The concept of process validation in tablet manufacturing: Review

Sindur Nag N, Gouthami B, Madhuri L, Lavanya reddy V, Krishnaveni N, Meyyanathan S, Suresh B
Department of Pharmaceutical Analysis, JSS College of Pharmacy, (Off Campus) - JSS University, Mysore 57001, India.
Vice-chancellor, JSS University, Mysore, Karnataka, India

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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. Quality is always an imperative prerequisite when we consider any product. Therefore, drugs must be manufactured to the highest quality levels. End-product testing by itself does not guarantee the quality of the product. Every step of the manufacturing procedure should be validated. Process Validation performs this task to build the quality into the product. According to ISO 9000:2000, Process Validation had proven to be an important tool for quality management of pharmaceuticals.

Key words: Process validation, Quality management, manufacturing procedure.

INTRODUCTION
Pharmaceutical industry has grown in leaps and bounds during the last three to four decades. Initial emphasis on validation started across the industry globally sometime in late sixties or early seventies. In the initial years it was only massive testing of a large number of samples to establish that the process has yielded a product meeting the specifications. Indirectly it was thus concluded that the process was under control. Soon it was realized that this is not the right scientific approach. Soon emerged several regulatory guidelines and publications on validation and today for the pharmaceutical industry successful validation is a pre-requisite.

Process Validation: “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 through production, which establishes scientific evidence that a process is capable of consistently delivering quality products”. 1

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. 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 comprise a mixture of active substances and excipients, usually in powder form, pressed or compacted into a solid. The excipients can include binders, glidants (flow aids) and lubricants to ensure efficient tableting; 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 need to be demonstrated to meet the various regulatory, technical requirements of cGMP expectations to achieve good quality of medicines throughout the global.

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 Process Verification

Product Lifecycle View:
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

Stage 2: Process Qualification
- Confirming that the process design is capable of reproducible commercial manufacturing

Stage 3: Continued Process Verification
- Gaining ongoing assurance during routine production that the process remains in control.
Phases of Process Validation:

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**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:**
Designed to verify that all established limits of the critical process parameters are valid and that satisfactory products can be produced.

**Validation Maintenance Phase:**
This phase is for monitoring and improving control and reducing product and process variation. This requires frequent review of all the process related documents, including validation audit reports to assure that there have been no changes, deviations, failures.

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**DOCUMENTATION:**

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**
- **Validation Protocol**

**SOP (Standard Operating Procedure):**

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 example, the laboratory operations involving the receipt of reagents, standards, preparation of reagents, labeling and storing, test procedures, reference material, identification, handling, storage and use deviations, errors. Even the details of the equipments and their maintenance were also involved.

The general format of the SOPs involves:

- **Title**
- **Code**
- **Objective**
- **Scope**
- **Definitions**
- **Description**
- **Safety**
- **Documentation**
- **Effective date, review date, version number.**

**Footer**: Prepared By, Reviewed By, Approved By, Authorized By.

**Validation Master Plan:**

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 be validated and the planning schedule. 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 even holds the Calibration and Qualification of Equipment, summary and conditions of Validation Protocol.

The format and content should include:

- **Objective**
- **Approach**
- **Scope & Justification**
- **Acceptance Criteria**
- **Support programs**
- **Organization**
- **Schedules**
- **Documentation formats.**

**Validation Protocol:**

A written plan stating how validation will be conducted is documented

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**Figure:**
Any stages can feed-back into a previous stage at any time

**Stage 1:** Process design

**Stage 2:** Process qualification

**Stage 3:** Continued Process verification

**Fig.1. Stages of process validation:**

Any stages can feed-back into a previous stage at any time.
including test parameters, product characteristics, production and packaging equipment, and decision points on what constitutes acceptable test results. This document should give details of critical steps of the manufacturing process that should be measured, the allowable range of variability and the manner in which the system will be tested. The validation protocol provides a synopsis of what is hoped to be accomplished. The protocol should list the selected process and control parameters, state the number of batches to be included in the study, and specify how the data, once assembled, will be treated for relevance. The date of approval by the validation team should also be noted.

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

- Scope and Objective
- Validation team and their qualification
- Number and selection of batches
- List of all equipments used
- Critical processing parameters
- Sampling points, methods of sampling and sampling plans
- Statistical tools to be used in analysis
- Forms and charts to be used for documenting.

**Responsible authorities for validation:**

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)

**Responsibilities of authorities:**

In the old guidelines the qualifications like design qualification, installation qualification, operational qualifications and performance qualifications were included, where these were not the part of new guidelines. In new guidelines the whole is referred to as just equipment qualification.

There had been too many objections to the previous Performance Qualification version, so that phase 2 of Process Qualification is divided into two areas viz., Design of Facilities & Qualification of equipment and Utilities, Process Performance Qualification.

The previous Guidance discussed in detail the revalidation which is performed in case of changes in raw materials, formulation etc. whereas in new guidance this is replaced with the Continued Process Verification which involves the ongoing assessments of the process.

The terms Prospective validation, Retrospective Validation, Concurrent Validation, Worst case, Critical process parameters were not in the part of new guidelines.

**Process parameters involved in Tablet manufacturing:**

The manufacture of oral solid dosage forms such as tablets is a complex multi-stage process under which the starting materials change their physical characteristics a number of times before the final dosage form is produced. Traditionally, tablets have been made by granulation, a process that imparts two primary requisites to formulate: compactibility and fluidity. Both wet granulation and dry granulation (slugging and roll compaction) are used. Regardless of whether tablets are made by direct compression or granulation, the first step, milling and mixing, is the same; subsequent step differ.

**Typical operations in wet granulation, dry granulation and direct compression:**

**Wet granulation:**

The unique portions of wet granulation process involve the wet massing of the powder, wet sizing or milling, and drying. The wet granulation technique employs a solution, suspension, or slurry containing a binder, which is usually added to the powder mixture; however the binder may be incorporated dry into the powder mix, and the liquid may be added by itself.

**Dry granulation:**

In the dry granulation method the granulation is formed not by adding a binder. Here, compacting large mass of the mixture and subsequently crushing and sizing these pieces into smaller granules takes place. The primary powder particles are aggregated under high pressure. There are two main processes. Either a large tablet (known as a slug) is produced in a heavy-duty tableting press (a process known as slugging) or the powder is squeezed between two rollers to produce a sheet of material (roller compaction).

**Direct compression:**

Some granule chemicals like potassium chloride, potassium iodide and ammonium chloride have special property that they are free flowing as well as cohesive in nature which enable them to be compressed directly in a tablet machine without any need for wet or dry granulation.

**Table 1: comparative study of the process parameters for different granulation processes.**

<table>
<thead>
<tr>
<th>Wet granulation</th>
<th>Dry granulation</th>
<th>Direct compression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milling and mixing of drugs and excipients</td>
<td>Milling and mixing of drugs and excipients</td>
<td>Milling and mixing of drugs and excipients</td>
</tr>
<tr>
<td>Preparation of binder solution</td>
<td>Compression into slugs or roll compaction</td>
<td>Compression of tablet</td>
</tr>
<tr>
<td>Wet massing by addition of binder solution or granulating solvent</td>
<td>Milling and screening of slugs and compacted powder</td>
<td></td>
</tr>
<tr>
<td>5. Drying of the wet granules</td>
<td>4. Mixing with lubricant and disintegrant</td>
<td></td>
</tr>
<tr>
<td>6. Screening of dry granules</td>
<td>5. Compression of tablet</td>
<td></td>
</tr>
<tr>
<td>7. Blending with lubricant and disintegrant to produce “running powder”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Compression of tablet</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2: Different Process Validation Parameters involved in the manufacturing of a tablet:**

<table>
<thead>
<tr>
<th>S. No</th>
<th>Process step</th>
<th>Control Variables (monitor)</th>
<th>Measured responses (test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pre-blending</td>
<td>Blending time, RPM, Load Size</td>
<td>Blend Uniformity</td>
</tr>
<tr>
<td>2</td>
<td>Granulation</td>
<td>Milling and mixing of drugs and excipients</td>
<td>Drug distribution, Water/solvent Content, Appearance (size),</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Granulation fluid, Feed rate, Granulation time, LOD,</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Drying</td>
<td>Initial temperature, Outlet temperature, Drying temperature, Drying time,</td>
<td>Particle size distribution, Density/Loss on drying, Assay (for heat sensitive materials)</td>
</tr>
<tr>
<td>4</td>
<td>Milling</td>
<td>Screen size, Milling speed, Feed rate,</td>
<td>Particle size distribution/shape, Loose/tapped densities,</td>
</tr>
<tr>
<td>5</td>
<td>Lubrication</td>
<td>Blending time, Blender speed, Load size.</td>
<td>Particle size distribution, Loose/tapped densities, Flow properties</td>
</tr>
<tr>
<td>6</td>
<td>Tabletting</td>
<td>Compression rate, Granule feed rate, Pre compression force, Compression force,</td>
<td>Appearance, Weight variation, Hardness/friability, Thickness, Moisture content, Dissolution/dissolution, Assay dose uniformity, Percent weight gain, Thickness, Dissolution, Assay, Dengradation level, Residual solvent, Dissolution</td>
</tr>
<tr>
<td>7</td>
<td>Coating</td>
<td>Pan load, inlet/exhaust temperatures, inlet/exhaust humidities, Pan speed, Atomizing pressure, Spray rate</td>
<td></td>
</tr>
</tbody>
</table>
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.

CONCLUSION:
Solid dosage form validation should be part of a comprehensive validation program within an industry. The multidisciplinary validation team must identify the product and process characteristics that must be studied and incorporate specific validation tests to ensure that the product will meet all quality, manufacturing, and regulatory requirements.

Finally, it can be concluded that Process validation is a key element in the quality assurance of pharmaceutical product as the end product testing is not sufficient to assure quality of finished product.

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