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An Overview of Pharmaceutical Process Validation of Solid Dosage Form.

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Abstract
The present article gives an introduction and general overview on process validation of pharmaceutical manufacturing process especially tablet manufacturing process. The principal objective of dosage form design is to achieve a predictable therapeutic response to a drug included in a formulation which is capable of large scale manufacture with reproducible product quality. Solid dosage forms include tablets and capsules. Quality is always an imperative prerequisite when we consider any product. Therefore, drugs must be manufactured to the highest quality levels. Process Validation is one of the important steps in achieving and maintaining the quality of final product**.** This article covers Introduction, type of validation ,Prospective validation Retrospective validation Concurrent validation Revalidation ,Elements of Process Validation, Product Lifecycle View ,Phases of Process Validation , Rationale for selection of critical steps and parameters for process validation, Documentation ,SOP, Validation Master Plan, Validation Protocol, General notes process variations, critical factors and sample thief ,sampling plan and acceptance criteria, the validation report, studies on the process validation by all these parameter highlight the quality output of finished dosage form.

Key Words
Process validation, Quality management, manufacturing procedure, protocol.

Introduction

The concept of validation was first proposed by two Food and Drug Administration (FDA) officials, Ted Byers and Bud Loftus, in the mid 1970 s in order to improve the quality of pharmaceuticals Assurance of product quality is derived from careful attention to number of factors including selection of quality parts and materials, adequate product and process design, control of the process, and in process and end product testing[1]. Due to the complexity today s medical products, routine end product testing alone often is not sufficient to assure product quality for several reasons. Some end-products tests have limited sensitivity E.g.:- In some cases, where end product testing does not several all variations that may occur in the product, which may have an impact on safety and effectiveness, destructive testing is required to show that the manufacturing process is adequate.

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Process Validation

Process Validation is "Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes" FDA Guideline, 1987. The FDA in its new guidelines had made some changes in the aspects of process validation and defined it as "The collection and evaluation of data, from the design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products". The manufacturing of solid dosage forms involves extensive powder handling. The powder must be blended for uniformity and converted into the dosage form either through compression or encapsulation. Typical requirements include weighing, blending, mixing/granulation areas, compression/encapsulation areas and coating areas. Despite the ongoing development of more sophisticated solid drug delivery systems, tablets are still by far the most prevalent solid dosage form .Tablets comprises a mixture of active substances and excipients, usually in powder form, pressed or compacted into a solid. The excipients can include binders, gllidant (flow aids) and lubricants to ensure efficient tablet in gm; disintegrates to promote tablet break-up in the digestive tract; sweeteners or flavors to enhance taste; and pigments to make the tablets visually attractive .A polymer coating is often applied to make the tablet smoother and easier to swallow, to control the release rate of the active ingredient, to make it more resistant to the environment (extending its shelf life), or to enhance the tablet's appearance. Depending up on the magnitude of production, the manufacturing and related facilities will vary in size. Whether the facility makes few thousands of tablets or capsules daily or millions of the same daily, the basic principles of validation will remain the same. The performance of the facility where the dosage form is manufactured is needed to be demonstrate to meet the various regulatory, technical requirements of cGMP expectations to achieve good quality of medicines throughout the global. Critical factors which affect conducting effective process Validation The quality system (infrastructure) should support the validation effort by way of document control, calibration preventive maintenance, etc All the critical points of the process should be clearly All the critical points of the process should be clearly identified The process should run using the extremes of the system The process should run using the extremes of the system at the critical points (worst case). Adequate run (data) are required to provide statistical support to demonstrate product consistency The execution of the protocol should follow the requirements of the validation document, where all deviations form the validation document well recorded and followed up properly Before approving validation the area should be conformed Before approving validation the area should

be conformed for the requirement of validation

Types of process validation

The various types of process validation are outlined below

Prospective validation (pre marketing validation)

This type of validation activity is normally completed prior to the distribution and sale of the drug product. It is generally considered acceptable that three consecutive batches/runs within the finally agreed parameters, giving product of the desired quality would constitute a proper validation of the process. It is preferred that the validation batches made should be of the same size as the intended production scale batches, when this is not practical, a reduced batch size corresponding to at least 10% of the intended batch size for full scale production can be considered.

Concurrent validation

This type of validation is carried out during routine production activity and in Exceptional cases [low volume product]. The document requirements are same as prospective validation. The decision to carry out concurrent validation must be justified, documented approved by authorized person. This validation involves in process monitoring of critical processing steps and product testing, this helps to generate the document evidence to show that the production process is in a state control.

Retrospective validation

This type of validation is acceptable only for well-established processes, without any change in the composition of the product, operating procedures, Equipment. The source of data for this type of validation may be include batch documents Process control chart, maintenance logbooks, process capability studies, Finished product data, including trend data and stability data. Batches selected for retrospective validation should be representative of all batches made during the review period including any batches that fail to meet the specification. The data generated from 10 to 30 batches should be examined to assess process consistency

Revalidation

Revalidation provides the evidence that changes in a process-introduced intentionally/unintentionally; do not adversely affect process characteristics and product quality. Revalidation may be required in following cases: Change in formulation, procedure or quality of pharmaceuticals ingredients, change in equipment, addition of new equipment and major breakdown [Maintenance which affect the performance of the equipment].Major change of process parameters, change in site, batch size change.

Elements of Process Validation[1,2]

Process validation involves a series of activities taking place over the lifecycle of the product and process. All the activities of the process validation were divided into three stages,

- Process Design
- Process Qualification
- Continued Proces Verification

Product Lifecycle View[1,2]

Stage 1: Process Design

Defining the commercial process based on development & scale-up experience. Creating a design space for each significant process unit operation – ideal situation Process design involves two important phases:
1) Building and capturing process knowledge and understanding,
2) Establishing a strategy for process control, which may or may not incorporate PAT principles

The process design stage delivers the planned commercial production and control records, which contain the operational limits and overall strategy for process control, which should be carried forward to the next stage for confirmation.

Stage 2: Process Qualification

Confirming that the process design is capable of reproducible commercial manufacturing. This has two elements: 1) Design of the facility and qualification of the equipment and utilities. Reference is made to the science and risk-based ASTM E2500 standard on equipment and facility verification 2) Process Performance Qualification (PPQ) The new document states: "The approach to PPQ should be based on sound science and the manufacturer's overall level of product and process understanding."

Stage 3: Continued Process Verification

Having confirmed that the process design is capable of reproducible commercial manufacture, the manufacturer must continually assure that the process remains in a state of control throughout commercial manufacture. Thus "An ongoing programme to collect and analyse product and process data that relate to product quality must be established". The Guidance goes on to say that "The data should be statistically trended and reviewed by trained personnel. The information collected should verify that the quality attributes are being appropriately controlled throughout the process".

Figure: Process design studies should follow ICH Q8 (R1) Pharmaceutical Development, Q10 Pharmaceutical Quality System; Multivariate studies of interrelationships between critical process parameters (CPPs), cGMP for processes impacting on drug safety and needed Good documentation practices. These studies consider effect of commercial-scale equipment, other sources of variation and control all unit operations, including high risk manufacturing procedures. Process Qualification starts with the documentation and approval of the clearly defined processes and controls, Operational limits and ranges and Specifications for in-process intermediates and final product. It involves technology transfer from development scale to the production scale and uses commercial production and control documentation. The objective is to generate scientific evidence that the process is capable of making product that can consistently meet quality acceptance criteria. Continued Process Verification is to ensure that the process remains in a state of control, it complies strictly with the master batch record, operates under cGMP and it must have a

written plan. At the early stages, higher level of monitoring, sampling, and testing will continue until significant process variability estimates can be made. It requires examination of many sources of data and the change may be needed to prevent the process from drifting out of control.

PHASES OF PROCESS VALIDATION[3]:

The goals of the process validation can be pursued in three stages,

Pre-Validation Phase:

Developing an understanding regarding the functional relationships between parameters (material and process) and quality attributes. 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.

Process Validation Phase

Process validation phase (Process Qualification phase) designed to verify that all established limits of the critical process parameters are valid and that satisfactory products can be produced even under the "worst case" conditions

Validation Maintenance Phase

Validation Maintenance phase requiring 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. This phase is for monitoring and improving control and reducing product and process variation. This

Documentation [3,6]

The main objective of documentation is to establish, monitor and record "Quality" for all aspects of Good Laboratory Practices and Quality Control". Documentation system should provide for a periodic review & revision if necessary, and such revised versions shall also be approved by the authorized persons. The most important documents in the pharmaceutical industry considering validation are the SOP (Standard operating procedure), Validation Master Plan and Validation Protocol

SOP (Standard Operating Procedure) [2,5]

Standard Operating Procedures (SOPs) are issued to specifically instruct employees in areas of responsibility, work instructions, appropriate specifications and required 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 eg., the laboratory operations involving the receipt of reagents, standards, preparation of reagents, labeling and storage, test procedures, reference material, identification, handling, storage and use deviations, errors.

Even the details of the equipments and their maintenance were also involved.

Validation Master Plan[6]

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 master plan should provide an overview of the entire validation operation, its organizational structure, its content and planning. The main elements of its being the list/ inventory of the items to, relevant to product and process controls within a firm should be included in the validation master plan. It even holds the calibration and qualification of equipments, summary and conditions of Validation Protocol.

Validation Protocol

A written plan of actions stating how process validation will be conducted, it will specify who will conduct the various tasks and define testing parameters, sampling plans, testing methods and specifications, will specify product characteristics, and equipment to be used. It must be specify the minimum number of batches to be used for validation studies, it must specify the acceptance criteria and who will sign \ approve \ disapprove the conclusions derived from such a scientific study. The validation protocol should contain the following elements,

- Short description of the process.
- Summary of critical processing steps to be investigated.
- In process, finished product specification for release.
- Sampling plans.
- Departmental responsibility.
- Proposed timetable.
- Approval of protocol.

Responsible authorities for validation[8,10]

The validation working party is convened to define, investigate, progress, collate, co-ordinate and ultimately approve the entire effort, including all of the documentation generated. The working part would usually involve the following staff members Production manager, Head of Quality Control (Manager), Executive-QC, Head of Engineering (Manager), Production executive, Validation Executive, Validation Manager, Head of Quality Assurance (Manager).

Selection of Critical Steps and Parameters for Process Validation

Granulation

It is the process of collecting particles by creating bonds between them. It is most critical step in tablet manufacturing as virtually all tablet characteristics like flow, weight variation, hardness, disintegration, and dissolution etc. depend on the granulation parameters. The granulation variables that need be controlled are;

- **Mixing speed**
- **Granulation time**
- **Feed rate**
- **Amount of binder solution and its concentration**

By controlling the above parameters, one can control the granule strength (fines) and density of granules, there by having a more smooth compression process. Another important aspects is the granulator used, because high shear-granulators like RMG, Iodize mixer produces denser granules compared to low shear granulators like FBG, their by questioning their suitability for fast-release preparation.

Drying

This step involves drying of wet mass. Moisture content in granules is an important factor, which has bearing on tablet characteristics. Hence to control moisture content, critical process variables like inlet temperature, drying time are to be monitored and controlled, if the moisture content is less (over dried granules). It produces fines upon milling, which in turn causes weight variation, capping and chipping. Drying time needs to be controlled, because shorter drying period results in granules having entrapped moisture, which during compression escapes from the granules having entrapped moisture, which during compression escapes from the granules and causes the granules to stick to punches (case hardening) where as longer drying period produces friable granules.

Blending

It involves mixing of granules with other blending materials. The purpose of blending is to get uniform distribution of drug, appoint that becomes critical for low dose products like tablet and to impart good flow and anti adhesion property to the blend. Here the critical controlling variable is the mixing time, as under blending will result in segregation of blend and increase in disintegration time due to coating of the granules with low melting lubricants like stearates. Hence content uniformity testing of drug is to be done at periodic intervals.

Compression

The major variables affecting the compression process are machine speed and compression force. Variation in the machine speed leads to varied die fill volume hence varied tablet weight. Compression force needs to be controlled as it affects the tablet hardness, thickness, and disintegration time and dissolution rate. Another controlling aspect is the machine vibration as excess vibration lead to segregation of blend in the hopper and altering the uniform distribution of the drug in the tablets.

Blister packing

This process involves packing in polyethylene lined aluminum foil and PVC blister pack. Temperature of rollers (sealing and forming) and speed of machine are critical variables. Adequate forming roller temperature is essential to get proper blister formation. Adequate sealing roller temperature is essential to get proper sealing. Less temperature will leaf to leakage and higher temperature will result in burning or spoilage of aluminum foil and PVC. Leak test and physical evaluation are carried out to

establish the above variables during blister packing operation.

Different Process Validation Parameters involved in the manufacturing is shown in table 1.

Control Parameter

In spite of the method we select for tableting we have some parameters which are to be considered during the process. These parameters were measured or estimated for process validation of the method. The parameters are: Process validation is generally done with three consecutive batches. All the critical parameters were evaluated for fixing the optimum process parameters. Every processing step is validated for all the three batches and the results obtained must be present within the acceptance criteria, such that the product can be forwarded for the commercial production. All the problems that arise during validation are overcome and the product will be kept ready for the commercial batch production.

Sample Thief

A significant improvement in sampling can be achieved with the use of sample thief, sometimes known as a grain thief of historical reasons. This device consists of 2 tubes one fitting tightly inside the other and with along holes cut through the tubes in corresponding positions. One end of the outer tube fitted to a point to facilitate is insertion in to a bulk powder the sampling procedure consists of rotating the inner tube to close the holes, inserting the device into the powder, rotating the inner tube to open the holes, allowing the powder to enter the device, rotating the inner tube once more to close the wholes and finally removing the thief from the bulk powder wholes and finally removing the thief from the bulk powder The thief sampling is better method than merely scoping off it is still an inferior technique the top of a bulk powder Even through most thieves have relatively sharp ends; the very act of plunging the thief through the bulk powder must perturb the sample to some degree. A compression force of the thief as propagates ahead it is pressed into the bulk thus potentially of the bulk changing the strata and alteringthe wall of powder at the outer walls of the thief. Furthermore, because large particles will flow more easily than will small particles, an opened thief is liable to be filled preferentially with the coarse fraction of the particle distribution

Working procedure by sample Thief

The sleeve rotates so that the interior compartment is isolated from the bulk powder, while in the closed position, the thief is plunged into the central mass of the powder. Once the thief is at the desired position, the unit is rotated so that the interior compartment is now exposed to bulk powder. Powder flows into the thief compartment of its own accord. Once the interior compartment of the thief is filled, the sleeve of the thief is rotated so that the interior compartment is again isolated from the bulk powder. The thief is then withdrawn from the powder, and the sample is analyzed.

Sampling Plan and Acceptance Criteria

It is the responsibility of the manufacturer to ensure that the sampling plan and acceptance criteria defined are adequate to ascertain that the manufacturing process is well-controlled and robust to produce drug product consistently meeting specifications. The following sampling plan and acceptance criteria provide a guide for the process validation of a typical solid oral dosage manufacturing process with medium risk indication. Other sampling plans may be acceptable if they are statistically sound and justified. The extent of sampling, tests and acceptance must take into consideration, the level of risk, e.g. the equipment type and capacity, to patient health of the drug product and should be considered on a case-by-case basis. The finished product specifications have to be adequately justified and the analytical methods have to be validated as per the ASEAN Guidelines for Validation of Analytical Procedures.

Sampling Plan and Acceptance Criteria is shown in table 2.

The validation report

A written report should be available after completion of the validation. If found acceptable, it should be approved and authorized (signed and dated) the report should include at least the following,

1. Title and objective of study 2.Reference to protocol
3. Details of material
4. Equipment
5. Programs and cycles used 6.Details of procedures and test methods
7. Result (compared with acceptance criteria), and 8.Recommendations on the limit and criteria to be applied on future basis.

Conclusion

Process validation is an integral part of among all validation like equipment validation, cleaning validation, vender validation etc. Validation is art step of assure to identity, strength, purity, safty, and efficacy of pharmaceutical product. Applicable and critical parameter for validation process of solid dosage form must be consider to fulfills the requirement of quality assurance of final product.

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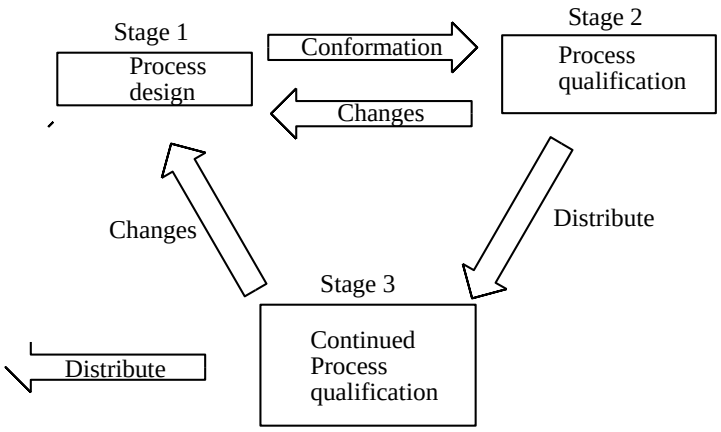

Fig.1: Stages of process validation.

Table 1: Different Process Validation Parameters involved in the manufacturing.

S. No	Process step	Control Variables(monitor)	Measured responses(test)
1	Pre-blending	Blending time, RPM, Load Size, Order of addition	Blend Uniformity
2	Granulation	Mixing speeds, Amount of granulation fluid, Feed rate, Granulation time, Load.	Drug distribution, Water/solvent Content, Appearance (size).Particle size distribution.
3	Drying	Initial temperature ,Outlet temperature ,Drying temperature Drying time	Densities ,Loss on drying, Assay (for heat sensitive)
4	Milling	Screen size, Milling speed, Feed rate. Loose/tapped densities.	Materials). Particle size, distribution/shape,
5	Lubrication	Blending time, Blender speed, Load size.	Particle size distribution, Loose/tapped densities, Flow properties.
6	Tableting	Compression rate, Granule feed rate, Pre compression force Compression force.	Appearance, Weight variation, Hardness/friability, Thickness, Moisture content, Disintegration/dissolution, Assay/dose uniformity.
7	Coating	Pan load, Inlet/exhaust temperatures , Inlet/exhaust humidity's Pan speed, Atomizing pressure ,Spray rate	Percent weight gain, Thickness, Dissolution, Assay, Degradation level, Residual solvent, Dissolution.

Table 2: Sampling Plan and Acceptance Criteria.

Stage	Sampling Plan	Test	Acceptance Criteria
Drying	At least 3 samples from at least three different locations or time points throughout the oven chamber or drying process (1).	Loss on drying (LOD) – analyze one sample per location	Based on production specification for LOD
Final Blend / Mix	At least 3 samples from at least ten different locations evenly distributed throughout the mixer(1) *(Twenty locations for convective blender)* Composite sample (may be performed as part of release testing)	Blend / Mix uniformity (Assay) – analyze one sample per location	Stage 1 Individual results: Mean ± 10% (absolute) All individual results: RSD ≤ 5.0%
		If required, Flowability Density Appearance	In-house
Tabletting	Stratified sampling	Uniformity Any other internal specifications, if required	Uniformity: As per compendia Others: Compendia / In-house
	Composite sample (may be performed as part of release testing	Visual inspection Uniformity Assay Friability Hardness Disintegration Dimension Dissolution Impurities	Uniformity: As per compendia MLT: As per compendial MLT method Others: Compendia / In-house

Stage	Sampling Plan	Test	Acceptance Criteria
Coating	1 sampling from each coating pan	Assay (for coating of active only) Moisture content / residual solvent	Assay: In-house Moisture / solvent: ICH guidelines
Printing	Stratified sampling	Visual inspection	In-house
Primary packaging (may be performed as part of equipment qualification	Stratified sampling	Visual inspection CCS integrity test, if required	In-house
Environmental Monitoring (Applicable for heat	Throughout the manufacturing process	Temperature Relative humidity	In-house

Where; RSD denotes Relative Standard Deviation; ICH denotes International Conference on Harmonisation; MLT denotes Microbial Limit Test; CCS denotes Container Closure System.

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