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REVIEW ARTICLE

A REVIEW ON PHARMACEUTICAL PROCESS VALIDATION OF SOLID DOSAGE FORM [TABLETS]

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ABSTRACT:

The article gives an introduction and general overview on process validation of pharmaceutical tablet manufacturing process. Process Validation is one of the important steps in achieving and maintaining the quality of final product. Process validation emphasizes the role of statistical tools and analyses, knowledge, detection, and control of variability and thus gives assurance on consistency of quality product. The validation study provides the accuracy, sensitivity, specificity and reproducibility of the established and documented test methods employed by the manufacturer. Thus, validation is an essential part of the quality assurance. This review examines the need for pharmaceutical validation, the various approaches, process and steps to be monitored during tablet manufacturing process.

Key words: Process Validation, Types, Validation Stages, Guidelines and Process.

1. INTRODUCTION:

The concept of validation was first proposed by two Food and Drug Administration officers, Ted Byers and Bud Loftus, in the mid 1970's in order to improve the quality of pharmaceuticals. Pharmaceutical Process Validation is the most important and recognized parameters of CGMPs.[1] 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. The process validation is standardization of the validation documents that must be submitted with the submission file for marketing authorization.[2] The process validation is intended to assist manufacturers in understanding quality management system(QMS) requirements concerning process validation and has general applicability to manufacturing process.[3]

Some Defination of Validation:

According to **FDA**, [4]

Assurance of product quality is derived from careful and systemic attention to a number of importance factors, including: selection of quality process through in-process and end-product testing.

According to **US FDA in 1978,** [5]

"A validation manufacturing process is one which has been proved to do what it purpose 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".

European Commission - 1991 - Validation - "Act of proving, in accordance of GMPs that Any" process actually leads to expected results.

European Commission - 2000 - Validation - "Documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes".[6]

WHO guidelines define validation as Validation is documented act of proving that any procedure, process, equipment, material, activity or system actually leads to the expected results. Validation act of proving, in accordance of GMPs that any process actually leads to expected results. Documented evidence that the process, operated with in established parameters, can perform effectively reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

2. Types of Validation [7]

2.1 Analytical Validation

Analytical validation is the evaluation of product quality attributes through testing, to demonstrate reliability is being maintained throughout the product

life cycle and that the precision, accuracy, specificity, LOD, linearity, selectivity, strength, purity and specification has not been compromised. The analytical method gives the detail steps necessary to perform an analysis. This may include: preparation of samples, standards and reagents, use of apparatus and use of formula for the calculation and many more.

2.2 Equipment Validation

Validation of equipments is known as qualification. Equipment validation is divided into Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ). An IQ documents specify static attributes of a facility or item to prove that the installation of the unit has been correctly performed and the installation specifications of the manufacturer have been met. After installation it must be ensured that the equipment can deliver operating ranges as specified in the purchase order. This is called OQ. The PQ is concerned with proving the process being done by the machine as it is supposed to do**.**

2.3 Process Validation

Process validation is "A documented procedure which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification and quality attributes". Process validation is divided into different types as follows:-

(a) Prospective validation

It is defined as the establishment of documented evidence that a system does what it purpose to do based on preplanned protocol. This approach to validation is normally undertaken whenever a new formula, process or facility must be validated before commercial routine pharmaceutical formulation commences. During the product development phase the production process should be broken down into individual steps. Each step should be evaluated on the basis of experience or theoretical considerations to determine the critical parameters that may affect the quality of the finished product. A series of experiments should be designed to determine the criticality of these factors. Each experiment should be planned and documented fully in an authorized protocol.

(b) Retrospective validation

It is defined as the establishment of documented evidence that a system does what it purpose to do based on review and analysis of historical data. This is achieved by the review of the historical manufacturing testing data to prove that the process has always remained in control. For the purpose of retrospective validation studies, it is considered acceptable that data from a minimum of ten consecutive batches produced be utilized. When less than ten batches are available, it is considered that the data are not sufficient to demonstrate retrospectively that the process is fully under control. In such cases the study should be supplemented with data generated with concurrent or prospective validation.

(c) Concurrent validation

It is similar to prospective, except the operating firm will sell the product during the qualification runs, to the public at its market price. This validation involves in process monitoring of critical processing steps and product testing. It is the repetition of a validation process or a specific part of it. This is carried out when there is any change or replacement in formulation, equipment, and plant or site location. The justification or conducting concurrent validation must be documented and the protocol must be approved by the Validation Team. A report should be prepared and approved prior to the sale of each batch and a final report should be prepared and approved after the completion of all concurrent batches. It is generally considered acceptable that a minimum of three consecutive batches within the finally agreed parameters, giving the product the desired quality would constitute a proper validation of the process.

(d) Revalidation

Re-validation is usually performed to the confirmation of initial validation for a Periodic review. Re-validation provides the evidence that changes in a process and /the process environment that are introduced do not adversely affect process characteristics and product quality.

2.4 Process/ Product Validation:

Process Validation is establishing documented evidence which provides a high degree of assurance that a specific system will consistently produce a product meeting its predetermined specifications and quality attributes.

Phases in Process Validation

Phase1: This is the Pre-validation Qualification Phase which 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 and storage, and handling of in-process and finished dosage forms, equipment qualification, installation qualification master production document, operational qualification and process capacity.

Phase 2: This is the process validation phase. It is designed to verify that all established limits of the critical process parameter are valid and that satisfactory.

Phase 3: Known as the validation maintenance Phase, it requires frequent review of all process related documents, including validation of audit reports, to assure that there have been no changes, deviations failures and modifications to the production process and that all SOPs, including change control procedures, have been followed and all lots or batches produced will meet their intended specifications.

Various Approaches in Process Validation [8]

Process Design: The goal of this stage is to design a process suitable for routine commercial manufacturing that can consistently deliver a product that meets its quality attributes.

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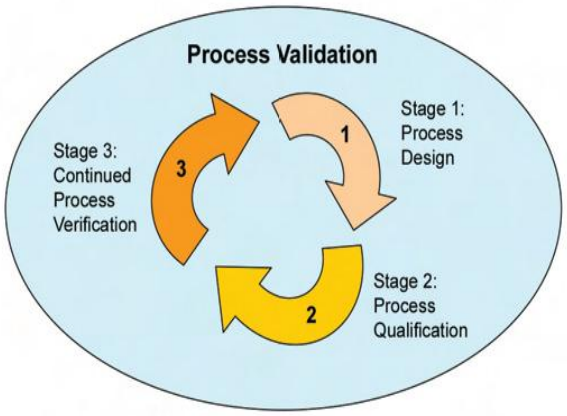
Process Qualification: This stage has two elements: a.design of the facility and qualification of the equipment and utilities and b.process performance qualification (PPQ).

Continued Process Verification: The goal of the third stage is continual assurance that the process remains in a state of control (the validated state) during commercial manufacture.



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2.5 Cleaning Validation

Cleaning validation is the methodology used to assure that a cleaning process removes residues of the active pharmaceutical ingredient of the product manufactured in a piece of equipment, the cleaning aids and ensures that all residues are removed to predetermined levels (product contamination below the acceptable level) to ensure the quality of the next product to be manufactured.

2.6 Vendor Validation

It includes the qualification of the vendor who provides all the active material and the excipients required for formulation.

2.7 Computer System Validation

Computer validation includes qualification of all software and hardware, which has a direct or indirect impact on the quality of a product.

Responsible Authorities for Validation [9]

- Head of quality assurance.
- Head of Production.
- Head of Quality Control.
- Head of engineering & Maintenance.
- Specialist validation member of other related areas

Validation Protocol [10]

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 & Packing Materials)
- HSE Requirements
- Review of Process Parameters Validation Procedure
- Sampling Location
- Documentation
- Acceptance Criteria
- Summary
- Conclusion.

Validation Master Plan[11]

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 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. 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.

Pre-Requisites for Successful Validation

There are some elements or tools that are required for conducting effective validations which are discussed in the following sections:

1) **Understanding:** The single most important element required is a good understanding of what validation is. This understanding activity must be anchored by sufficient years of practical experience and knowledge. It will permit sound and logical decisions even under most intense situations [12].

2) **Communication:** Communication is one of the best methods of improving understanding and is essential for any activity that requires more than one resource to complete as conducting effective validation involves multi-departments.

3) **Co-operation,Plan and Focus:** Multiple departments are involving and interacting during the validation process such as Quality Assurance, Production, Quality Control, Maintenance, project

management, accounting etc so they should have a commendable co-operation, focus and plan in order to get good team synergy.

4) **Experience:** To get success in validation program well experienced validation team are required.
5) **Resources:** Resources means personnel who will plan and execute equipment on which validations will be performed on materials with which to conduct validations.
6) **Budget:** It is important to understand that a successful validation must be done to completion and it should not be limited by a budget as validations cost money.
7) **Standard Operating Procedures (SOP's):** The SOPs capture activities that routinely occur within an organization so all the concerned department must be trained about SOPs and its implementation.
8) Quality Control lab support: During the validations, some laboratory testing will be required which are handled by the QC so well facilitated qc lab is required to get results in expected time.
9) **Permission to conduct preliminary runs.**
10) **Realistic completion dates.**

Objective of Process Validation [13]

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.
6. A fully validated process may require less in-process controls and end product testing.
7. To ensure the existence of all necessary quality assurance system within organization.

Guidelines for process validation of tablets:[14]

Typical pharmaceutical manufacturing processes comprise a serious of unit operations which includes: machinery, methods, people, material, measuring systems and environmental conditions, etc. To assure batch uniformity and integrity of drug products, written procedures need to be established and followed to test for each batch. Such control procedures are established to monitor the output and to validate the performance of the manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.[15].

Process control[4]

Modern methods of process control in process validation are

➢Six sigma

➢Process capability index

➢Statistical process control (SPC) include:

Sampling plan, experimental design, variation reduction, process capability analysis, process improvement plans,SPC will not improve a poorly designed product's reliability, but can be used as a tool to maintain the consistency of how the product is made.

In-process specifications establishment: In process specifications are established based on the previous acceptable process average and process variability determined by the application statistical procedures wherever appropriate. Samples must represent the batch under analysis. Statistical quality control criteria as condition of approval and release of batch must meet its predetermined specifications.

For Process validation of tablet, each and every step involved during formulation of tablet should be taken into consideration. Following are the steps and the parameter which should be considered during process validation of tablet.

A. **Raw Material Validation**:

Active pharmaceutical ingredient

- Excipients
- Variation in raw material is one of the major causes of product variation or deviation from specification
- API may represent the most uncontrollable component.
- State a good pre-formulation program at early phase of product
- Critical steps in the development cycle

Chemical characteristics

- Drug impurities, Impurity levels.
- Physical properties:

Drug morphology, solubility, particle size/surface area, shape, drug density, hygroscopic nature

B. **Analytical method Validation**:

- Accuracy
- Precision
- Specificity
- Intra / Inter day variance
- Between operator variation
- Between instrument variation

C. Process evaluation, selection and validation: [16]

1. Dispensing:

Dispensing is done prior to formulation. Ensure dispensing booth is clean and line clearance is given as per SOPs. Ensure that balance is calibrated and ensure that the expiry date of product to be released is later than that of batch expiry date. Check and ensure that the all materials are issued as per BMR. And all the rooms such as granulation room, Compression room, coating room, packing room etc are clean and line clearance has been done prior to processing.

2. 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. Parameters to be considered are:

- Mixing or blending technique: Diffusion (tumble), convection (planetary or high intensity), or pneumatic (fluid bed).
- 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: The mixing or blending time will be dependent on the mixing or blending technique and speed.
- 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 in obtaining valid content uniformity results. For the final lubricated granules, the sample taken should be equivalent to the weight of a single tablet.
- Excipient uniformity: Lubricant,Color
- Equipment capacity/load.

3. Wet Granulation

The type of wet granulation technique used will produce granules with different physical properties and will require monitoring of different processing parameters.

- Binder addition.
- 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.
- Binder solution/granulating solvent addition rate.
- Mixing time.
- Granulation end point: Granulation end point is determined or controlled by granulation end point equipment (e.g., ammeter) or 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.

4. Wet Milling

Wet granules need to be milled to break up the lumps and enhance drying of the granulation. Factors to be consider are:

- Equipment size and capacity.
- Screen size.
- Feed rate.
- Mill Speed.

5. 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 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.

- Inlet/outlet temperature.
- Moisture uniformity: Heat uniformity of the dryer, 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: A larger load will require more moisture to be removed on drying and will affect the drying time.
- Airflow.

6. 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: impact or screen.
- Screen size: The screen size will affect the particle size. A smaller screen size will produce a smaller particle size and a greater number of fines.
- Mill speed.
- Feed rate.

7. Lubrication

- Grade of the lubricant used.
- Compatibility with other ingredients.
- Mixing time:
- Amount of lubricant added: Too much lubricant will form hydrophobic layer on the tablet resulting in dissolution problems.

8. 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 to 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. Factors to consider during compression are as follows:

- Tooling: The shape, size, and concavity of the tooling should be examined based on the

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formulation properties and commercial specifications.

- Compression speed: The formulation should be compressed at a wide range of compression speeds to determine the operating range of the compressor.
- 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 following in-process tests should be examined during the compression stage:

- Appearance
- Hardness, Thickness
- Tablet weight
- Friability
- Disintegration Time
- Weight uniformity

9. Tablet Coating

Tablet coating can occur by different techniques (sugar, film, or enteric) where film coating is the most common. Factors to be considered for tablet coating are:

- Tablet properties: Tablet properties such as hardness, shape, are important to obtain a good film-coated tablet.
- Equipment type.
- rpm of the coating pan.
- Spray guns: Angle of spray.
- Application/spray rate: The optimal 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.
- Tablet flow.
- Inlet/outlet temperature and airflow.
- Coating solution: The concentration and viscosity of the coating solution will need to be determined. 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 to provide a uniform appearance.
- Residual solvent level: If solvents are used for tablet coating, the residual solvent level will need to be determined.

.10. In-process tests

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

11. Finished product tests

- Appearance
  - Tablet mottling
  - Picking of the monogram
  - Tablet filming
  - Capping of the tablets
  - Tablet colored
- Assay.
- Content uniformity
  - Beginning
  - Middle
  - End
- Tablet hardness
- Tablet friability
- Impurity profile

12. Labelling and packing:

Check and record the temperature of the heating roller and sealing roller, over printing instructions on labels and cartons. Check and verify that price overprinted on label and carton is as per current price list. After ensuring the proper labeling of tablets, check, for correctness of cartons packing for the same.

Finished product analysis and release:

Finished product needs to be analyzed as per in-house specification and product released only after predetermined specifications and quality attributes. 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.

Reason for choosing three consecutive batches for Validation:

Generally it is considered if we get the desired quality in first batch it is accidental, second batch quality is regulator, and quality in third batch is validation. When two batches are taken as validation the data will not be sufficient for evaluation and to prove reproducibility because statistical evaluation cannot be done on two points, it needs minimum three points because two points always draw a straight line. Therefore, minimum three consecutive batches are evaluated for validation of manufacturing process. More than three batches can be taken in validation but it involves the cost and time.

Final Process Validation Report [17]

At the conclusion of validation activities, a final report should be prepared. This report should summarize and reference all protocols and results. It should derive conclusions regarding the validation status of the process and necessary recommendation for routine process. The final report should be reviewed and approved by the validation team and appropriate management.

- A validation report shall be prepared to assess the adherence to the protocol after execution of batches.
- Data can be collected in pre design format during execution wherever application but not limited to.
- Name of ingredients, quality of ingredients used and product batch number, Name of the equipments used at each processing stage, equipments numbers and make/model/capacity of the equipments shall

be checked against the formulation order of the validation batch processing records.
- The environmental condition during batch execution at each processing stage shall be checked against the formulation order of the validation batch processing records.
- Stage of process, details of process variables the respective observations and recommendations shall be checked against the formulation order of the validation batch processing records.
- Any work done in addition to that specific in the protocol or any deviation from the protocol should be formally noted along with an explanation.
- All sampling location shall be specified.
- The actual yield obtained at different stages shall be checked against the formulation order of the validation batch processing records.

CONCLUSION:

It is concluded that Process validation is a step to assure the identity, strength, purity, safety and efficacy of pharmaceutical drug products, and it is the most common word in the drug development, manufacturing and specification of finished product. Process validation is major requirement of cGMPs regulation for the process efficiency. The multidisciplinary validation team must identify the product and process characteristics that must be studied and incorporate specific validation tests to ensure that that product will meet all quality, manufacturing, and regulatory requirements. The total program should begin with validation of the active pharmaceutical ingredient (API) characteristics so that this material will be uniform batch after batch, providing a solid pillar under which the dosage form will be built. The parameters chosen must be relevant indicators of a controlled process. Continued awareness of validation requirements and a diligent application of validation principles will thus help to ensure that pharmaceutical products will be able to be developed and produced with the quality and reproducibility required from regulatory agencies across the world.

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