression step where variability may be anticipated. Included in this category are the intervals at initiation of compression and at its termination. High speed equipment is available to assess all individual tablets and reject those falling outside acceptable range. While tablet weight is relatively straightforward to control, it rests on the assumption of perfect content uniformity within the powder blend. This content uniformity requirement includes not only the active drug substance, but also each excipient. While it is the active drug that causes the pharmacological effect, it is the excipients that are critical to successful disintegration, dissolution, tablet hardness, and durability. Segregation is a particularly challenging factor that may occur in any

powder movement operation. Frequently a tablet lot is defined at the time of final blending before compression. All components of the tablet are brought together in the blending vessels (except the coating and printing materials, if any). Sampling of the blend for uniformity is typically performed while the powders are within the blender, and the uniformity may be well within acceptable limits at this stage. Air entrainment or sifting mechanisms may act when the powder blend is moved, perhaps at the time of discharge from the blender into intermediate bulk containers or when the blend is fed from the intermediate bulk container to the compressing machine. Vibration segregation may also be produced by HVAC or other equipment operation during storage or during compression, and its extent may be widely variable from one location within a plant to another. Segregation may also appear sporadically within the commercial lifecycle of a product, as formulation component or equipment modifications evolve. A once robust product may trend toward or erratically exceed limits, in which case an investigation or even a formulation or process modification may be necessary.

Consistent Stability Throughout The Expiry Period

Compressed tablet stability throughout the expiry period is also required of each and every unit. As part of this requirement, the container-closure system must protect from moisture ingress. Reduced moisture content of the tablet tends to maintain chemical stability and minimize the appearance and quantity of degradation compounds.

Sufficient Durability Until The Time Of Ingestion

The compressed tablet needs to possess sufficient durability for subsequent manufacturing, packaging, and transportation to the patient, and to continue this while with the patient or care providers. This includes resistance to chips, capping, swelling, discoloration, and abrasion. It requires a balance between durability during shipping and handling, and the requirement to release the drug substance in a consistent manner. These two requirements, durability in handling and rapid availability in the body, act opposite to one another.

Show Product Identification Marking

Identification marks are typically made either by designing the compression tooling to deboss the tablet with characters and symbols, or by applying a printed ink to the surface in a separate step. Either approach is acceptable, and each is associated with its own benefits and risks. Debossing the tablets places additional demands on the compression operation because the embossed tooling tip characters create zones where powder sticking or picking is most likely to start. Smooth, relatively flat surfaces of tablet punches are relatively less likely to encounter sticking/picking challenges. Maintenance polishing of tooling tips is less likely to reach these zones along the base of each raised character, perhaps resulting in reduced tooling durability and causing frequent interruptions of production while the tooling tips are cleaned. On the other hand, printing of tablets requires a separate unit operation and its associated costs. There are challenges in achieving high quality printed characters and yields are reduced at initiation and termination.

Facilitate Swallowing Or Ease Of Administration For Patient Use

The majority of tablets are intended to be swallowed; therefore, shape and size parameters need to be carefully considered. Physically small stature people are more likely to have narrow throat structures, and pediatric or geriatric patients may have difficulty with the act of swallowing tablets. As a result, elongated or elliptical shapes are suggested. Film or sugar coating may enhance the act of swallowing, or concurrent swallowing with milk with its fats and sugars may ease the passage through the throat. It is possible for tablets to lodge in the trachea and block breathing. For this and all previous reasons, small size tablets are clearly preferred by patients.

Minimize Production Costs

In the competitive environment of business, it is also necessary for the compression operation to be efficient in terms of production cost. These considerations include facility requirements, personnel, machine maintenance, and productivity.

WHAT ARE THE SPECIFICS OF COMPRESSING?

The tablet compressing processes, as performed with typical pharmaceutical compressing equipment, may be divided into four distinct stages. These stages include filling, metering, compressing, and ejection. Actual tablet formation and control of tablet quality attributes occurs during the compressing stage (see Table II).

Filling

The filling stage of the tablet compression process involves transfer of raw materials into position for tablet compression. These raw materials have undergone prior processing by wet granulation, dry granulation (roller compaction), sizing, or other processes. The final formulation is then blended to yield a homogeneous blend. The blend then flows to the compressing machine punch-die cavity. The punch-die cavity is composed of punch die and lower punch. The position of the lower punch within the die determines the volume of the punch-die cavity. This volume must be appropriately sized for the weight of granulation to be compressed into tablets. The granulation is overfilled on the die table (turret) to ensure complete filling of the punch-die cavity volume.

Metering

The metering stage of the tablet compressing process involves removal of excess granulation from the compressing machine. This stage enables the exact weight (volume) of granulation to be compressed into tablets. The exact weight of granulation is controlled by the height of the lower punch in the die. The height of the lower punch is controlled by the metering cam (also called the dosage cam). The lower punch is raised to the appropriate level in the die to provide the exact weight of granulation in the punch-die cavity. The excess granulation is scraped from the surface of the die table. The metering stage is similar to the method used to measure flour when baking a cake. A measuring cup is first over-filled with flour; then a knife is used to scrape off the excess. The exact amount of flour is then left in the measuring cup.

TABLE II: Tablet compressing stages.

Filling	Formulation is overfilled at the compressing station
Metering	Overfill is removed
Compression	Tablet is formed by pressure of punches within die
Ejection	Tablet is ejected from die

Compression

The compression stage of the tablet compressing process forms the tablet. This stage involves bringing together the upper and lower punches under pressure within the die to form the tablet. As the punches enter the compressing stage, the upper and lower punches move between two large wheels called pressure rolls. These pressure rolls push the punches together to form the tablet. The distance between the upper and lower punches determines the thickness and the hardness of the tablet. When the punches are close together, a thin and hard tablet is created. When the punches are farther apart, the tablet made is softer and thicker. The proper balance of thickness and hardness determines the optimum roll distance for any specific product. These adjustments are made while keeping the tablet weight constant.

Ejection

The ejection stage of the tablet compressing process involves removal of the tablet from the lower punch-die station. In this stage, the upper punch retracts from the die cavity and rises above the turret table. Then the lower punch rises in the die, which in turn pushes the tablet upward to the top surface of the die table and out of the die cavity. A scraper (also called takeoff scraper or tablet rake-off) then pushes the tablet off the die table away from the compressing machine into the collection container.

COMPRESSION OPERATION

What are the characteristics of an efficient compression unit operation?

A successful compression operation comprises several activities including fundamental machine assembly and operation, formulation powder flow to the compressing machine, machine set-up for the product to be manufactured, and tablet compressing including

in-process control of the compressing process. The compressing operation also includes ancillary activities such as tablet dedusting. Post compression analysis of compression-related data is useful to monitor compression performance.

Compression Machine Assembly And Operation

The tablet compressing machine must function flawlessly for optimum performance. Cleaning from the prior product needs to be thorough and complete. The machinery must be assembled to within appropriate tolerances and lubricated, the compression tooling needs to be from a matched set for length, and the machine needs to run cleanly. Included in the machinery is not only the tablet press itself, but also the powder feed mechanism, deduster, metal detector, weight check device, and associated equipment. A smooth and clean compression step will promote maximum machine life and lead to optimal yield of high quality product. Dust accumulation should be minimized as possible. Minimal dust accumulation will benefit employee health by reducing exposure to inhaled drugs or powders, and will minimize abrasion between moving machine components.

Powder Flow And Associated Equipment

Powder flow control and uniformity is essential to achieving consistent tablet weight. Depending on equipment complexity, granulation flow may occur by simple gravity feed or may be transferred by an automated transfer mechanism. The relative speeds of the automated feeding system and the compressing machine must be coordinated. Feed frame settings and operation can have a significant impact on maintaining consistent weight. Tablet weight is determined by the volume available for filling within the die cavity, the powder flow characteristics, and the equipment that delivers powder to the die cavity.

Compressing Machine Setup

When the compressing machine, component parts, punches and dies for the product to be manufactured, and associated equipment (e.g., deduster, metal detector, others) have been assembled, the compressing machine operating parameters are determined with the powder blend. These parameters provide appropriate tablet weight, tablet hardness, and tablet thickness. The target compressing force to yield these attributes will be set. Depending on the complexity of the compressing machine and its component control mechanisms, control of compressing force, tablet weight, and tablet hardness is then established.

Early compressing machines required periodic sampling and testing for quality attributes by compressing operators. For example, samples would be removed every few hours, and the operator would adjust the compressing machine force and speed as needed to yield acceptable tablets. Modern compressing machines are built with sophisticated control systems that measure compressing forces and automatically make machine adjustments. Compressing machines may also be interfaced with tablet weight instruments and tablet hardness instruments to make automatic adjustments when test data exceed predetermined limits.

Control of tablet weight by compression force. Control of tablet weight by means of tablet force occurs during the compression stage. Because the distance between the pressure rolls remains essentially constant once the hardness and thickness of the tablet is set, it follows that a given amount of raw material compressed between the two punches at a fixed distance would produce the same compression force for each tablet. If the compression force does not remain constant, it must be due to variations in the amount of granulation in the punch-die cavity. By measuring the compression force and comparing it against a set of control parameters, it can be determined whether or not the tablet is within its weight tolerance.

Measurement of compression force is accomplished by means of strain gauges or load cells at a pressure station. Compression force is proportional to deformation of the pressure station according to Hooke's law. Strain gauges or load cells are measurement transducers used for the electrical measurement of mechanical parameters. The output voltage is then amplified and converted for data collection by the tablet press computer.

There are several control parameters important to the operation of the tablet weight control system. These include the following:

- **Target force.** The target force is the force that will produce a tablet having optimum tablet weight,

optimum tablet thickness, and optimum tablet hardness. It is also the compressing force set point for the control system of the compressing machine.

- **High and low adjust forces.** The high and low adjust forces form the high and low boundaries for compressing machine adjustment of tablet force. Force outside of these limits causes automatic adjustment by the tablet compression machine. The metering cam is adjusted to increase or decrease the tablet weight to produce tablets at the target force. The high and low adjust forces are automatically computed by the compressing machine.
- **High and low reject forces.** The high and low reject forces are the forces beyond which tablets are unacceptable and are automatically rejected at the ejection stage of tablet compressing. The high and low reject forces are the values that respond to individual tablet force, not the average tablet force. If a tablet is made whose force exceeds the high or low reject force, the control unit will reject the tablet. The high and low reject forces are set for each specific product based on the product weight requirements. Just ahead of the scraper (rake-off) is the reject station. Unacceptable tablets are removed at this station by means of a mechanical arm, air blast, or other means into a rejected tablet container. Rejected tablets are thus segregated from acceptable tablets before they are collected in the acceptable tablet container.
- **High and low shutdown forces.** The high and low shutdown forces are the forces beyond which the compressing machine will stop. The high and low shutdown forces are set to protect the compressing machine and its components from damage due to excessive compressing force. For example, if blockage occurred in the flow of granulation, upper and lower punches could be compressed directly against each other resulting in punch breakage and possible machine damage. The high and low shutdown forces are the values that respond to individual tablet force, not the average tablet force. If a force is detected that exceeds the high or low shutdown force, the control unit will reject the tablet made and stop the compressing machine. The high and low shutdown forces are computed by the compressing machine based on the specific tooling size and design, machine design, and other considerations. Table III demonstrates the relationship between all aforementioned control forces.

Tablet Compression Including In-Process Monitoring

After all control systems are set, tablet compressing is initiated. Manual sampling by compressing operators or quality unit personnel may also be periodically performed to confirm acceptable performance. In-process sampling and evaluation aids in controlling the compression sequence. Monitoring the overall time required to complete a batch or lot of compressed tablets provides insight into the efficiency of operation. When optimal, the tablet press is capable of finishing the entire lot or batch without stopping or interruption and of operating at top speed. Production halts for cleaning, weight adjustment, hardness fluctuation, or anything else indicates variability in the process and could indicate the need for additional sampling or testing to ensure high quality product. Investigation of the reasons for halting compression, and trend monitoring of these factors, may elucidate characteristics of the production sequence that need refinement or narrowing of specifications to ensure optimal compression.

In addition to the time required for compression, the overall yield from a batch or lot is a key quality indicator. Optimal efficiency is achieved when the machinery is assembled properly; there are minimal losses during initiation; the machinery functions flawlessly during the entire run; and all tablet weight, potency, content uniformity, hardness, thickness, and all other parameters are maintained till cessation.

Post Compression Equipment

Additional auxiliary equipment may be used in connection with the tablet-compressing machine. These include the following:

- **Tablet deduster or definger.** This equipment removes excessive dust or fringes from the tablets by means of gentle agitation and vacuum.
- **Metal detector.** This equipment detects metal fragments within the tablet.
- **Tablet weight checker.** This equipment au-

TABLE III: Compressing machine force control.	
High shutdown force	+X% above target compressing force—depends on punch configuration
High reject force	+20% above target compressing force
High adjust force	+2% above target compressing force
Target compressing force	
Low adjust force	-2% below target compressing force
Low reject force	-20% below target compressing force
Low shutdown force	-X% below target compressing force—depends on punch configuration
Note: Above percentages are approximate.	

tomatically weighs individual tablets and rejects out-of-specification tablet weights.

Process Monitoring

Trend monitoring of the time required for compressing and yields can be powerful tools in controlling compression and delivering high quality product. Expect production of a commercial product to evolve throughout its commercial life span. Expect suppliers of excipients to modify their equipment and install new controls. Expect the drug substance to show a greater range of physical characteristics than observed during the relatively brief development period. Expect assays to evolve for all components. Anticipate sporadic difficulties with particular lots, and have defined ranges for machine operation that may allow continued production of high quality product. Among parameters with ranges, compression force and turret speed are frequently included. With challenging lots, it may be necessary to increase the main compression force to achieve sufficient tablet hardness. This may not be entirely successful. There are limits to the bonding a powder blend can achieve, and at high levels increased force may actually diminish tablet strength (see Figure). A plateau region appears where there is no significant increase in tablet hardness as more compression force is applied, and at higher forces there may actually be a reduction in tablet hardness. Also, the increased force may be detrimental to tooling punch durability. For example, splitting of punch tips is possible; the metal may fatigue relatively more rapidly at higher compression force, and cracks may form that eventually break into chips. A second alternative may be reduction of the turret speed, which allows a longer dwell time at maximum compression force to form tablet bonds. Pre-compression, in which partial force is exerted on the powder blend ahead of final tablet compression, can further increase tablet bonds. For smooth operation, it is recommended that routine compression forces be adjusted to produce tablet hardness values in the range of 70% to 85% of the maximum attainable for that product. The 15% to 30% higher hardness capacity remaining provides flexibility when addressing lot-to-lot variability, moisture fluctuation, and other challenges.

PRIOR TO COMPRESSION

The powder blend or granulation delivered for compression will exhibit variability. The following are key parameters that have significant ramifications for compression.

Product Formulation

The product formulation contains several formulation components in addition to the active drug. These components function to facilitate flow into manufacturing process equipment and enable compaction of the compressed tablet. The formulation disintegrant enables the tablet to disintegrate and speed dissolution of the drug into biological fluids after ingestion and thus directly enables the tablet to provide a bioavailable drug substance.

Manufacturing Unit Operations

There may be several manufacturing unit operations conducted prior to tablet compressing. For example, these may include the following:

- Deagglomeration of the active pharmaceutical ingredient (API) and the inactive excipients
- Wet granulation to agglomerate "fines" and to form appropriate size particles
- Drying of the wet granulation

- Sizing and milling to form appropriate particle size distribution for compressing
- Mixing and blending of all formulation ingredients.

Tablet compressing is conducted on the blended formulation.

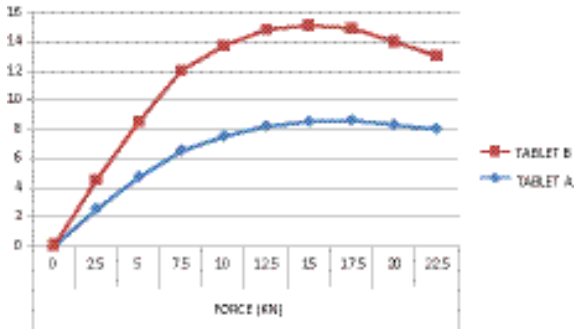
After compressing, unit operations such as the following may be performed as follows:

- Tablet coating
- Tablet printing for identification purposes.

More complex tablet dosage forms may be manufactured including tablets containing coated beads, two-layer tablets, tablet within a tablet, and other products manufactured with modifications or combinations of the unit operations.

At a fundamental level, the powder must flow uniformly and fill the die cavity consistently. Uniformity of flow is essential for achieving tablet weight control. The powder must be blended uniformly with all components including the drug substance, the disintegrant, the lubricant, the compression enhancer, the flow enhancer, the diluents, and all other items. The powder blend needs to retain this blend uniformity until it reaches the die cavity. Once compression has taken place, there is no opportunity for changing potency or content uniformity. The powder blend needs ample compressibility to form the bonds that will retain tablet shape until delivered to the site of drug release. Critical to compressibility behavior is moisture content. Relatively higher moisture content delivers stronger tablet bonds. Moisture tends to make the powders more cohesive, which may reduce segregation tendencies. However, higher moisture content may also be detrimental to product stability and may impair powder flow. This requires characterizing minimal moisture contents necessary for compressibility along with characterizing the maximum moisture quantity that can be tolerated for stability or flow purposes. Consider defining both the maximum moisture content specification allowed and the minimal moisture content specification.

Figure:
Force-hardness compression profile.



IMPLICATIONS FOR COMPLIANCE

Compliance professionals have great involvement in the various stages of manufacturing prior to compression, during compressing, and in post-compression evaluation. Much of what is demonstrated during process validation and throughout the product lifecycle is based on work performed in the product design stage of the product lifecycle.

Risk Analysis

Compliance personnel should be knowledgable of high-risk products for which they are responsible. High-risk products are those with low bioavailability, high toxicity, or other high-risk attributes. Products containing highly potent drugs (i.e., product with low dosages of active ingredients) are high-risk products. Greatest attention, especially regarding evaluation of formulation or process changes, should be given to process monitoring and evaluation of changes to highest risk products.

The following are the key areas about which compliance professionals should exercise the greatest vigilance.

Manufacturing Prior To Compressing

All formulation ingredients (including inactive ingredients) and manufacturing processes prior to compressing have impact on the compressing process. Compliance personnel should be vigilant of even subtle changes to the formulation and manufacturing process, and especially so for products known to have marginal compressing characteristics. For example, changes in suppliers of major inactive ingredients, even though the ingredients are technically the same, may have significant effects on compressing and other

processes. Particle size differences may be especially significant. A new supplier of an inactive ingredient with smaller particle size than expected may produce smaller granulated particles, which in turn may result in compressing problems by hindering flow or reducing tablet bonding.

Compressing Machine Assembly

The following should be considered in compressing machine assembly:

- **Equipment complexity.** Modern manufacturing equipment is complex. Personnel assembling and operating this equipment must be adequately trained. Training should be "hands on training" reflective of the skills necessary for operating complex equipment.
- **Equipment cleaning.** Cleaning compressing machines is difficult, especially machines that are not equipped with "clean-in-place" capability. Equipment should be carefully inspected to assure acceptable cleaning from previous manufacturing.
- **Equipment preventive maintenance (PM) and calibration.** Equipment PM and calibration must be current. Often outside services must be contacted to perform equipment PM and calibration.
- **Tooling maintenance.** Punches and dies must be adequately maintained. Punch lengths should be routinely measured to ensure consistent length.

Compressing Machine Setup

The following should be considered in compressing machine setup:

- **Product specific setup.** Personnel performing equipment setup must understand the intricacies of equipment setup. Each setup is specific for a given product. For example, pressure limitations on compression punches are different for each punch diameter and shape.
- **Compressing machine noise and vibration.** Excessive noise during compression and excessive vibration during operations are not acceptable. Machine vibration can cause powder segregation that may be especially significant for low drug concentration products (most likely when less than approximately 5-10% drug substance). Machine set-up can be improved when excessive noise or vibration are noted.

Compression In-Process Controls

Sampling intervals are usually specific by procedure. Compliance personnel must use judgment when unexpected problems occur. Out-of-specification product is most likely to occur at the time of equipment stops and starts, during intermediate bulk container changeover, and other unexpected occurrences.

Process Monitoring

The following should be considered in process monitoring:

- **Annual product reviews.** Annual product reviews typically monitor product quality attribute testing such as potency, uniformity of dosage units, moisture, and other product specifications. These reviews provide a broad overview of product performance, but do not focus on compressing problems.
- **Compressing reviews.** Compliance professionals should be mindful of specific indicators of compressing problems. These include products that have difficult set-up resulting in low yields, products requiring frequent process adjustments, products with frequent punch breakage, products with frequent stoppages for punch polishing, and other occurrences. Technical personnel should be contacted to address these problems.

Change Control

Changes to formulation, processing, equipment, facilities, and so on (i.e., anything connected with the compressing process) must be carefully evaluated to determine its effect on compressing. A good change control system is fundamental to maintaining the validated state.

Product Design

The formulation, process design and development work in support of tablet dosage forms is typically performed by research and development or technical support functions within the organization. This work should be utilized as needed through the product lifecycle.

Experimental work may be the justification for process adjustment and changes. Compliance personnel should have ready access to technical reports that support the formulation and manufacturing process of their products. These reports should be available and quickly retrieved as needed for regulatory audits.

Process Validation Guidance

Compliance professionals should be familiar with the concepts discussed in the November 2008 FDA draft process validation guidance, *Process Validation: General Principles and Practices*. This guidance identifies three stages in the lifecycle approach to process validation: design, performance qualification, and continued process verification. The guidance emphasizes that validation must not be considered a single distinct event, but must be continued through monitoring and maintenance of the manufacturing process as long as the product is manufactured. The guidance also recommends identification of potential process variables and development of a control strategy. The concepts discussed in this article are consistent with the recommendations of the FDA guidance.

CONCLUSIONS

This discussion has addressed the basics of tablet compressing with emphasis on considerations for the compliance professional. Tablet compressing is established technology, and its principles have been well documented for many years. The actual specific stages of tablet compressing on the compressing machine are very simple: filling or overfilling, metering to remove excess, compressing under pressure, and ejecting the formed tablet. The activities in a typical compressing operation are repetitive and controlled by procedures. Technological innovations have resulted in faster machines with increased productivity, new and creative applications, greater monitoring capabilities, and other improvements. These improvements, however in some cases, have come with more stringent requirements for material and process control.

Compliance personnel must be continually vigilant of factors that may impact the performance characteristics of tablet dosage forms. These may be obvious, such as a change in supplier of a key formulation ingredient. Vendor changes are quite frequent as our economy becomes more global and sensitive to cost pressures. On the other hand, changes may be subtle and essentially invisible, such as a change in an intermediate bulk storage container that may induce particle segregation. A strong change control program is critical to evaluating the potential impact of such changes.

Compliance personnel should be knowledgable of high-risk products for which they are responsible. Greatest attention should be given to process monitoring and evaluation of changes to highest risk products. Annual product review programs provide an overview of product performance that is acceptable to meet regulatory expectations. These reviews, however, usually do not address indicators of compressing problems. Problems such as low yields, products requiring frequent process adjustments, and punch breakage should be brought to the attention of technical personnel to address these problems.

The 2008 FDA process validation draft guidance has clearly identified expectations for validated processes during the product lifecycle. In brief, processes should be well understood and based on scientific and technical principles and sources of variation should be identified and controlled, processes must be validated using validated equipment and validated analytical methods, and validated processes must be continually monitored and maintained. This approach should be applied to tablet compression as well as all unit operations in pharmaceutical manufacturing. **GXP**

ABOUT THE AUTHOR

Armin H. Gerhardt, Ph.D., is an industry consultant who spent more than 16 years at Abbott split between formulation services in R&D and project management for new drug product development teams. Armin retired from Abbott in 2007. He has taught various courses in pharmaceutical processing for many years. Armin has also authored book chapters on pharmaceutical unit operations. He can be reached at arminhg@comcast.net.