ISSN:2347-4742

Review Article
Journal of Pharmaceutical and Biomedical Analysis Letters
www.pharmaresearchlibrary.com/jpbmal

A Review on Process Validation of Pharmaceutical Manufacturing Processes

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Abstract

Pharmaceutical Process Validation is the most important and recognized parameters of CGMPs. The requirement of process validation appears of the quality system (QS) regulation. The goal of a quality system is to consistently produce products that are fit for their intended use. Process validation is a key element in assuring that these principles and goal are met and it is an important component in the design, prototyping and manufacturing process and assures that a process will consistently produce product, meeting its predetermined quality characteristics and attributes. The present article focuses mainly on the process validation aspects of solid and liquid dosage forms.

Keywords: CGMPs, Process validation, Quality system regulation, manufacturing process.

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MS. ID: PRL2014-JPBMAL1959

PAPER-QR CODE

1. Introduction

Validation is the act of demonstrating and documenting that a procedure operates effectively.Process Validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process validation involves a series of activities taking place over the lifecycle of the product and process [1, 2].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”.

2. Description

Stages of process validation:[3, 4,]

Stage 1: Process Design:

The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities. It covers all activities relating to product research and development, formulation, pilot batch studies, scale-up studies, transfer of technology to commercial scale batches, establishing stability conditions, storage and handling of in-process and finished dosage forms, equipment qualification,

installation qualification, master production documents ,operational qualification, process capability. Also this is the stage in which the establishment of a strategy for process control is taking place using accumulation knowledge and understanding of the process [5].

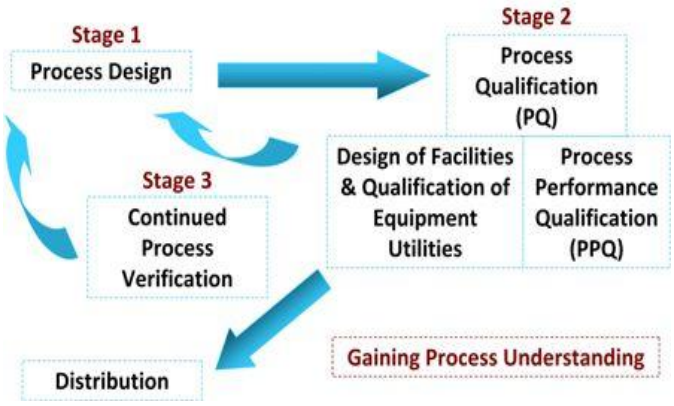

Fig.1: Three model of process validation according to FDA Guidance for Industry – Process Validation

Stage 2: Process Qualification/ characterization[6,7]:

During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing. It confirm that all established limits of the Critical Process Parameters are valid and that satisfactory products can be produced even under "worst case" conditions. GMP compliant procedures must be followed in this stage and successful completion of this stage is necessary before commercial distribution of a product.

There are two aspect of process qualification:

(a) Design of facilities and qualification of equipment and utilities:

Design & commissioning of facilities & utilities precede process performance qualification (PPQ).Qualification refers to demonstration that utilities and equipment are suitable for their intended use and perform properly. Qualification of utilities and equipment generally include

- Selection of utilities and equipment construction materials, operating principles, and performance characteristics.
- Verification that utility systems and equipment are built and installed in compliance with the design specifications.
- Verification that utility systems and equipment operate in all anticipated operating ranges.
- Challenge to the equipment or system functions while under load comparable to that expected during routine production.
- Performance of interventions, stoppage, and start-up as is expected during routine production.
- Performance for as long as necessary during actual production at operating ranges
- Studies or tests to use,
- Criteria appropriate to assess outcomes,
- Timing of qualification activities,
- Responsibilities of relevant departments and the quality unit, and procedures for documenting and approving the qualification.

(b) Process Performance qualification:

Process Performance Qualification Combines the actual facility, utilities, equipment (each now qualified), and the trained personnel with the commercial manufacturing process, control procedures, and components to produce commercial batches.

- Confirms process design
- Demonstrates that the commercial manufacturing process performs as expected.
- Commercial distribution succeeds PPQ completion

Stage 3: Continued Process Verification:

Ongoing assurance is gained during routine production that the process remains in a state of control. Goal to ensure that process remains in a state of control during commercial manufacture. The validation maintenance stage requires frequent review of all process related documents, including validation audit reports to assure that there have been no changes, deviations, failures, modifications to the production process, and that all SOPs have been followed, including change control procedures. A successful validation program depends on the knowledge and understanding and the approach to control manufacturing processes. These include the source of variation, the limitation of the detection of the variation, and the attributes susceptible of the variation[8].

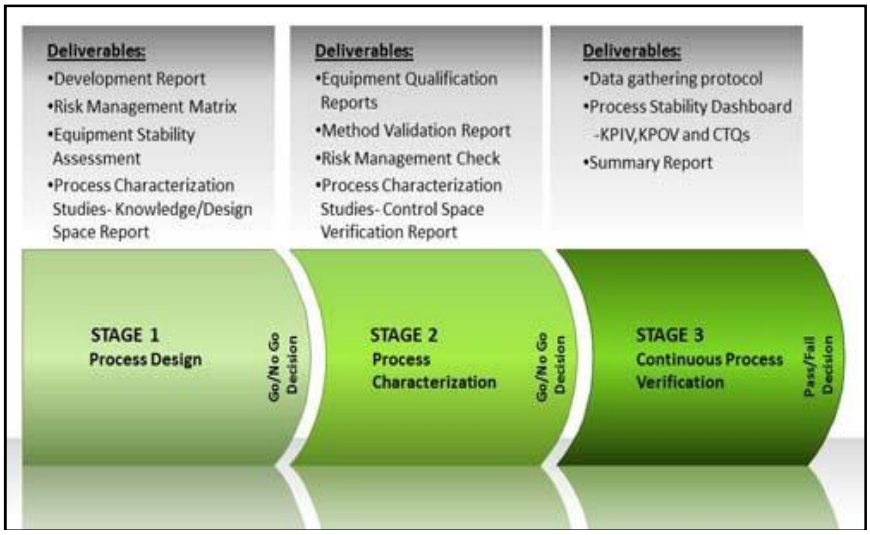

Fig.2: New Process Validation Stage Gate Approach

Process validation of pharmaceutical processes[9]:

1. MIXING

"Mixing is the process of thoroughly combining different materials to produce a homogenous product." Mixing may be defined as the process in which two or more than two components in a separate or roughly mixed condition are treated in such a way so that each particle of any one ingredient lies as nearly as possible to the adjacent particles of other ingredients or components. The purpose of blending is to get uniform distribution of drug that becomes critical for low dose products like tablet and to impart good flow and anti adhesion property to the blend. The terms "mixing" and "blending" are often used interchangeably. Mixing and Blending are the most important unit operations in the production process.

Importance of Mixing

Mixing is a critical process because the quality of the final product and its attributes are derived by the quality of the mix. Improper mixing results in a non-homogenous product that lacks consistency with respect to desired attributes like chemical composition, color, texture, flavor, reactivity, and particle size.

Types of Mixing Equipment

Mixing equipments are classified based on the principle and mechanism of mixing,
Tumbler Blender*:* Double Cone Blender, V-Blenders, Octagonal Blender
Convective Blender: Ribbon Blender, Paddle Blender, Vertical Screw Blender
Fluidization Blenders / Mixers: Plow Mixer, Double Paddle Mixer (Forberg Mixer)

Parameters to be considered are:

Mixing or blending technique:

Diffusion, convection, or pneumatic techniques can be used to mix or blend materials. Determine the technique that is required for the formulation or process objective. The mixer must apply suitable shear forces to bring about local mixing and a convective movement to ensure that the bulk of the material passes through this area.It may be different, depending on whether mixing of the drug and excipients for a direct compression formulation or adding the lubricant (e.g., magnesium stearate) to the granulation.

Mixing or blending speed:

Determine the intensity (low/high shear) and/or speed (rpm) of the mixing or blending. Mixing the drug and excipient will require more intense mixing than adding the lubricant to the final blend.

Mixing or blending time:

Mixing must be carried out for an appropriate time, since the degree of mixing will approach its limiting equilibrium value asymptotically. 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. Experiments should be done to determine if the materials are over mixed, resulting in demixing or segregation of the materials. Demixing can occur due to the physical property differences (e.g., particle size distribution and density). For example, demixing can occur in a direct compression formulation in which the drug substance is micronized (5 microns) and the excipients are granular (500–1000 microns).

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 factors in obtaining valid content uniformity results. Segregation of the sample can occur by over

handling, resulting in inaccurate results. For the final blend (blend prior to compression), the sample taken should be equivalent to the weight of a single tablet.

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

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 performance problems (low dissolution due to excessive lubricant in some tablets).

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 uni- formally dispersed in the blend prior to compression to avoid speckling or shading of the color.

Equipment capacity/load: The mixer must allow sufficient space for dilation of the bed. Overfilling reduces the efficiency and may prevent mixing entirely. 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.

2. Granulation

Granulationis the process of collecting particles together by creating bonds between them. Bonds are formed by compression or by using a binding agent.

A) Wet Granulation

Wet granulation is the most widely used process of granulation in the pharmaceutical industry.It involves addition of a liquid solution (with or without binder) to powders, to form a wet mass or it forms granules by adding the powder together with an adhesive, instead of by compaction. 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. Wet granulation parameters to be considered during development and validation are:

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.

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.

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.

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?

Mixing time: How long should the material be mixed to ensure proper formation of granules? Should mixing be stopped 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.

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 excipient 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.

B) Dry Granulation

The dry granulation process is used to form granules without using a liquid solution because the product to be granulated maybe sensitive to moisture and heat. Forming granules without moisture requires compacting and densifying the powders. Dry granulation can be conducted on a tablet press using slugging tooling or on a roller compactor commonly referred to as a chilsonator. Dry granulation comprises of six steps: a) milling of drug and excipients, b) mixing of milled powders, c) compression into large hard tablets called slugs, d) screening of slugs, e) mixing of lubricants, f) tablet compression. The parameters that are to be checked for are

- Shifting time and speed
- Premixing time
- Blending time and speed
- Screw feeder speed
- Roller speed

- Pregranulator speed
- Post granulator speed

3. DRYING

Drying is a mass transfer process which involves the removal of water or another solvent by evaporation from a solid, semi-solid or liquid. 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 tablet properties such as hardness, disintegration, dissolution, and stability. The optimal moisture content of the dried granulation needs to be determined.

High moisture content can result in

(1) Tablet picking or sticking to tablet punch surfaces and

(2) 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

Inlet/outlet temperature: The inlet temperature is the temperature of the incoming air to the dryer, while the outlet temperature is the temperature leaving the unit. The inlet temperature is critical to the drying efficiency of the granulation and should be set high enough to maximize drying without affecting the chemical/physical stability of the granulation. The outlet temperature is an indicator of the granulation temperature and will increase toward the inlet temperature as the moisture content of the granulation decreases (evaporization rate).

Airflow: There should be sufficient airflow to ensure removal of moisture laden air from the wet granulation. Insufficient airflow could prolong drying and affect the chemical stability of the drug. Airflow and the inlet/outlet temperature are interrelated parameters and should be considered together.

Moisture uniformity: The moisture content could vary within the granulation. Heat uniformity of the dryer (e.g., tray), amount of granulation per tray, and incomplete fluidization of the bed are factors that could affect the moisture uniformity of the granulation.

Equipment capability/capacity: The load that can be efficiently dried within the unit needs to be known. A larger load will require more moisture to be removed on drying and will affect the drying time. In the case of fluid bed drying, a maximum dryer load is that load above which the dryer will not fluidize the material.

4. 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:

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.

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 in to 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?

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:

- Appearance
- Hardness
- Tablet weight
- Friability
- Disintegration
- Weight uniformity

5. Tablet Coating

Coating is a process by which an essentially dry, outer layer of coating material is applied to the surface of a dosage form in order to confer specific benefits over uncoated variety.

Tablets may be coated for various reasons such as

- 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. Key areas to consider for tablet coating include the following:

Tablet properties:

Tablet properties such as hardness, shape, and intagliation 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 tablet 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.

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

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.

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.

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.

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.

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.

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.

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.

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.

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 that are to be looked after include:

- 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.

3. Conclusion

Validation is art step of assure to identity, strength, purity, safty, and efficacy of pharmaceutical product. Process validation is a key element in the quality assurance of pharmaceutical product as the end product testing is not sufficient to assure quality of finished product. It is an integral part of among all validation like equipment validation, cleaning validation, vender validation etc. The cGMP regulation requires that manufacturing processes be designed and controlled to assure that in-process materials and finished product meet predetermined quality specifications. Critical parameter for validation process of solid dosage form must be consider to fulfill the requirement of quality assurance of final product. The product should be designed robustly enough to withstand variations in the manufacturing process and the manufacturing process should be capable and stable to assure continued safe products that perform adequately. Process validation involves a series of activities taking place over the lifecycle of the product and process.

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