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A Review on Solid Oral Dosage Forms with an Industrial Perspective for Process Validation

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ABSTRACT

Aim of the present review is to summarize various steps involved in process validation of the oral solid dosage forms in pharmaceutical industries. Oral solid dosage form such as tablets, capsules etc are widely used due to its easy administration and easily available to the market at affordable price. Validation it is an important part of current good manufacturing practice. Process validation is an integral part of GMP as it provides evidence for the quality of drug product. Performing process validation in pharmaceutical industries, will help to design, control and maintain the particular process. The critical process steps such as sifting, mixing, compression etc and critical process parameters such as sieve integrity before and after passing the raw materials, sieve size, mixing time, mixing speed, compression force etc., it is well stated. Process validation establishes evidence and provides high degree of assurance that a particular process will consistently produce a product meeting its predefined specifications.

KEYWORDS: *Validation, Process validation, Oral solid dosage forms, Critical process parameters*

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INTRODUCTION

Nowadays validation plays an important role in pharmaceutical industries compared to the past years or past decades and it is an important part of Current Good Manufacturing Practices.[1] Performing or conducting process validation in pharmaceutical industries is mandatory to obtain a product or drug which fulfills all the regulatory requirements as well as all the standard requirements to achieve the drug at lowest cost which can be affordable to all people as it helps to reduce the cost of quality.[2]

Validation is a systematic approach to define, quantify, review, report and reassess a number of crucial parts during production process requiring supervision for obtaining a standard product.[3] It is a necessary step in the production, storage, handling and distribution of medicinal products. "Quality or value cannot be measured in products; it should be integrated or planned".[4] Thereby all the steps involved in the manufacturing process from raw materials to finished product must be controlled with an intention of obtaining a product meeting all standard specifications.[5]

Validation can be categorized as;-

- Process validation (PV)
- Analytical method of validation
- Equipment validation
- Cleaning validation.
- Computer system validation.[6]

From the above mentioned types of the validation, focus is given to Process validation (PV). According to USFDA Guidelines, the definition of PV is establishing documented evidence that provides high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics.[7] Effective PV contributes significantly in assuring the drug quality.[8] PV should be carried out in the following circumstances

- Modification of production area
- Transfer of products from parent company to sister concerned companies or loan license companies.
- New product transferred from R & D to Production department (Technology transfer)
- Alterations in Batch size.[9]
- Change in equipments, instruments, replacing the parts of the machine
- Replacement of the excipients or API with others
- Change of API/Excipients vendor
- Based on the historical data from trend analysis.[10,11]

The major objectives of performing or conducting process validation in any of the pharmaceutical industries are as follows:

- Reducing variation between different lots
- To provide high degree of product quality control
- To reduce internal and external failure costs
- To reduce the risk of expenditure towards defects and failure

- To ensure the process manufacturing procedure meets reliability and reproducibility.
- Demonstrating the process robustness.[12]

Performing process validation in pharmaceutical industries as an ongoing process leads to the following consequences:

- Each and every step/process will be well maintained and controlled
- Reducing cost of quality
- Reduction of dismissals (rejections)
- Increased performance
- Faster and efficient start up of new equipment
- Facilitated equipment maintenance.[13]

In order to carry out or accomplish process validation in pharmaceutical industries, the following phases/stages should be considered:
Pre validation or Qualification phase
Process validation or Process Qualification phase
Validation maintenance phase.[14]

Pre-validation phase or qualification phase: This is the first phase considered at a time of performing process validation. It includes activities related with product development along with research including formulation, pilot batch studies, scale-up studies, transfer of technology to commercial scale batches, establishment of stability conditions. It also cover storage and handling of in process and finished dosage forms, equipment qualification, installation qualification, master production documents, operational qualification, process capability.

Process validation phase: Second phase of process validation which is implemented to validate that documented limits of critical process parameters are applicable and even under worst conditions satisfactory products can be produced.

Validation maintenance phase: Third phase of process validation which involves reviewing documents of the entire process, such documents are validation audit reports to make sure that no changes, deviations, failures occurs when the manufacturing process has been modified and other documents such as Standard Operating Procedures (SOPs) including changes in control procedures have been followed.[15,16,17]

There are four types of PV (process validation) which are;

- Prospective PV
- Retrospective PV
- Concurrent PV
- Revalidation PV.[18]

Prospective PV: It can be defined as establishing documented evidence in which a process does what it purports to do on the basis of preplanned protocol. In PPV, the written document with procedures, quality control tests of bulk, in process and finished product and its acceptance requirements, handling of equipment and reporting (which is validation protocol) it should be implemented before the process is put into commercial use. In conjunction with introduction and manufacturing of new pharmaceutical formulations, the PPV is typically performed. PPV must be carried out only if the below mentioned practice has been fulfilled;

- Facilities in which PPV is going to be carried out along with the machines used should comply with current good manufacturing practice specifications.
- The whole PPV process must be understood by the facilitators along with supervisory.
- Manufacturing process must be developed, selected and optimized.
- Detailed documentation should be available regarding drug and the entire production steps.

Before performing PPV, validation protocol must be prepared then approved by QA. PPV protocol must contain the following information;

- Objective, scope, responsibilities
- List of members / coordinators involved in validation
- Detailed formula of the formulation
- Authorized vendors/suppliers of raw materials, API and Packaging materials
- Manufacturing process followed during validation
- List of equipments used along with number in production process
- Equipment qualification details
- Identification and explanation of critical steps and critical parameters
- Scientific rationalization of critical steps
- Sampling plan at all steps
- Detailed analytical procedures for bulk product, semi-finished products and finished products (QC test)
- Statistical methods for the analysis of data.
- Acceptance criteria.[19,20,21]

Retrospective PV; -It provides recorded proof about the entire manufacturing process or system whether it does what it intends to do or not, based on historical data analysis and evaluation.[22] Retrospective PV can only be preferred if the existing products whose manufacturing processes are considered to be stable.

Various steps are as follows:

- Collect numerical data from completed lot documentation, including assay values, final product test results and in process data.
- Then arrange the above collected information in order according to batch production record in the worksheet.
- If the referred data contains more than 30 manufactured lots/batches, then the minimum data to be entered should contain the last 20 to
- 30 manufactured lots/batches and if the data contains less than 20 batches, then include all lots.
- Shorten the information by extracting experiment outcome from noncritical processing steps and unnecessary statistical data.
- Provide statistical analysis and assessment with the resulting data.
- Then, the obtained results should be concluded.
- Final report should be submitted to the particular person for the documentation evidences.

Concurrent PV; - It can be defined as establishing documented evidence in which a process performs in the intended manner on the basis of information generated during actual implementation of the process in according with a pre-planned protocol. Concurrent PV can only be performed if any of the following conditions exist:

- If there is a transfer of the earlier validated process from

one production site to the other production site
- If the product to be manufactured has similar active ingredients but it contains different strength compared to validated product
- If the number of batches is not sufficient to run retrospective PV to attain higher degree confidence that system is completely managed.

Revalidation;- Is carried out in instances such as any changes in the vital system parameters, formulation procedure, primary packaging elements, main equipment or premises. It is done to analyze whether the above modifications might have impact on quality of final product or not. In other way revalidation is redoing the same work which was already done to ensure that standards are maintained.[23,24,25]

Oral solid dosage forms such as Tablets, Capsules, Powders and Dry syrups are widely used worldwide due to its easy administration of the drug and affordability at the lowest cost to all types of patients and also due to their effortless availability in the market.[26]

Performing or conducting PV for these types of dosage forms is important as the main goal is to obtain a product which meets all the required quality specifications and standards at a particular period of time and at the lowest cost which can be easily obtained by all kind of people. So, all the steps involved in the manufacturing process from the starting of the raw material to the finished product should be well controlled.27

METHODOLOGY

Process Validation of the manufacture of solid dosage form, process should be carried out for three consecutive batches as per protocol. During the process validation following steps should be followed.
- Preparation of PV protocol
- Preparation of batch manufacturing record(BMR)
- Identification of critical process parameters (CPP) for critical steps in the manufacturing process.
- In process quality control test at every stage of manufacturing
- Sampling plan.
- Quality control test for tablets
- Acceptance criteria.
- Stability studies
- Recording and analyzing results of critical control variables and response variables as per process parameters considered.
- Identify the productivity of tablets and prepare a validation report.[28]

1. **Preparation of PV protocol:** make sure that PV protocol must be prepared then approved by Quality assurance personnel as it will guide on how the PV should be performed.
2. **Preparation of BMR:** It is an important document which covers the overall records of the production history of a particular batch of product. It also assures that the quality and regulatory requirements are attained. BMR contains the following:
- Product name
- Batch number
- Dispensing of raw and packaging material details
- Raw and packaging materials verification details
- The process involved in manufacturing
- Exactly date for starting and finishing of manufacturing process
- Signatures of the operators and reviewers
- All test carried out, the results should be recorded
- Name of the equipment used, cleanliness, line clearances etc

3. **PV of solid dosage form to be carried out for three consecutive batches as per protocol:** PV should be conducted for three consecutive batches to confirm that process consistently will produce a product meeting predetermined specifications along with its quality attributes. Three consecutive batches means in sequence such as 1, 2, 3 (correct) and not by skipping one batch example 1, 3, 4 (incorrect).

4. **Manufacturing process:**
- **Step 1: Sifting:-** The accurately weighed amount of the raw materials should be sifted by using sieve shaker machine with the specified sieve number for example sieve number 20, 40, 60 etc.
- **Step 2: Dry granulation:-** The sifted raw materials should be mixed at a particular blender for the specified period of time. Examples of blender used for mixing dry powder and granules are; double cone blender, v cone blender etc.
- **Step 3: Paste preparation:-** The mixed raw materials are taken and forming paste with the help of binding agent. Equipment used for this process is paste preparation kettle.
- **Step 4: Wet granulation:-**The formed paste is going to be mixed by using specific granulator to achieve optimized mixing and consistent granules at higher productivity and lower operating cost.
- **Step 5: Drying**:- After wet mixing process, drying process follows in which Fluid bed dryer is going to be used by following the specified set parameters.
- **Step 6: Dry milling:-**The obtained dried granules should be milled by using multi mill equipment to get uniform particle size.
- **Step 7: Blending:-**The obtained uniformly sized powder or granules should be mixed by using double cone blender by following the specified set parameters in order to obtain the uniformity of the blended material.
- **Step 8: Compression**:- Then the blended material should be compressed using tablet compression machine to get tablets by following all the standard set parameters so that to achieve the product of high quality.[29]
- **Step 9: Tablet coating:-** This step should be applied to in case of coated tablets. Its major importance is to mask the taste or odor of the drug. It also protects the drug from physical and chemical degradation. Equipments used for tablet coating such as standard coating pan, perforated coating pan, fluidized bed coater etc need to be qualified before processing.[30]
- **Step 10: Packaging:-** Last is packaging of the product, in which the tablets are going to be packed in different packaging material such as blisters, strips, bottles etc. Packaging step it is important as it protects the product during storage.[31]

5. Identification of Critical process parameters (CPP) during manufacturing process.[32]

Identifying CPPs during manufacturing process is important as it will detect any deviation/variations which rises during the manufacturing process and immediately corrective actions and preventive actions can be implemented and this will lead to produce a standard quality product.

Table 1:Critical process parameters (CPP) for manufacturing process

Critical steps	CPP
Sifting	• Sieve size • Sieve integrity before and after passing the raw material • Vibration of shifter • Metallic substance in raw material • Foreign material in raw material Presence of static charges
Dry granulation	• Mixing time at different time intervals e.g. total mixing time is 15minutes. Collect the samples before 5 min and after 5 min of specified time. • Mixing speed ✓ High speed ✓ Medium speed ✓ Low speed • Volume occupancy ✓ Full ✓ Half Bottom
Paste preparation	• Capacity of the vessel • Mixing speed of stirrer Temperature of solution
Wet granulation	• Mixing time at different time intervals e.g. total mixing time is 10minutes. Collect the samples before 5 min and after 5 min of specified time. • Mixing speed of Impeller ✓ High speed ✓ Medium speed ✓ Low speed • Mixing speed of Chopper ✓ High speed ✓ Medium speed ✓ Low speed • Volume occupancy ✓ Full ✓ Half ✓ Low End point determination
Drying	• Volume occupancy of product bowl ✓ Full ✓ Half ✓ Low • Time taken to attain the in-let temperature. • Inlet temperature • Inlet air pressure • Exhaust air pressure • Exhaust temperature • Fluidization level • Bed temperature of granules • Finger bag shaking • shaking interval of Finger bag Total drying time
Dry milling	• Screen used for milling • Type of blade used for milling • Feed rate of dried granules to the multi mill • Speed of milling blade ✓ High speed ✓ Medium speed ✓ Low speed • Output of dried granules % of fine after milling

Blending	• Volume occupancy of the granules in the mixer. • Volume occupancy ✓ Full ✓ Half ✓ Low • Time required for loading of granules • Mixing time at different time intervals e.g. total mixing time is 10minutes. Collect the samples before 5 min and after 5 min of specified time. • Mixing speed of Impeller ✓ High speed ✓ Medium speed ✓ Low speed • Mixing speed of Chopper ✓ High speed ✓ Medium speed ✓ Low speed Sampling of blend
Compression	• Compression speed ✓ High speed ✓ Medium speed ✓ Slow speed • Compression force ✓ High force ✓ Medium force ✓ Low force • Pre compression ✓ High ✓ Medium ✓ Low • Main compression force ✓ High ✓ Medium ✓ low • Hopper level ✓ Full hopper level ✓ Half hopper level Low hopper level
Tablet coating	• Inlet air pressure • Inlet temperature • Tablet bed temperature • Exhaust temperature • Pan speed • Spray rate • Distance between the guns • Distance between the guns and tablet bed • Peristaltic pump rpm • Coating vessel stirrer RPM • Viscosity of the coating solution • Temperature of coating solution Baffles used in the coating pan
Packaging a. Blistering	• Machine speed • Vibration speed of hopper • Machinability of blister material • Web forming temperature • Forming pressure • Sealing temperature • Sealing pressure • Chilled water temperature
b. Labeling process	• Machine speed, Printing assembly speed • Distance between label and printing assembly • Distance between label and barcode assembly Distance between label and sensor assembly

6. In process quality control (IPQC) test at every stage:

IPQC test should be carried out during the manufacturing process is in progress so that to monitor the entire features of produced product that might affect quality of product.

Table 2: In process quality control (IPQC) tests at every stage:

Sr. no.	Critical steps	IPQC
1	Sifting	Sieve integrity before and after sifting process
2	Dry mixing	Content uniformity
3	Wet mixing	Uniformity of granules
4	Drying	Moisture content of granules
5	Blending	Bulk density, Tapped density, Angle of repose, Carr's index, Hausner's ratio, Drug content
6	Compression	General appearance, Diameter, weight variation, Hardness, Friability, Thickness, Disintegration time.
7	Tablet coating	General appearance, weight variation, Spray rate, Disintegration time.
8	Blister packaging	Leak testing, Appearance, Minimum information is legible, Printing matter, Cutting of blisters.
9	Labeling process	Appearance of labels, Functioning of label printing assembly, Functioning of label barcode assembly, Functioning of label sensor assembly.

7. Sampling plans:

Samples should be collected in a logic way from each critical step during manufacturing process and the test will be performed using the collected samples. For example:

- During mixing/blending, if the formulation is going to be mixed for 15mins then the sample will be collected before 5mins and after 5mins at specified locations of the blender and the sample should be sent to the Quality Control department.
- During compression, compression force is considered as one of the CPP, in this compression force should be adjusted at high, medium and low force and at every adjustment the sample should be collected and sent for analysis to the Quality Control laboratory.

8. Quality control (QC) test for tablets during process validation (PV).

QC test are carried out for the finalized product to assure that the product is fit to be commercialized.

Table 3: Quality control (QC) test for tablets during process validation (PV).

Sr. no.	Product type	QC tests
1	Semi finished product	• General appearance • Thickness • Diameter • Hardness • Friability • Disintegration test • Dissolution test • Drug content • Weight variation test
2	Finished product	• Leak testing • Appearance • Minimum information is legible • Printing matter • Cutting of blisters • Yield

9. Acceptance criteria.33

This will help to observe whether the obtained results are within limit or not, and by obtaining this we will be able to conclude that it has passed or not.

Table 4: Acceptance criteria for Carr's index and Hausner's ratio

Carr's index (%)	Flow characters	Hausner's ratio
< or = 10	Excellent	1-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very very poor	>1.6

Table 5: Acceptance criteria for Angle of repose

Angle of repose	Character's
<25	Excellent
25-30	Good
30-40	Passable/ average
>40	Very poor

Table 6: Acceptance criteria for uniformity of weight

Dosage forms	Average weight	% Deviation
Uncoated or film coated tablets	80mg or less	±10
	More than 80mg and less than 250mg	±7.5
	More than 250mg	±5

Table 7: Acceptance criteria for Hardness and friability

Sr. no.	Test	Acceptance criteria
1	Hardness (kg/cm^2)	3-6kg/cm^2
2	Friability (%)	Not greater than 1%

Table 8: Acceptance criteria for uniformity of weight.

Test	Limits
Uniformity of content	Each individual content should be within 85 to 115% of the average content.

Table 9: Acceptance criteria for disintegration test

Sr. no.	Types of tablet	Limits
1	Uncoated tablets	Not more than 15mins
2	Coated tablets	Not more than 30mins
3	Enteric coated tablets	In 0.1N HCL within 2hours tablets should not disintegrate. Tablets should disintegrate within 1hr in 6.8 phosphate buffer.
4	Dispersible tablets	Not more than 3mins

Table 10: Acceptance criteria for dissolution test

Stage	Number tested	Limit
S1	6	Each unit not less than D*+5%
S2	6	Average of 12 units (S1+S2) is equal to or greater than D and no unit is less than D-15%
S3	12	Average of 24 units (S1+S2+S3) is equal to or greater than D, not more than 2 units are less than D-15% and no unit is less than D-25%

D* is the amount of dissolved active ingredient specified in the individual monograph and expressed as % labeled amount.[33]

10. Carry out the stability studies:

Stability studies are an important test performed to assure that, when the drug is stored under recommended storage conditions, whether it will remain within specifications or not.[34]

Then finally the results should be recorded and validation report should be prepared.

Process validation is adapted in pharmaceutical industries to attain and maintain the quality and all standards of the drug. Before implementing all personnel involved in particular process should be trained about the process validation concepts and they should implement it in regular work. The major benefits of doing all these are to meet the entire regulatory basis, identifying critical process parameters, Identifying the rejection level. The man power used for the process, reduce cost of product and to produce a product of high standards.

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