Review Article

Functional Overview of Process Validation of Tablets - A Critical Review

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ABSTRACT

Purpose: Validation is a main tool in achieving and maintaining the quality and safety of the final product as per cGMP(current Good Manufacturing Practice). The purpose of this present work is to give introduction, general overview and how to plan, develop, execute process validation of pharmaceutical manufacturing process especially tablet manufacturing process.

Approach: When we consider any product, quality is always an imperative pre requisite hence a highest quality levels must be included in the manufacturing of the drug.

Findings: To assure the identity, purity, safety, efficacy and also maintaining the quality of final product process validation is the key element. Three consecutive batches were considered to execute the process validation activity.

Conclusion: Process validation is a major requirement of cGMP's regulation. Process validation is a key element to maintain product quality, safety, identity and efficacy.

INTRODUCTION

Pharmaceutical process validation is a key element in assuring that these quality assurance goals are met. The concept of validation was first proposed by 2 food and drug Administration (FDA) officials, Ted Byer's and Bud Loftus, in the mid 1970's in order to improve the quality of pharmaceuticals. The goal of the validation is to ensure that quality is built into the system at every step, and not just tested at the end, this validation activities will commonly include training on production, material, operatingprocedure, people involved and monitoring of the system in production[1] .Validation itself does not improve process but confirms that the process have been properly developed and under control. Different agencies defined the validation as follows;

European Commission (EC):

Validation is defined as "Action providing in accordance with principles of GMP (Good Manufacturing Practice), that any procedure, process, equipment, material, activity orsystem actually lead to the expected results"[2].

World Health Organization (WHO) :

Validation is defined as "Action providing that any procedure, process, equipment, material, activity or system actually lead to the expected results[3].

USFDA:

USFDA defined process validation as "establishing documented evidence which provides high degree of assurance that a specific process will consistently produce a product meeting its pre determined specifications and quality characteristics"[4].

GOVERNMENT REGULATION:

Validation is considered to be integral part of cGMP's essentially worldwide, compliances with validation requirements is necessary for obtaining approval to manufacture and to introduce new products. The FDA's cGMP refer to the concepts of validation in both sections. They state that such control procedure shall be established to monitor output and to validate the performance of those manufacturing process that may be responsible for causing variability in the characteristics of in process materials and drug materials. The Accuracy, sensitivity, specificity and reproducibility of test methods employed by the firm shall be established and documented. A generally stated requirement for process validation is contained in the medicinal device GMP regulations. Where deviations from device specification could occur as result of manufacturing process itself. There shall be written procedures describing any process controls necessary to assure conformance to specification[5].

PERSONNEL FOR VALIDATION: The working party would usually include the following staff members,

1. Head of quality assurance.
2. Head of engineering.
3. Validation manager.
4. Production manger.
5. Head of quality control.
6. Specialist validation discipline: all areas[6].

NEED FOR VALIDATION:

When we consider any product quality is always an imperative prerequisite. Although it is mandatory from government and regulatory bodies but it is also a fact that quality of a pharmaceutical product cannot be adequately controlled solely by pharmacopoeia analysis of the final product.

Validation gives confident over the product manufacturing process. Validation gives assurance to the product quality as per customer requirements. Validation is mandatory as per regulatory requirements[7].

If validation is not done then following problems can occur, Process capability will be low, Scarp, rework will be more, Low capacity utilization, Cost of compliance will be high Risk of, Drug shortages, Releasing a poor quality products, Recalls, Delay in approval of new drugs,Quality problems confounding clinical trial data

So, as to minimize these problems we need to do validation[8].

BENEFITS OF PROCESS VALIDATION: Process validation has following benefits,

SL. NO.	BENEFITS
1	Fewer batch failures and may operate more efficiently with greater output.
2	Validation makes good business sense[9].
3	Reduction in rejections and reworks.
4	Reduction in utility cost.
5	Avoidance of capital expenditures.
6	Reduced testing process and finished goods.
7	More rapid and accurate investigation into process deviation.
8	Easier maintenance of equipment
9	Improve employee awareness of processes.
10	More rapid automation[10].

REASONS FOR PROCESS VALIDATION : The possible reason of performing process validation may include[11],

SL NO	Reasons for process validation
1	New product or existing product as per SUPAC changes.
2	Site of manufacturing changes.
3	Change in batch size.
4	Equipment changes.
5	Change in process existing products.
6	Change in the composition or components.
7	Change in critical control parameters.
8	If there is any change in vendor of API or excipients.
9	Change in specification on input material.
10	Abnormal trends in quality parameters of product through review during Annual Product Review(APR).

STRATEGY FOR PROCESS VALIDATION :

There are following strategy for process validation[12],

1. Identification of critical process variables and preparation of process flow charts.
2. Preparing process validation protocol.
3. Develop SOPs for executing the method routinely.
4. Monitoring process validation batches.
5. Doing in process testing during manufacturing.
6. Selection of three consecutive batches having same batch size and manufacturing formula.
7. The failure to meet the requirements of the validation protocol should be subjected to process revalidation following a thorough analysis of process data and formal discussion by the validation team.
8. Document the validation experiment and results in the validation report.
9. Documents like batch manufacturing record, in process and finished product specification, other related documents to BMR and specification, related SOPs and batch packing record all are necessary for process validation.

PRE-REQUISITES FOR SUCCESSFUL VALIDATION:

There are some elements or tools that are required for conducting effective validations. Each are presented and discussed in the following sections,

1. Understanding:

The important element required is a good understanding of what validation is. This understanding activity goes beyond the concept of "requiring a minimum of three runs" and understanding must be anchored by sufficient years of practice experience and knowledge.

2. Communication:

Communication is one of the best methods of improving environmental understanding. Communication is essential for any activity that requires more than one resource to complete. With this point we can understand that conducting effective validation involves multi-departments.

3. Co-operation and Focus:

Multiple departments that sometimes interact during the course of executing validation program are project management, accounting, quality control, project engineering, process engineering, quality assurance, facilities regulatory etc should have a commendable co-operation.

4. Experience:

Validation team should have experienced people to get success in their validation program.

5. Resources:

Resources mean personnel who will plan and execute equipment on which validations will be performed on materials with which to conduct validations. Laboratories that will perform necessary analysis should provide necessary funding for the validation and allocate sufficient time to perform validations[13].

6. Plan:

In most of the companies performing validation will involve number of departments. These departments need a perfect plan in order to get good team synergy.

7. Budget:

It is important to understand that validation cost money. Validation should not be limited by the budget for successful completion of validation[14].

8. Quality Control lab support:

In most of the validations, some laboratory testing will be required. In most cases this testing is handled by the QC group. QC is expected to provide results in timely manner.

TYPES OF VALIDATION :

1. PROCESS VALIDATION:

As per (1987), process validation is establishing documented evidence which provides a high degree of assurance that a specified process will consistently produce meeting its predetermined

specification and quality characteristics. Effective process validation contributes significantly assuring drug quality.

It includes;

A. Prospective validation

B. Concurrent validation

C. Retrospective validation

D. Revalidation

2. Equipment qualification:

Equipment validation involves qualifying the design, installation, operation, instrumentation, control system and performance of the equipment. The pharmaceutical companies offer a wide range of equipment validation services whether it is in laboratory or in manufacturing area. Equipment validation helps us to:

- Identify the risk associated with the process, equipment and materials.
- Assess the impact of failure.

3. Facility validation:

Facility validation should include planning, documentation, construction and testing to design specifications and cGMP requirements. Facility validation can be a tool for enhancing reliability, cost and quality.

4. Service validation:

This involves qualification activities like:

- Environmental control system e.g. HVAC, AHU.
- Water storage and distribution system.
- Compresses air system.
- Steam distribution system etc.

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 ensure that all residues are removed to predetermined levels to ensure the quality of the next product to be manufactured. It involves the cleaning procedure , so as to give a high degree of assurance that the given cleaning process results in equipment/area having product contamination below the acceptable level.

6. Analytical method validation:

Analytical method validation is just one type of validation required during drug development and manufacturing. It involves evaluation of product quality attributes through testing to demonstrate reliability is being maintained through the life cycle and that the precision, accuracy, specificity, LOD, LOQ, linearity, selectivity have not been compromised. The analytical method details the 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 etc.

7. Vendor validation:

It involves the qualification of the vendor who provides the active material and the excipients required for formulation by conducting audits.

8. Computer system validation:

Computer validation encompasses computers, which directly control process or system or collect analytical data. Computer validation includes the qualification of all software and hardware, where has an impact, direct or indirect, on the quality of a product. The validation approach to programmable logic controller(PLC) is similar, both to one another and to the general overall approach top validation, in that the end user should define each requirement[15].

PROCESS VALIDATION HAS 4 TYPES :

1. Prospective validation:

In prospective validation the validation protocol is executed before the processes put into the commercial use. During the product development stage 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 finished product.

2. Concurrent validation:

It is similar to prospective, except the operating firm will sell the product during the qualification runs , to the public as its market price. This validation in process monitoring of critical processing documented evidence to show that production process is in its state of control.

3. Retrospective validation

In this historical data is taken from the records of completed production batches are used to provide the documented evidence that the process as been in ,state of control prior to request for such evidence.

4. Revalidation

It's the repetition of validation process or part of it. This is carried out when there is any change or replacement in formulation , a equipment plan or site, location, batch size and in the case of sequential batches that do not meet product specifications and is also carried out at specific time intervals in case of no changes[5].

STAGES OF PROCESS VALIDATION :

There are three stages of validation they are,

Stage 1:-process design or pre-qualification:

The commercial process is defined during this stage based on the knowledge gained through development and scale up activities.

Stage 2:-process qualification:

During this stage, the process design is confirmed as being capable of reproducible commercial manufacturing.

Stage 3:-continued process verification:

Ongoing assurance is gained during routine production that the process remains in a state of control. Tablets are comprises of mixture of active ingredients and excipients which are compressed or molded into a cylinder or biconvex solid. The principle objective of this dosage form is to achieve a predictable therapeutic response to a drug which include into a formulation which is capable of large scale manufacturing with reproducible product quality. Their cost is lowest of all the oral dosage forms. They are lightest and compact of all oral dosage form[16, 17].

PHASES OF PROCESS VALIDATION :

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

Phase 1:-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 form.

Phase 2 :-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.

Phase 3 :-validation maintenance phase:

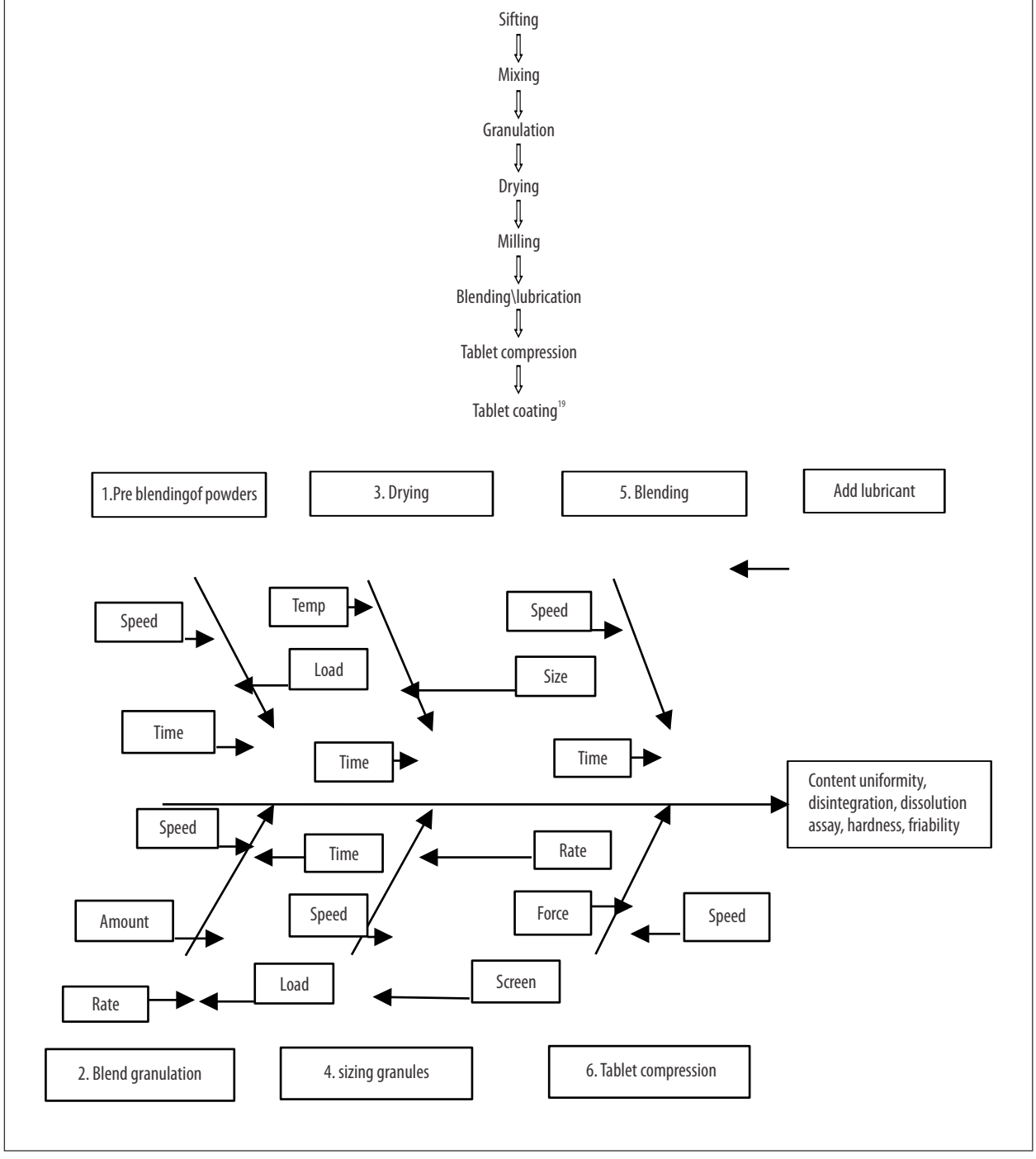
Validation maintenance phase requiring frequent review of all process related documents, including validation audit reports to assure that there have been no changes, deviation, failure, modifications to the production process, and that all SOPs have been followed, including change control procedures. This phase is for monitoring and improving control and reducing product and process variation.

EVALUATION AND SELECTION OF PROCESS CONTROL VARIABLES

Following unit operations should be needed to determine during the manufacturing of tablets and steps involved.

Process description: manufacturing of tablets includes the following processes;

Figure 2: Decision tree for processing steps and respective in process variables during tablet manufacture.



Mixing or Blending:

The mixing or blending unit operation may occur once or several times during the tablets manufacture. For example, a direct compression formulation may involve one blending step in which the drug and the excipients are blending together prior to compression. A wet granulation formulation may require two mixing\blending steps:

Prior to granulation to have a uniform drug\excipients mixture

⇩

After milling the dried granulation to add other excipients, such as the lubricant

The following physical properties of the drug and excipients are factors in creating a uniform mix or blend:

Bulk density

⇩

Particle size distribution

⇩

Surface area

Mixing or blending operation parameters to be considered during development and validation are:

Mixing or blending technique

⇩

Mixing or blending speed\time

⇩

Drug uniformity

⇩

Lubrication

⇩

Distribution of colorant

⇩

Equipment capacity\load[20]

Wet granulation: The type of granulation technique to be used is to decided, on the basis of low shear (e.g., Hobart), high shear (e.g., Diosna, GEI-Collette) or fluid bed (e.g., Glatt, Fluid Air). Each technique will produce granules with different physical properties and will require monitoring of different processing parameters as listed below:

Wet massing: The following factors should be considered to get uniform wet mass

during wet massing

Binder addition

⇩

Binder concentration

⇩

Amount of binder solution\granulation solvent

⇩

Binder solution\granulation solvent addition rate

⇩

Mixing time

⇩

Granulation end point

Drying: The following factors should be considered during drying

Inlet\outlet temperature

⇩

Air flow

⇩

Moisture uniformity

⇩

Equipment capacity\capability

Dry milling: The following factors should be considered during dry milling

Mill type

⇩

Screen size

⇩

Mill speed

⇩

Feed rate

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 and compression properties. Compression process parameters to be considered during development and validation are:

Tooling

⇩

Compression speed

⇩

Compression\ejection force

The following in process tests (as discussed above) should be examined during the compression stage:

Appearance

⇩

Hardness

⇩

Friability

⇩

Disintegration

⇩

Weight uniformity

Tablet coating: A basic understanding of surface chemistry and rheology two primary sciences of liquid flow and solid-liquid interaction is necessary for understanding coating and printing processes materials. A generally qualitative treatment of these subjects will suffice to provide the insight needed to use and apply coating and inks and to solve the problems associated with their use, of pan coating. Tablet coating process parameters to be considered during development and validation are:

Pan load

⇩

Inlet\exhaust temperature\humidity

⇩

Pan speed

⇩

Spray nozzle size

⇩

Atomizing pressure

⇩

Spray rate

⇩

Spray angle

⇩

Gun to bed distance

⇩

Tablets core characteristics[21, 22]

IN-PROCESS TEST

Moisture content of dried granulation:

Loss of drying (LOD) can be used to determine whether or not the granulation solvent has been removed to sufficient level during the drying

Granulation particle size distribution:

An extremely important parameter that can affect tablets compressibility, hardness, thickness and content uniformity. This parameter which can be done by sieve analysis, which should be monitored throughout the tablets validation process.

Blend uniformity:

Samples of the blend are taken and analyzed to ensure that the drug is uniformly dispersed throughout the tablets blend. The proper blend time must be established so that the blend is not under or over mixed. The sampling technique is critical for this test to be valid.

Individual tablets weight:

The weight of individual tablets is determined throughout compression to ensure the material is flowing properly and the equipment is working consistently. The individual weight should be within 5% of nominal weight.

Tablets hardness:

Tablets hardness is determined periodically

throughout the batch to ensure that the tablets are robust enough for coating, packing and shipping and not too hard to affect dissolution.

Tablet thickness:

Tablets thickness is also determined periodically throughout the batch and is indirectly related to the hardness. It is another indication whether or not the formulation has proper flow and compression properties.

Disintegration:

Disintegration is determined during the manufacture as a predictor of tablets[23].

FINISHED PRODUCT TESTS

Appearance:

The tablets should be examined for such problems as tablets mottling, picking of the monogram, tablets filming and capping of the tablets. If the tablets are colored, the color quality needs to be examined.

Assay:

This test will determine whether or not the product contains the labeled amount of drug.

Content uniformity:

Samples are taken across the batch profile (top, middle, bottom) and analyzed to ensure that the dosage form comply with the standards. It will indicate whether there is improper mixing during the manufacturing operation (i.e., segregation during flow of granulation from a storage bin).

Tablets hardness:

A critical parameter for dosage form handling and performance.

Tablets friability:

Friability is an important characteristics on the tablets ability to withstand chipping, cracking or dusting during the packing operations and shipping.

Dissolution:

Dissolution is important to ensure proper drug release characteristics (in vitro availability) and batch to batch uniformity.

These key test parameters are the yardsticks by which the major processing variables in solid dosage form are evaluated[24].

CONCLUSION

From the review validation data on overview of process validation of tablets it can be stated that the process validation is a major requirement of cGMP's regulation. Process validation is a key element to maintain product quality, safety, identity and efficacy.

In manufacturing of tablets all the process steps should be validated according to the protocol prepared by the validation team. One has to select three consecutive batches for the execution of process validation. Sampling has to be done and the samples are sent to quality control department for analysis to ensure that the dosage form comply with the standards\specifications. Process validation builds quality into the product as it is an important tool for quality management of pharmaceutics.

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