**Chapter 1: PROCESS VALIDATION OF TABLETS**

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* **ABSTRACT**

Process validation is the collection and analysis of data from the process design stage through the manufacturing stage to generate scientific evidence that a method can reliably produce a high-quality drug substance. Validation is intended to guarantee that quality is included into the overall system not just a final assessment. It involves collecting and evaluating data to establish scientific evidence that a process can reliably produce high-quality APIs, starting with the process design stage; continuing till production. In the context of cGMP, process validation is an important aspect of quality assurance (QA). Verification and QA will work together to ensure overall product quality. As a result, the exam is highlighted, giving a detailed view of the validation. Validation studies must be carried out according to a predetermined protocol as per GMP. The aim of this chapter is to introduce and describe pharmaceutical manufacturing process validation, with specific reference to the United States Food and Drug Administration (US-FDA) requirements for tablet regulation.

**Keywords:** Process validation, tablets, quality, manufacturing process.

* **INTRODUCTION [1]**

Validation of pharmaceutical processes is an important factor in ensuring that these quality assurance objectives are met. Manufacturers may generate a high level of trust by carefully designing and validating processes and process controls that all manufacturing units in a continuous batch are acceptable. Successful process validation reduces reliance on In-process and end product testing is extensive. End product testing, in most circumstances, plays a key role in ensuring that quality assurance objectives are satisfied.

The collecting and assessment of data from the process design stage is known as process validation through commercial production, establishing scientific evidence that a process can consistently produce a quality product.

* **BACKGROUND [2,4]**

The FDA published a notice in the Federal Register (52 FR 17638) on May 11, 1987, a guidance document named "Guidelines for General Principles of Process Validation". Since then, we have acquired additional expertise through regulatory monitoring, which has enabled us to refine our advice to the industry on this subject. These revised guidelines reflect the FDA's current view of process validation and adhere to key principles first described in the 1987 guidelines. The updated guidelines also include recommendations that reflect some of the goals of the FDA's "21st Century Pharmaceutical CGMPs: A Risk-Based Approach" initiative, particularly with respect to the use of technological advances and the implementation of risk management and the quality in the manufacture of drugs. This revised guide replaces the 1987 guide.

* **PROCESS VALIDATION [6,7]**
* **According to the ICH:** "Process validation is the means of assuring and providing documented evidence that a process, within its specified design parameters, can repeatedly and reliably produce a finished product of the desired quality."
* **According to the World Health Organization:** "Validation is the written action to demonstrate that any procedure, process, equipment, material, activity or system actually leads to an expected result." The act of verification to demonstrate that any process actually leads to the expected result in accordance with GMP. A documented process that operates within established parameters can operate efficiently and reproducibly to produce a drug product that meets its predetermined specifications and quality characteristics.
* **According to the United States Food and Drug Administration:** "Process validation is the establishment of documented evidence that provides a high degree of assurance that a particular process will consistently produce a product that meets its predetermined specifications and quality characteristics."

The above definitions are based on the 1987 guidelines. The revised guidance was published in January 2011. According to the 2011 guidelines.

* The government agency defines process validation because the assortment and analysis of knowledge, from the method style stage through industrial production, that establishes scientific proof that a process is capable of systematically delivering a top-quality product.
* The three stages of process validation are 1) Design Method, 2) Qualification method, and 3) continued method Verification.
* Current smart producing Practices (cGMP) come back powerfully into play once taking part in pharmaceutical process validation activities. variety of them are lawfully enforceable requirements.
* The FDA has multiple recommendations for practices that business leaders will adopt to make sure uniformity in data collection and alternative data and to maximize accessibility so advantages may be achieved anon within the product life cycle.
* Pharmaceutical method validation activities offer confirmation that a producing process is protected to the extent potential from variances that would interfere with the ultimate pharmaceutical product, the meant provide chain, or public health. Adherence to those factors is very important to the protection and effectiveness of prescribed drugs and to quality patient care.

The FDA believes that process validation is necessary because,

* Has good engineering significance.
* It reduces product recalls and troubleshooting tasks in manufacturing operations.
* This leads to a technically and economically sounder product and manufacturing process.

**A. Process validation and drug product quality [2,4]**

Effective method validation contributes considerably to making sure the quality of pharmaceutical products. the essential principle of quality assurance is the assembly of medication appropriate for his or her meant use. This principle assumes that the subsequent conditions are met:

* Quality, safety and efficiency are designed or built into products.
* In-process and finished product inspection or testing is not sufficient to guarantee quality.
* Each step of the production process is monitored to ensure that the final product meets all quality characteristics, including specifications.

**B. Process validation methods [5]**

 Process validation is outlined as the gathering and analysis of knowledge from the method style stage through industrial production that offers scientific proof that a process is capable of manufacturing consistent high-quality product. method validation includes bound activities that manifest itself throughout the merchandise life cycle. the method validation activities occur in 3 phases, as shown in Figure 1.

* Phase 1- Process Design: In this phase, the commercial manufacturing process is defined on the basis of the knowledge gained through development and scale-up activities.
* Phase 2 - Process Qualification: In this phase, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.
* Phase 3 -Ongoing process validation: continuously ensuring that the process remains under control during the day-to-day production process.

 This guide describes typical activities for each phase, but some activities may actually take place in more than one phase. Before a process batch is sold commercially for consumer use, manufacturers must obtain a high level of assurance on the performance of the manufacturing process so that they can consistently produce APIs and pharmaceuticals. That meet the characteristics, potency and qualities of purity and strength Objective information and data from laboratory, pilot, and/or commercial scale research should be used to establish assurance. Data and information should show that under commercial manufacturing settings, commercial manufacturing methods consistently generate goods of acceptable quality.

**Manufacturers must:**

* Identify sources of variation
* Determine the presence and extent of variation
* Recognize the impact of changes on the process and the quality of the final product
* Control changes commensurate with the risk they pose to the process and product

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**FIGURE 1: Stages of Process Validation**

**Stage I – Process Design: Recommendations and Expectations:**

The main objective of process style is to see the suitable process for the industrial producing of a product.

* Although early process design experiments don't ought to be performed per cGMP, they must be conducted beneath tips of sound scientific principles.
* Good documentation practices should be followed. In particular, studies that lead to improvement of process understanding are expected to be documented.
* Continuous testing and re-testing at this stage till the method fails is not ordinarily expected by the government agency.
* The institution of process controls serves to confirm product quality, and by an equivalent token address variability within the product. The FDA expects that process managements include examination of material as well as equipment watching. In particular, method control and monitoring is important once:
	+ the product attribute is either not detectable or otherwise measurable (eg. microorganism contamination).
	+ Or when intermediates/products aren't well-characterized.

### ****Stage 2 – Process Qualification: Recommendations and Expectations:****

### **The main purpose of process suitability is to find out if the process design is effective in commercialization.**

### **cGMP authorizations require proper design of the manufacturing facility.**

### **The right choice of operating systems and devices built according to the required design requirements.**

### **Ensures that systems and equipment are operating to required specifications.**

### **Process Performance Qualification (PPQ) links plant, utility and equipment with appropriately trained personnel. FDA recommends using objective measures, such as statistical measures, whenever possible. Written protocols and expected results are very important at this stage of process validation. It is recommended that protocol descriptions include manufacturing conditions, data collection, experiments to be performed, and sampling plan. Implementation of the PPQ protocol should not begin until it is approved by all relevant departments in the organization, including quality assurance units.**

### ****Stage 3 – Process Verification: Recommendations and Expectations****

### The main purpose of process verification is to ensure that the process remains in a validated state during commercial production.

### cGMP requirements include an ongoing program to collect and analyze data related to product quality.

### cGMP processes and principles are critical to identifying areas of variation that require analysis and/or improvement.

### FDA recommends that monitoring and sampling continue at the level determined during process qualification until sufficient data are available.

###  Maintenance of premises, facilities and equipment should not be neglected.

* **Reasons for process validation[9]**

The main reasons for validation are

 1. Quality assurance: Quality cannot be assured through daily quality control testing due to statistical sampling limitations and limited opportunities to test finished products. Validation checks the accuracy and reliability of a system or process to meet predetermined criteria. Successful validation provides high assurance that each unit of finished product maintains a consistent quality level across batches.

 2. Economics: Successful validation results in fewer trial and testing procedures and fewer product rejections and retests. This leads to cost savings.

 3. Compliance: Validation is essential for current GMP-CGMP compliance.

* **Regulatory basis [10]**

 When the concept of predicting process performance to meet user requirements emerged, FDA regulators determined that the required process validation had a legal basis. The ultimate legal authority is found in FD&C Act, which states that if a drug product is not manufactured, processed, packaged, or held in accordance with CGMPs or is not regulated in accordance with the CGMP.

The 21CFR 210 and 211 CGMP Finished Drug Regulations were issued to implement the requirements of the law, which state that "there shall be written manufacturing and process control procedures to ensure that the drug product retains the desired identity, strength, quality and purity.”

* **Responsible Authorities for Validation:** The validation working party is convened to define progress, coordinate and ultimately, approve the entire effort, including all of the documentation generated. The working party would usually include the following staff members,

• Head of quality assurance.

• Head of engineering.

• Validation manager.

• Production manager.

• Specialist validation discipline: all areas

* **Types of process validation [11]**

 General principles of process validation involve 4 types of validation:

A) Prospective validation

B) Concurrent verification

C) Retrospective validation

D) Reauthentication

**A) Prospective validation of the process**

 Before the marketing of the process, an experimental plan called validation protocol is carried out (after completion of the qualification tests). To generate data to support validation, most validation efforts require some degree of prospective experimentation. This type of process validation is often done in conjunction with the process of launching and manufacturing a new drug product. Formal process verification procedures should not be initiated until the following actions and procedures have been satisfactorily completed:

1. Facilities and equipment used for process validation should comply with CGMP standards. (Installation qualification completed)
2. Familiarize the operators and supervisors of the verification run group with the process and its requirements.
3. Formula design, selection and optimization are complete.
4. Completion of qualification testing for ten pilot-scale groups to identify significant process steps and process variables, as well as preliminary operational control limits for each key test parameter.
5. Detailed technical information on the product and production process has been provided, including written verification of product stability.
6. Finally, at least the qualification tests of the pilot production batch have been carried out and the inspection has shown no significant deviation from the expected performance of the process.

The purpose of prospective validation is to demonstrate or demonstrate that the method can be added according to a validation procedure or protocol for testing the product under test. Sometimes 2 or 3 pre-production batches are ready to validate the functionality. The first batch included in the sequence may be a first pilot batch of size 100 times successfully completed, sometimes prepared under the direction of the structure directly in charge of pilot-scale activities. Subsequently, pharmaceutical production operators also carry out repeated batch productions.

The strategy chosen for method validation should be simple and straightforward. The following factors are specified for readers to consider:

1. The use of various components such as APIs and major excipients should be included.
2. The group must work consecutively on different days and shifts (this last condition, if applicable).
3. Mass production must be performed in equipment and facilities designed for final commercial production.
4. During process operation, critical process variables must be within the operating limits and must not exceed their upper and lower control limits. The output response must exactly match the parameters of the final product. 5. Non-compliance with validation protocol requirements regarding process input and output control must be re-certified after proper analysis of process data and review by the CMC Coordinating Committee.

**B) Concurrent verification**

Process monitoring of critical processing steps, as well as continuing production end product testing, can give verifiable proof that the manufacturing process is under control. This type of validation documentation can be obtained from the test parameters and data sources described in the retrospective validation section.

 None of the ongoing tests listed below are required to demonstrate that our process is in control. Test parameters must be selected using the main process variables to be evaluated.

**Table 1: List of Test parameters of in process and End product testing**

|  |  |
| --- | --- |
| **Test parameters** | **Data source** |
|  Weight variation | End-product testing |
| Content uniformity | End-product testing |
| Dissolution time | End-product testing |
| Average unit potency | End-product testing |
| Powder-blend uniformity | In-process testing |
| Moisture content | In-process testing |
| Particle/ granule size distribution | In-process testing |
| Weight variation | In-process testing |
| Tablet hardness | In-process testing |
| Viscosity/ density | In-process testing |
| Color | In-process testing |
| pH value | In-process testing |

**C) Retrospective validation**

The retrospective validation option is suitable for mature products where the manufacturing process is considered stable and where a prospective validation program cannot be justified based on economic considerations and resource constraints alone. Equipment’s and facilities used in the manufacturing process must comply with CGMP requirements prior to retrospective validation, including statistical analysis of in-process test data and/or final product batches of previous productions.

 The valid in-process specification for these properties should be consistent with the final drug product specification and should, where possible, be derived from previously accepted estimates of process mean and variability., and where appropriate, applying appropriate statistical procedures to determine. Audit trail can be done by the following means, using data-driven computer systems or manual methods:

* For analysis, include data from at least the last 20-30 production batches. If there are less than 20 batches, include all the batches produced and commit to obtaining the quantities necessary for the analysis.
* Slice data by removing test results from non-critical processing steps and removing any superfluous numeric data.
* Statistical analysis and evaluation of the resulting data.
* Draw conclusions about the state of manufacturing process control based on retrospective validation data studies.
* Issue a report of your findings (documentary evidence). One or more of the following output values ​​(measured responses) are typically selected which are critical to the particular manufacturing process being evaluated and are typically selected for statistical analysis.
1. Solid dosage form
2. Content Uniformity Test Results
3. Individual tablet hardness value
4. Individual tablet thickness value
5. Change in weight of tablets
6. Dissolution time/disintegration time
7. Moisture content of individual tablets

**D) Reauthentication [10]**

The conditions that require revalidation of studies and documents are listed below:

1. The source of the active raw material manufacturer has changed.
2. Changes to packaging materials (primary container/closure system).
3. Raw material variations (which may affect the physical properties of the process or product such as density, particle size distribution, moisture, etc.).
4. Variations in the process (e.g mixing time, batch size).
5. Equipment changes (such as adding an automatic detection system).
6. Equipment changes involving the replacement of equipment on an “as-is” basis generally do not require revalidation unless the new equipment qualifies.
7. Plant/Facility Changes.
8. Changes revealed by trend analysis (eg process changes).

* **Periodically revalidate:**

To implement periodic revalidation, the decision should be based primarily on a review of historical data, i.e., data obtained during the process and during testing of the finished product after the current validation, for the purpose of to validate the process under control. When reviewing this historical data, any trends in the collected data should be assessed. Additionally, during a planned revalidation, the following should be checked:

1. Changes to master recipes and procedures, batch sizes, etc., if any, should be evaluated for their impact on the product.
2. Determine if the calibration was performed according to the established procedure and schedule.
3. Revalidation confirms that preventive maintenance has been performed according to plan and schedule.
4. Update standard operating procedures (SOPs) as needed.
5. Verify that the cleaning and sanitizing schedule is followed.
6. Has the analytical control method changed?

# **The Significance of Process Validation in Pharmaceutical Industry**

Documented verification of certain processes and systems against required specifications is called process validation. Validation is an integral process in the pharmaceutical industry, as compliance with national and international FDA and EMA standards is mandatory. Validation ensures that all processes meet established CGMP standards. All validation processes require full documentation that follows standard operating procedures and ongoing operations. This includes production plans, validation protocols, development reports and analysis documents. Every step of the manufacturing process, including downstream processes and changes, is unquestionably controlled to ensure the complete safety of the pharmaceutical products that people rely on in their daily lives. Process management validation helps bridge the gap between ever-changing quality standards and dynamic market forces.

**The Fundamental Requirements of Pharmaceutical CGMP**: Good manufacturing practice is concerned with quality control and production which requires:

•    Trained, qualified, and competent personnel
•    Adequate production space
•    Appropriate equipment
•    Correct labels and containers
•    Suitable storage space
•    Safe transportation facilities
•    Adherence to approved procedures

**Pharma Manufacturing:** Future Validation Technologies According to the latest validation guide, the entire product life cycle is divided into three phases. The first step is to plan the processes where all the information is collected during the expansion. The second step is process qualification, where the production system is validated at strategic points. The final step is continuous verification, which is an ongoing process. These three principles are essential to ensure consistent quality and production throughout. Pharmaceutical companies use the following approaches to improve efficiency and increase productivity.

 **PAT Framework:** Process Analytical Technology is designed to evaluate and monitor production methods and packaging processes to ensure timely and efficient operation. This concept emphasizes the need to ensure a given quality while reducing production cycle time. Essentially, PAT allows manufacturers to control their processes to reduce scrap and loss. This concept requires close collaboration between suppliers and customers during the design process. This innovative concept is gradually gaining ground as smart machines with integrated controllers and sensors enter the market.

**Validation Program Consistency:** When different manufacturers implement customized validation procedures, the end user can become confused by different structures and complex vocabularies. Continuity plays a key role in operational improvement and can be achieved through comprehensive integration. When OEMs implement software solutions for subroutine validation, the entire package line will improve significantly.

 **Factory Acceptance Test:** FAT is designed to ensure quality systems operate at peak performance. This reduces the overall validation burden for pharmaceutical companies by involving suppliers in the infrastructure deployment process. Each company has a different validation procedure, so it is important to follow standard practice and check it regularly. As machines and processes work together, one-off systems become the norm and companies become more successful. Installation times are reduced, cross-contamination risks are greatly reduced, and operating costs are greatly reduced.

 **Outsourcing:** Drug production is now outsourced to third party service providers to achieve higher production revenue. To reduce production costs, single-use technology is widely used in drug development. Single-use bioreactors have made processes more flexible and significantly reduced the risk of cross-contamination. This leads to reliable products and faster market entry. Single-use technology facilitates the full integration of drug production to produce uniform products while consuming fewer resources. This necessitated the establishment of a continuous monitoring process to ensure strict adherence to regulations.

**CGMP Documentation:** Today, process flow diagrams must clearly describe each item and its location and functional role in the overall process. All elements of the production process must be detailed, from command and control points to material inputs and products. It is also important to record and record process flows to facilitate decision making and comparison. Documentation requirements become important during process adoption and ongoing monitoring. This new practice is already becoming an expectation for validation compliance.

 **Equipment Cleaning and Maintenance Program:** The structural integrity and performance of all equipment will change over time due to extensive use. When residues of chemicals and detergents accumulate, cleaning becomes difficult. Fixing a broken piece or installing a part can create more problems by creating new stress centers. All of these issues lead to a new equipment maintenance program that includes:

 • Strict adherence to standard operating procedures

 • Regular operational inspections

 • Regular mechanical maintenance

 • Evaluation program that verifies cleanability, repairs and replacements.

**Good Manufacturing Practices:** The pharmaceutical industry has realized the cost benefits of a compliant CAPA system. This not only keeps bio and pharmaceutical manufacturers on track, but also reduces consumer complaints. Compliance with all CAPA protocols and related documents is mandatory for the validation task. Good manufacturing practices require that all critical component changes, plant changes, and lot size changes be validated against process requirements. GMP has been around for over a decade and ensures that all products consistently meet approved manufacturing and quality regulations. This is an essential mechanism that must be implemented from time to time.

 **Validation Process Overview**

The pharmaceutical industry is moving from the traditional tripartite validation method to a continuous monitoring process with regular quality control. The success of any validation program depends on the accuracy of the data, which further defines the effectiveness of the product. The use of critical support systems plays a decisive role in the quality of the final product. Therefore, it is important to control every routine activity from design and construction to commissioning and qualification. To achieve satisfactory results, drug production standards must meet both qualitative and quantitative requirements. This data-intensive approach provides a clear direction for efficient and accurate validation.

**Validation Master**:

Plan A: validation master plan is a document that summarizes the General philosophy, intentions and approaches of the company to can be used to determine adequacy of performance. management must agree on a master plan for validation.

Validation usually requires careful preparation and careful planning of the various steps in the process. Furthermore, all work must be done in a structured manner according to officially mandated standard operating procedures. All observations must be documented and, where possible, recorded as actual numerical results. The general validation plan must provide an overview of the entire validation activity, its organizational structure, content and design. Its main elements are the list of items to be validated and the planning schedule. All validation activities related to critical technical activities related to product and process management within the enterprise should be included in the master validation plan. This should include all future, concurrent and retrospective validations and rechecks.

The valid master plan should be a summary document and therefore should be short, concise and clear. It should not repeat information documented elsewhere, but should refer to existing documents such as policy documents, SOPs and validation protocols and reports.

The format and content should include:

• Introduction: validation policy, scope, location and schedule

• Organizational structure: personnel responsibilities

• Plant/ process /product description: rational for inclusions or exclusions and extent of validation

• Specific process considerations that are critical and those requiring extra attention

• List of products/ processes/ systems to be validated, summarized in a matrix format, validation approach

• Re-validation activities, actual status and future planning

• Key acceptance criteria [10].

* **Process validation for solid dosage forms**

The critical parameters considered during the process validation of tablets are

1. Mixing or Blending

2. Granulation

3. Wet milling

4. Drying

5. Milling

6. Compression

7. Coating

* **Mixing or Blending**

Mixing is a critical step used at various stages of tablet manufacturing. Materials with similar physical properties can easily form a homogeneous mixture or mixture and do not separate as quickly as materials with significant differences.

 **A. Mixing or Mixing Technique:** Diffusion (drum), convection (planetary or high intensity), or pneumatic (fluidized bed) techniques can be used to mix materials. Determine the technology required for the purpose of the formulation or process. It can be different.

**B. Agitation or Agitation Speed:** Set agitation intensity (low/high shear) and/or speed (low/high/optimal shear)

 (rpm). Mixing the drug and excipient requires more efficient mixing than adding a lubricant to the final mixture.

**C. Mixing or blending time:** How much mixing or blending is required to obtain a uniform mixture? The mixing or blending time will be dependent on the mixing or blending technique and speed. If the materials are overmixed, this would result in demixing or segregation of the materials. Demixing can occur due to difference in the physical properties (e.g., particle size distribution and density).

**D. Drug uniformity**: Content uniformity is usually performed to determine the uniformity of drug throughout the mix or blend. Representative samples should be taken throughout the mix or blend. The sampling technique and handling of the materials are key points in obtaining valid content uniformity results. For the final blend (blend prior to compression), the sample taken should be equivalent to the weight of a single tablet.

**E. Excipient uniformity:** Besides drug uniformity, excipients need to be uniform in the granulation or blend. Two key excipients are

I. Lubricant: The lubricant needs to be distributed uniformly in the mixture/granulation for the high-speed compression operation. Uneven distribution of the lubricant can result in picking and sticky problems during compression. It can also lead to tablet low dissolution due to excessive lubricant in some tablets.

II. Color: The colorant(s) need(s) to be evenly distributed in the mixture so that the tablets have a uniform appearance (e.g., color, hue, and intensity). The coloring agent may need to be prescreened or more uniformly dispersed in the blend prior to compression to avoid speckling or shading of the color.

**F. Equipment capacity/load:** The bulk density of materials or granules will affect the capacity of the equipment. If an excipient in the formulation affects the density of the final blend to a greater extent than any other ingredient, then a well-controlled density specification for that excipient may be warranted. Test different-sized loads in the mixer/blender (e.g., 30, 50, and 70% of working volume) for optimal mixing or blending. Undercharging or overcharging a blender can result in poor drug or tablet lubricant distribution [11, 12].

**Granulation:** If a powder blend's properties do not suit direct compression tableting, manufacturers will turn to granulation processes to create the desired flowability and low dustability. These characteristics are required to minimize tablet weight variations, and ensure high density for high tablet filling weight and high mouldability for hard tablet manufacture. However, granulation is a more time-consuming technique compared with direct compression and there is also a risk of product cross-contamination and product loss during the different processing steps (granulation, drying, sieving). All of these factors can increase costs compared with direct compression [13].

A. **Wet Granulation**: In wet-granulation, a liquid binder solution is combined with a bed of mixed powders to mass the particles together into granules. The damp mass is then screened, dried and milled to the desired size. The mass may also be dry screened, lubricated and compressed or extruded through a perforated screen and then dried.

**I. What type of wet granulation technique will be used?**

Will it be low shear (e.g., Hobart), high shear (e.g., Diosna, GEI Collette) or fluid bed (e.g., Glatt, Fluid Air)? Each technique will produce granules with different physical properties and will require monitoring of different processing parameters.

**II. Binder addition:** Should the binder be added as a granulating solution or dry like the other excipients? Adding the binder dry avoids the need to determine the optimal binder concentration and a separate manufacture for the binder solution.

**III. Binder concentration:** The optimal binder concentration will need to be determined for the formulation. If the binder is to be sprayed, the binder solution needs to be dilute enough so that it can be pumped through the spray nozzle. It should also be sufficiently concentrated to form granules without over wetting the materials.

**IV. Amount of binder solution/granulating solvent:** How much binder or solvent solution is required to granulate the material? Too much binder or solvent solution will over wet the materials and prolong the drying time. The amount of binder solution is related to the binder concentration.

**V. Binder solution/granulating solvent addition rate:** Define the rate or rate range at which the binder solution or granulating solvent can be added to the materials. Can the granulating solution be dumped into the mixer or does it have to be metered in at a specific rate?

**VI. Mixing time:** How long should the material is mixed to ensure proper formation of granules? Should mixing stop after the addition of the binder or solvent solution or should additional mixing be required? Granulations that are not mixed long enough can form incomplete or weak granules. These granules may have poor flow and compression properties. On the other hand, over mixing the granulation can lead to harder granules and a lower dissolution rate.

**VII. Granulation end point:** How is the granulation end point determined? Is it determined or controlled by granulation end point equipment (e.g., ammeter or wattmeter)? Is it controlled by specifying critical processing parameters? For example, a drug or excipients mixture may be granulated by adding a predetermined amount of water (granulating solution) at a certain rate. The granulation is completed after mixing for a set time after the water has been added [15, 16, 17].

**B. Dry granulation:** In the dry granulation method the granulation is formed not by adding a binder. Here compacting large mass of the mixture and subsequently crushing and sizing these pieces into smaller granules takes place. The primary powder particles are aggregated under high pressure. There are two main processes. Either a large tablet (known as a slug) is produced in a heavy-duty tablet press (a process known as slugging) or the powder is squeezed between two rollers to produce a sheet of material (roller compaction).

**Wet Milling**: Does the wet granulation need to be milled to break up the lumps and enhance drying of the granulation? Wet granules that have a wide aggregate range can lead to inefficient drying (long drying times and partially dried large granules or lumps).

**Factors to consider are**

**A. Equipment size and capacity:** The mill should be large enough to de lump the entire batch within a reasonable time period to minimize manufacturing time and prevent the material from drying during this operation.

**B. Screen size:** The screen needs to be small enough to de lump the material, but not too small to cause excessive heating of the mill, resulting in drying of the granulation.

**C. Mill speed:** The speed should be sufficient to efficiently del ump the material without straining the equipment. **D. Feed rate:** The feed rate of the wet granulation is interrelated to screen size and mill size and speed [16].

**Drying**

 The type of drying technique (e.g., tray, fluid bed, and microwave) required for the formulation needs to be determined and justified. The type of technique may be dependent on such factors as drug or formulation properties and equipment availability. Changing dryer techniques could affect such tablet properties as hardness, disintegration, dissolution, and stability. The optimal moisture content of the dried granulation needs to be determined. High moisture content can result in tablet picking or sticking to tablet punch surfaces and poor chemical stability as a result of hydrolysis. An over dried granulation could result in poor hardness and friability. Moisture content analysis can he performed using the conventional loss-on-drying techniques or such state-of the-art techniques as near infrared (NIR) spectroscopy.

**Factors to be considered are**

• Inlet/outlet temperature

• Airflow

• Moisture uniformity

• Equipment capability/capacity [17]

**Milling**

 The milling operation will reduce the particle size of the dried granulation. The resultant particle size distribution will affect such material properties as flow, compressibility, disintegration, and dissolution. An optimal particle size/size distribution for the formulation will need to be determined.

**Factors to consider in milling are**

• Mill type

• Screen size

• Mill speed

• Feed rate [18]

**Lubrication**

**1. Selection of lubricant:** what kind of lubricant should be used? Grade of the lubricant used. Compatibility with other ingredients.

**2. Amount of lubricant added:** How much lubricant is required? Too much lubricant will form hydrophobic layer on the tablet resulting in dissolution problems.

**3. Mixing time:** How long should the material is mixed to ensure proper formation? Should mixing stop after the addition of the lubricant or should additional mixing be required? If not mixed long enough form problems like chipping, capping, etc [19]. Compression Tablet weight, turrent speed, main compression force, pre compression force, feeder speed, upper punch entry, room temperature, humidity [20].

**Tablet Compression**

Compression is a critical step in the production of a tablet dosage form. The materials being compressed will need to have adequate flow and compression properties. The material should readily flow from the hopper onto the feed frame and into the dies. Inadequate flow can result in “rat holing” in the hopper and/ or segregation of the blend in the hopper/feed frame. This can cause tablet weight and content uniformity problems.

As for the compressibility properties of the formulation, it should be examined on an instrumented tablet press. **Factors to consider during compression are as follows**

**A. Tooling:** The shape, size, and concavity of the tooling should be examined based on the formulation properties and commercial specifications. For intagliated (embossed) tablets, factors such as the position of the intagliation on the tablet and the intagliation depth and style should be examined to ensure that picking of the intagliation during compression or fill-in of the intagliation during coating does not occur.

**B. Compression speed:** The formulation should be compressed at a wide range of compression speeds to determine the operating range of the compressor. The adequacy of the material’s flow into the dies will be determined by examining the tablet weights. Is a force feeder required to ensure that sufficient material is fed into the dies?

**C. Compression/ ejection force:** The compression profile for the tablet formulation will need to be determined to establish the optimal compression force to obtain the desired tablet hardness. The particle size/size distribution or level of lubricant may need to be adjusted in order to have a robust process on a high-speed compressor.

The following in-process tests should examine during the compression stage:

Factors to consider during compression are

• Appearance

• Hardness

• Tablet weight

• Friability

• Disintegration

• Weight uniformity

Tablet Coating Tablets may be coated for various reasons.

• Stability

• Taste masking

• Controlled release

• Product identification

• Aesthetics

• Safety–material handling

Tablet coating can occur by different techniques (e.g., sugar, film, or compression). Film coating has been the most common technique over recent years and will be the focus of this section. Key areas to consider for tablet coating include the following:

**A. Tablet properties:** Tablet properties such as hardness, shape, and intagliation (if required) are important to obtain a good film-coated tablet. The tablet needs to be hard enough to withstand the coating process. If tablet attrition occurs, the tablets will have a rough surface appearance. For shape, a round tablet will be easier to coat than tablets will multiple sides or edges because of the uniformity of the surface. For intagliated tablets, the intagliation style and depth should be developed to prevent fill-in or chipping of the intagliation.

**B. Equipment type:** The type of coater will need to be selected. Conventional or perforated pan and fluid bed coaters are potential options.

**C. Coater load:** What is the acceptable tablet load range of the equipment? Having too large a pan load could cause attrition of the tablets because of the overall tablet weight in the coater. In the case of a fluid bed coater, there may not be sufficient airflow to fluidize the tablets.

**D. Pan speed:** What is the optimal pan speed? This will be interrelated to other coating parameters, such as inlet temperature, spray rate, and flow rate.

**E. Spray guns:** The number and types of guns should be determined in order to efficiently coat the tablets. The spray nozzles should be sized properly to ensure even distribution over the tablet bed and to prevent clogging of the nozzles. The location and angle of the spray gun(s) should be positioned to get adequate coverage. Having the guns positioned too close together can lead to a portion of the tablets to be over wet.

**F. Application/spray rate:** The optimal application/spray rate should be determined. Spraying too fast will cause the tablets to become over wet, resulting in clumping of tablets and possible dissolution of the tablet surface. Spraying too slowly will cause the coating materials to dry prior to adhesion to the tablets. This will result in a rough tablet surface and poor coating efficiency.

**G. Tablet flow:** The flow or movement of the tablets in the coater should be examined to ensure proper flow. There should be sufficient tablet bed movement to ensure even distribution of the coating solution onto the tablets. The addition of baffles may be required to provide adequate movement of tablets for tablet coating.

**H. Inlet/outlet temperature and airflow:** These parameters are interrelated and should be set to ensure that the atomized coating solution reaches the tablet surface and then is quickly dried.

**I. Coating solution:** The concentration and viscosity of the coating solution will need to be determined. The solution will need to be sufficiently diluted in order to spray the material on the tablets. The concentration of the coating solution will also determine the amount and volume of solution to be applied to the tablets. The stability of the coating solution should be investigated to establish its shelf life.

**J. Coating weight:** A minimum and maximum coating weight should be established for the tablet. Sufficient coating material should be applied to the tablets to provide a uniform appearance; however, it should not be great enough to cause fill-in of the intagliation.

**K. Residual solvent level:** If solvents are used for tablet coating, the residual solvent level will need to be determined. Appearance testing of the tablets is critical during the coating operation. Items to look for include the following

• Cracking or peeling of the coating

• Intagliation fill-in

• Surface roughness

• Color uniformity Coating efficiency should be determined for the coating operation. The efficiency will determine the amount of coating solution overage that may be required [24, 25, 26, 27].

**Conclusion**

Nowadays Validation is the art of designing and practicing the designed steps together with the documentation in pharmaceutical industry. Validation itself does not improve processes but confirms that the processes have been properly developed and are under control in achieving, maintaining the quality of the final product. Process validation involves a series of activities taking place over the lifecycle of the product and process. Validation and process control variables of tablets manufacturing processes in industry and it is the full-fledged quality attributing tool for the pharmaceutical industries. Solid dosage form validation should be part of a comprehensive validation program within an industry. It is concluded from the review that pharmaceutical validation and process controls are important to assure that the drug product can meet standards for the identity, strength, quality, purity and stability.

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