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Process validation of tablet dosage form: A comprehensive review

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Abstract

Validation is one of the important steps in achieving and maintaining the quality of the final product. If each step of production process is validated we can assure that the final product is of the best quality. Process validation is an essential component for the safety of drug product and also to maintain the quality of the product. Validation is establishing documented evidence which provides a high degree of assurance that a specific process for manufacturing of tablets will consistently produce a product meeting its pre-determined specifications and quality attributes. Validation and quality assurance will go hand in hand, ensuring the quality for the products. The present article gives an introduction and general overview on process validation of pharmaceutical manufacturing process especially tablet manufacturing process.

Keywords: Validation, process validation, solid dosage form, tablets

Introduction

Validation is a concept that has been evolving continuously since its first formal appearance in the United States in 1978. The concept of validation has expanded through the years to encompass a wide range of activities from analytical methods used for the quality control of the drug substances and drug products to computerized systems for clinical trials and is the important step in gaining and maintaining the quality of the final product ^[1].

Validation can also be said as- "The collection and assessment of data, from the process design stage all the way through production, which establishes logical indication that a process is capable of consistently delivering quality products" ^[2].

The concept of validation was first proposed by two Food and Drug Administration officials, Ted Byers and Bud Loftus in the mid 1970's in order to improve the quality of pharmaceuticals ^[3].

According to US FDA in 1978, "A validation manufacturing process is one which has been proved to do what it purports or is represented to do. The proof of validation is obtained through the collection and evaluation of data, preferably, beginning from the process development phase and continuing the production phase. Validation necessarily includes process qualification (the qualification of materials, equipment, system, building, personnel), but it also includes the control on the entire process for repeated batches or runs ^[4]."

USFDA defined process validation as "establishing documented evidence which provides high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics ^[5]".

Why is validation required?

- ✓ It would not be feasible to use the equipment without knowing whether it will produce the product we wanted or not.
- ✓ The pharmaceutical industry uses expensive materials, sophisticated facilities & equipment and highly qualified personnel. The efficient use of these resources is necessary for the continued success of the industry.
- ✓ The cost of product failures, rejects, reworks, and recalls, complaints are the significant parts of the total production cost.
- ✓ Detailed study and control of the manufacturing process i.e. validation is necessary if failure to be reduced and productivity improved.
- ✓ Therefore the pharmaceutical industries are concerned about validation because of the following reasons.

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- Assurance of quality.
- Cost reduction.
- Government regulation ^[6, 7]

When process validation is required?

The process validation should be performed whenever there is-

- New product or existing products as per SUPAC changes.
- Change in site of manufacturing.
- Change in batch size.
- Change in equipment.
- Change in process existing products.
- Change in composition or components.
- Change in the critical control parameters.
- • Change in vendor of API or critical excipient.
- Change in specification on input material ^[3]

Validation Protocol

For performing the process validations the detailed protocols are required for ensuring that the process is been adequately validated.

The protocol should contain the following components:

- a. The purpose and scope of the validation.
- b. Validation team with their qualifications and responsibilities.
- c. Type of validation: Prospective, Concurrent, Retrospective, Re-validation
- d. Total Number batches should be validated.
- e. A complete list of equipments and apparatus to be used; with their parameters
- f. Installation Qualification and Operation Qualification of equipments.
- g. The calibration criteria for all instruments.
- h. All possible critical process parameters with their criteria.
- i. All the process variables/ attributes with their risk and management should be given.
- j. Production related all processing details should be clearly described in the form of master documents.
- k. Sampling schedule with all details of sampling points, methods and sampling plans.
- l. Statistical tools to be used in the analysis of data.
- m. Training schedule for operators
- n. Validated test methods to be used in in-process testing and for the finished product.
- o. Specifications for raw and packaging materials and test methods.
- p. All performs for documenting the results, conclusions and for approval of study results should be given ^[8].

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 ^[9].

Validation Master Plan

A validation master plan is a document that summarizes the

company's overall philosophy, intentions and approaches to be used for establishing performance adequacy. The validation master plan should be agreed upon by management.

Validation in general requires meticulous preparation and careful planning of the various steps in the process. In addition, all work should be carried out in a structured way according to formally authorized standard operating procedures. All observations must be documented and where possible must be recorded as actual numerical results.

The validation master plan should provide an overview of the entire validation operation, its organizational structure, its content and planning. The main elements of it being the list inventory of the items to be validated and the planning schedule. All validation activities relating to critical technical operations, relevant to product and process controls within a firm should be included in the validation master plan. It should comprise all prospective, concurrent and retrospective validations as well as re-validation.

The validation master plan should be a summary document and should therefore be brief, concise and clear. It should not repeat information documented elsewhere but should refer to existing documents such as policy documents, SOP's 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

Materials that have similar physical properties will be easier to form a uniform mix or blend and will not segregate as readily as materials with large differences.

- A. Mixing or blending technique:** Diffusion (tumble), convection (planetary or high intensity), or pneumatic (fluid bed) techniques can be used to mix or blend materials. Determine the technique that is required for the formulation or process objective. It may be different.
- B. Mixing or blending speed:** Determine the intensity (low/high shear) and/or speed (low/high/optimal shear) (rpm) of the mixing or blending. Mixing the drug and excipient will require more intense mixing than adding the lubricant to the final blend.
- 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^[14].

- 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 be 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 be examined 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 with 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 [21, 22, 23, 24].

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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