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Review Article

Comprehensive Study of Pharmaceutical Process Validation of Solid Dosage Forms: Quality Assurance Point of View

KOMAL M JADHAV[1], JAMEEL AHMED S MULLA[2*], RAJENDRA C DOIJAD[3],

[1]Department of Quality Assurance, Shree Santkrupa College of Pharmacy, Ghogaon, Tal- Karad, Dist- Satara, Maharashtra, India
[2] Department of Pharmaceutics, Shree Santkrupa College of Pharmacy, Ghogaon, Tal- Karad, Dist- Satara, Maharashtra, India
[3] Department of Pharmaceutics, Krishna Institute of Medical Sciences Deemed University's Krishna Institute of Pharmacy, Karad, Dist- Satara, Maharashtra, India

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ABSTRACT

The purpose and interest of this overview on pharmaceutical process validation of immediate release tablets, is to highlight the critical process parameters to be validate during the activity of validation of solid dosage form. It is the most common dosage form for orally administration of drug. The Process validation should confirm that the control strategy is sufficient to support the process design and the quality of the product. This validation review covers the solid dosage form of process validation. The process is developed in such a way that the required parameters are achieved and it ensures that the output of the process will consistently meet the required parameters during routine production, the process is validated. A manufacturer can assure through careful design of the device, processes, process controls and process variable that all manufactured units will meet specifications and have uniform quality. This review provides info on objectives and advantages of method validation, varieties of method validation, major phases in validation and regulative aspects. Guidelines and strategy for process validation of solid dosage form validation and regulatory aspects. Guidelines and strategy for process validation of solid dosage form are also discussed.

INTRODUCTION

Validation is an integral part of quality assurance; it involves the systematic study of systems, facilities and processes aimed at determining whether they perform their intended functions adequately and consistently as specified. A valid method is one that has been incontestable to supply a high degree of assurance that uniform batches are created that meet the specified specifications and has so been formally approved. Validation in itself does not improve processes but confirms that the processes have been properly developed and are under control [1]. The objective of the design and manufacture of the immediate release tablet is to deliver orally the correct amount of drug in the proper form, over a period of time and in the desired location, and to have its chemical integrity protected to that point. Numerous features are required to ensure product quality and the validation is one of them. It is through careful design and validation of both the process and process controls that a manufacturer can establish a high degree of confidence that all manufactured units from successive lots will be acceptable. Successful validation of a method could cut back the dependence upon intensive in-process and finished product testing. In most cases, end-product testing plays a major role in assuring that quality assurance goals are meet. A valid method is one that has been incontestable to produce a high degree of assurance that uniform batches are made that meet the desired specifications and has so been formally approved. Validation in itself doesn't improve processes however confirms that the processes are properly developed and are under control [2].

Process Validation Definition [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,

Author for Correspondence:
Email: jameelahmed5@rediffmail.com

beginning from the process development phase and continuing the production phase. Validation essentially includes method qualification (the qualification of materials, equipment, system, building, personnel), however it conjointly includes the management on the entire method for continual batches or runs''.

In 1987, "Process validation is establishing documented evidence which provides a high degree of assurance that a specific process (such as the manufacture of pharmaceutical dosage forms) will consistently produce a product meeting its predetermined specifications and quality characteristics".

In 2008, "Process Validation is defined as the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products".

In 2011, "The revised guidance also provides recommendations that reflect some of the goals of FDA's initiative entities "Pharmaceuticals CGMPs for the 21st century – A Risk-Based Approach," particularly with regards to the use of technological advances in pharmaceutical manufacturing, as well as implementation of modern risk management and quality tools and concepts".

According to EMEA, in March 2012, "Process validation can be defined as documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medical product meeting its predetermined specifications and quality attributes."

The Regulatory Basis for Process Validation [4]

Once the concept of being able to pre-directs process performance to meet user requirements evolved, FDA regulatory officials established that there was a legal basis of requiring process validation. The ultimate legal authority is in section 501(a)(2)(B) of the FD&C Act, which states that a drug is deemed to bead ultimate differ the methods used in or the facilities or controls used for its manufacture, processing, packing or holding do not conform to or administrated in conformity with CGMP. The CGMP regulations for finished pharmaceuticals 21CFR 210 and 211 were promulgated to enforce the requirements of the act which states that: There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality and purity they purport or are represented to possess.

Objective of Process Validation [5]

1. To reduce variation between various batches.
2. To provide a high degree of assurance of quality of the product.
3. To decrease the risk of defect costs and regulatory noncompliance.
4. To ensure the consistency of the manufacturing operation and reproducibility of the Process.
5. To demonstrate the robustness of the process.

Advantages of Process Validation [6,7]

1. It is simple process and moisture sensitive and heat sensitive products can also be processed.
2. Expanded real time monitoring and adjustment of process.
3. Decreases the risk of preventing problems and thus assure the smooth running of the process.
4. Enhanced ability to statistically evaluate process performance and product variables e.g. individuals; mean; range; control limits.
5. Enhanced data and evaluation capabilities and increased confidence about process Reproducibility and product quality.
6. Improved ability to set target parameters and control limits for routine production, correlating with validation results.
7. Enhanced reporting capability.

Elements of Validation [8]

Design Qualification (DQ): it's documented review of the planning, at Associate in nursing applicable stage of stages within the project, for agreement to operational and restrictive expectations.

1. GMPs and regulatory requirements
2. Performance criteria
3. Facility air flow, movement flow & pressure regimes
4. Reliability& efficiency
5. Commissioning requirements
6. Construct ability & installation of equipment
7. Maintenance& access to critical equipment & instrumentation
8. Safety& environment impact

Installation Qualification (IQ)

It is documented verification that every one aspects of a facility, utility or instrumentality which will have an effect on product quality adhere to approved specifications and square measure properly put in.Important IQ considerations are:

1. Installation conditions (wiring, utilities, and functionality)
2. Calibration, preventative maintenance, cleaning schedules
3. Safety features
4. Supplier documentation, prints, drawings and manuals
5. Software documentation
6. Spare parts list
7. Environmental conditions (such as clean room requirements, temperature and Humidity)
8. Equipment design features (i.e. materials of construction clean ability)

Operational Qualification (OQ)

It is documented verification that everyone aspects of a facility, utility or instrumentality that may have an effect on product quality operate to intend throughout all anticipated ranges. OQ considerations include:

1. Process control limits (time, temperature, pressure, line speed and setup conditions)
2. Software parameters
3. Raw material specifications
4. Process operating procedures
5. Material handling requirements
6. Process change control
7. Training
8. Short term stability and capability of the process.
9. Potential failure modes, action levels and worst-case conditions.

Performance Qualification (PQ)

It is documented verification that each one aspects of a facility, utility or instrumentality perform as meant in meeting planned acceptance criteria. PQ considerations include:

1. Actual product and method parameters and procedures established in OQ
2. Acceptability of the product
3. Assurance of process capability as established in OQ
4. Process repeatability, long term process stability.

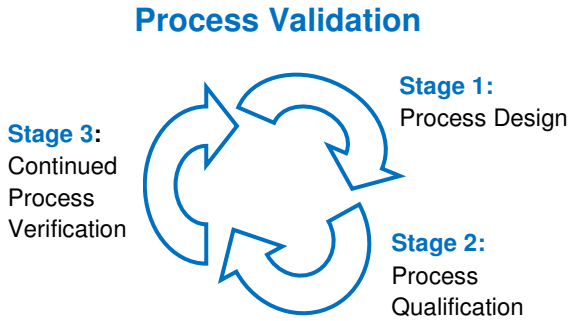
Three Stages of Process Validation [9]

Process validation involves a series of activities taking place over the lifecycle of the product and process.

Stage 1 – Process Design: The business method is outlined throughout this stage supported data gained through development and scale-up activities.

Stage 2 – Process Qualification: During this stage, the process design is confirmed as being capable of reproducible commercial manufacturing.

Stage 3 – Continued Process Verification: On-going assurance is gained during routine production that the process remains in a state of control.



Types of Process Validation [10]

1] Process Validation

The documented proof that the method operated among established parameters will perform effectively and reproducibly to supply a medicative product meeting its present specifications and quality attributes.

2] Prospective Validation

Validation conducted prior to the distribution of either a new product, or product made under a revised manufacturing process, where the revisions may affect the product's characteristics. (FDA) Validation carried out before routine production of products intended for sale.

3] Concurrent Validation

Validation carried out during routine production of products intended for sale.

4] Retrospective Validation

Validation of a process for a product already in distribution based upon accumulated production, testing and control data. (FDA)Validation of a method for a product that has been marketed primarily based upon

accumulated producing, testing and management batch information.

5] Re-Validation

A repeat of the process validation to provide an assurance that changes in the process/equipment introduced in accordance with change control procedures do not adversely affect process characteristics and product quality.

Process Validation Phases [11]

The activities relating to validation studies may be classified into three:

Phase1: This is the Pre-validation Qualification part that covers all activities with reference to product research and development, formulation pilot batch studies, scale-up studies, transfer of technology to business scale batches, establishing stability conditions and storage, and handling of in-process and finished indefinite quantity forms, instrumentation qualification, installation qualification master production document, operational qualification and method capability.

Phase 2: This is often the method validation part. It's designed to verify that everyone established limits of the vital method parameter are valid which satisfactory. Merchandise is often created even underneath the worst conditions.

Phase 3: Known as the validation maintenance section, it needs frequent review of all method connected documents, as well as validation of audit reports, to assure that there are no changes, deviations failures and modifications to the assembly method which all customary crepitating procedures (SOPs), as well as modification management procedures, are followed**.** At this stage, the validation team comprising of people representing all major departments conjointly assures that there are no changes/deviations that ought to have resulted in requalification and revalidation. A careful style and validation of systems and method controls will establish a high degree of confidence that each one heaps or batches created can meet their supposed specifications. It's assumed that throughout producing and management, operations area unit conducted in accordance with the principle of fine producing follow (GMP) each generally and in specific relevance sterile product manufacture.

Strategy for Validation of Methods [12]

The validity of a specific method should be demonstrated in laboratory experiments using samples or standards that are similar to the unknown samples analysed in the routine. The preparation and execution ought to follow a validation protocol ideally written in a very step by step instruction format as follows: Develop a validation protocol or operating procedure for the validation.

- Define the application purpose and scope of method.
- Define the performance parameters and acceptance criteria.
- Define validation experiments.
- Verify relevant performance characteristics of the instrumentality.
- choose quality materials, e.g. standards and reagents;
- Perform pre-validation experiments;
- Adjust method parameters and/or acceptance criteria, if necessary;
- Perform full internal and external validation experiments;
- Develop SOPs, for executing the method routinely;
- Define criteria for revalidation.
- Define sort and frequency of system suitableness tests and/ or analytical internal control (AQC) checks for the routine; and Document validation experiments and ends up in the validation report.

Industrial Process Evaluation and Selection for Tablets [13]

Determine the unit operations needed to manufacture the tablets.

1. Mixing or Blending

Mixing or blending ensures production of uniform mixture of active pharmaceutical ingredients and excipients that don't segregate post mixing. Therefore this step is fastidiously scrutinized and valid. Parameters to consider:

- Mixing or blending technique
- Mixing or blending speed
- Mixing or blending time:
- Drug uniformity
- Excipient uniformity
- Equipment capacity/load.

2. Wet Granulation

Different types of wet granulation techniques may be used like low shear (e.g., Hobart), high shear (e.g., Diosna, GEI-Collette) or fluid bed (e.g., Glatt, Fluid Air). Every technique can turn out granules with totally different physical properties and can need watching of various process parameters. Wet granulation parameters to be considered during development and validation are:

- Binder addition
- Binder concentration
- Amount of binder solution/granulating solvent
- Binder solution/granulating solvent addition
- Mixing time
- Granulation end point

3. Wet Milling

The wet granulation may have to be compelled to be polished to interrupt up the lumps and enhance drying of the granulation. Wet granules that have giant} mixture vary will result in inefficient drying (long drying times and partly dried large granules or lumps). Factors to contemplate are:

- Equipment size and capacity
- Screen size
- Mill speed

4. Drying

The type of drying technique (e.g., tray, fluid bed, and microwave) needed for the formulation must be determined and even. The sort of technique is also keen about such factors as drug or formulation properties and instrumentality accessibility. Dynamical appliance techniques may have an effect on such pill properties as hardness, disintegration, dissolution, and stability. The best wetness content of the dried granulation must be determined. High wetness content may end up in pill selecting or projecting to pill punch surfaces and poor chemical stability as results of reaction. Associate in Nursing over dried granulation may end in poor hardness and bearableness. Wetness content analyses will he performed victimisation the standard loss-on-drying techniques or such progressive techniques as close to infrared (NIR) spectrographic analysis. Factors to be thought-about are:

1. Inlet/outlet temperature
2. Airflow
3. Wetness uniformity

5. Milling

The edge operation will reduce the particle size of the dried granulation. The resultant particle size distribution will have an impression on such material properties as flow, softness, disintegration, and dissolution. Associate in nursing best particle size/size distribution for the formulation will ought to be determined. Factors to suppose in edge are:

- Mill kind
- Screen size
- Mill speed
- Feed rate

6. Lubrication

Lubricants are added to reduce the friction during tablet ejection between the walls of the tablet and die cavity in which the tablet was formed. Factors like amount of lubricant added, grade of lubricant used, compatibility with other ingredients and mixing time must be considered.

7. Tablet Compression

Compression could be a vital step within the production of a pill dose type. The materials being compressed can ought to have adequate flow and compression properties. The fabric ought to without delay be due the hopper onto the feed frame and into the dies. Inadequate flow may end up in "rat holing" within the hopper and/or segregation of the mix within the hopper/feed frame. This could cause pill weight and content uniformity issues. As for the softness properties of the formulation, it ought to be examined on associate degree instrumented pill press. Factors to think about throughout compression area unit as follows:

- Tooling
- Compression speed
- Compression/ejection force

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

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

8. Tablet Coating

Tablet coating will occur by totally different techniques (e.g., sugar, film, or compression). Film coating has been the foremost common technique over recent years and can be the main focus of this section. Key areas to think about for tablet coating embrace the following tablet properties.

- Equipment type
- Coater load
- Pan speed
- Spray guns:
- Tablet flow
- Inlet/outlet temperature and airflow
- Coating solution
- Coating weight
- Residual solvent level

9. In-process tests

- Moisture content of "dried granulation"
- Granulation particle size distribution
- Blend uniformity
- Individual tablet weight
- Tablet hardness
- Tablet thickness
- Disintegration
- Impurity profile

10. Finished product tests

- Appearance
- Assay
- Content uniformity
- Tablet hardness
- Tablet friability
- Impurity profile
- Dissolution

These key take a look at parameters area unit the yardsticks by that the foremost process variables in solid dose forms area unit evaluated. Some process variables are:

- Mixing time and speed in blenders and granulators
- Solvent addition rates in granulators
- Time, temperature, and airflow conditions in dryers and coaters
- Screen size, feed rate, and milling speed in mills
- Machine speed and compression force in tablet presses.

Process validation testing is generally done on the first three batches of product made in production-size equipment. Revalidation testing is only done when a "significant" change has occurred. A significant change is one that will alter the in-process or final product specification established during the validation program or a change in formula, process, or equipment.

Steps for Validation and Acceptance Criteria

The following steps (Table 1) are used in industry for validation of tablets in wet granulation process [13].

Type of Documentation in Validation Process

Validation: Type of documentation [14]

1. Validation master plan (VMP)
2. Validation protocol (VP)
3. Validation reports (VR)
4. Standard operating process (SOPs)

1. Validation master plan

An approved written plan of objectives and actions stating how and when a company will achieve compliance with the GMP requirements regarding validation. VMP is a summary intention document stating the scope of the validation and outlining the methods to be used to establish the performance adequacy. The validation program ought to give a summary of the complete validation operation, its structure, it's content and designing. The most components of its being the list/ inventory of the things to, relevant to product and method controls at intervals a firm ought to be enclosed within the validation program. It even holds the activity and qualification of equipments, outline and conditions of Validation Protocol.

2. Validation Protocol [15]

The validation protocol should be numbered, signed and dated, and should contain as a minimum the following information:

- Title
- Objective & Scope
- Responsibility.
- Protocol Approval
- Validation Team.
- Product Composition.
- Process Flow Chart.
- Manufacturing Process Review of Equipments / Utilities
- Review of Raw Materials and Packing Materials Review of Analytical and Batch Manufacturing Records
- Review of Batch Quantities for Validation (Raw Materials)
- Review of Batch Quantities for Validation (Packing Materials)
- HSE Requirements.
- Review of Process Parameters Validation Procedure
- Sampling Location.
- Documentation.
- Acceptance Criteria
- Summary
- Conclusion

Table 1: Steps for Validation and Acceptance Criteria

S.N.	Steps	Control Variable	Critical Parameters to be checked	Acceptance criteria
1	Dry mixing	Time Impeller speed	Mixing time Mixing speed	Mixing time:……min Impeller speed: ... (slow/medium/high)±5RPM. Content uniformity : 90%-110% RSD : ±5%
2	Binder preparation and addition.	Time Temperature, solvent used	Mode and time of addition	Depending up on the formulation.
3	Drying Inlet/outlet temperature & time	Inlet/outlet temperature & Drying time	Initial drying:…….°C Drying time: …….min.	Final drying : …….°C±5°C Loss on drying : ……% below 3% or depending on formulation
4	Lubrication	Time Blender/granulator speed	Mixing time and speed	Mixing time: ……min. Speed slow: ……..rpm. Content uniformity: Physical parameters – for information.
5.	Compression	Pressure and turret speed	Machine speed and compression pressure	Average weight: ….mg±5%, 7.5%, 10%. Uniformity of weight : …. mg Thickness : ……mm Hardness : …..KN or Kg/cm2 Disintegration time: NMT…..min. Friability : NMT……%w/w Assay : As per the label claim Dissolution:……..%
6.	Coating	Pan speed and spray rate	Pan speed Inlet & outlet temperature Spray rate	Average weight : …..mg±5% Weight of 20 tablets :…..mg Thickness : …….mm Disintegration time: NMT….min. Assay : As per the label claim Dissolution: ……

3. Validation reports [16, 17]

A written report should be available after completion of the validation. If found acceptable, it ought to be approved and approved (signed and dated). The report ought to embrace a minimum of the following: Title and objective of study.

- Reference to protocol.
- Details of material. Equipment.
- Programmes and cycles used.
- Details of procedures and test methods.
- Results (compared with acceptance criteria).
- Recommendations on the limit and criteria to be applied on future basis.

4. SOP (Standard Operating Procedure)

Standard operative Procedures (SOPs) area unit issued to specifically instruct staff in areas of responsibility, work directions, applicable specifications and needed records**.** These outline procedures, must be followed to claim compliance with GMP principles or other statutory rules and regulations. The general aspects covered under the SOPs are the Preparation and maintenance of work area like washing and sterilization, decontamination and testing area. Even the work done in the laboratory were documented, for example, the laboratory operations involving the receipt of reagents, standards, preparation of reagents, labelling and storage, test procedures, reference material, identification, handling, storage and use deviations, errors. Even the details of the equipment sand their maintenance were also involved [18].

Change Control [19]

Process validation of a solid dosage form should include an SOP to reassess a process whenever

there are significant changes in the process, equipment, facilities, reactants, process materials, systems, and so on that may affect the *critical* quality attributes and specifications of the solid dosage forms. Such changes should be documented and approved in accordance with the scope of the change control SOP. The change control SOP should consist of the following elements:

- Documentation that describes the procedure, review, approval, and basis for formal revalidation studies
- Identification of the change and assessment of its likely implication
- Requirements for monitoring change and testing needs
- Assessment of information and justification for the change
- Review and formal approval to proceed Identification of changes made to the physical and chemical composition of the solid dosage forms.
- Possible regulatory action and customer notification.

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