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Process Validation of Tablets

[1]Ayushman Shukla[*], [2]Parul Bisht*, [3] Dr. Shivanand Patil
[1]Student, [2]Assistant Professor, [3]HOD of Department
Department of Pharmaceutical Sciences, Shree Dev Bhoomi Institute of Education Science and Technology, Dehradun, Uttarakhand

Abstract:
To survive in competitive market and to be successful, it is necessary to achieve high level of product quality Validation is one of the important steps in achieving and maintaining the quality of the final product batch after batch. Without equipment, we cannot manufacture a product. By validating each step of production process we can assure that the final product is of best quality. This review provides information on objectives and benefits of process validation, types of process validation, major phases in validation and regulatory aspects.
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I. INTRODUCTION

Validation is a systematic approach to identifying, measuring, evaluating, documenting and re-evaluating a series of critical step, in the manufacturing process that requires control to ensure a reproducible final product. It has become a necessary step to ensure better quality of medicinal product, throughout manufacturing, storage, handling and distribution. Quality cannot be inspected or tested into finished product. Thereby each step must be controlled to maximize probability that finished products meet all specifications. 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 Standards.[1] Process Validation has now become a part of Current Good Manufacturing Practices Regulations (cGMP), it is mandatory for manufacturers to go through Process Validation much more rigorously than earlier. Process Validation ensures improved levels of quality which intern is bound to lead to reduced production costs by way of prevention of product failures. Thus Process validation also can be seen as a sound business proposition. By careful design and validation of both the process and process controls that a manufacturer can establish a high degree of confidence that all manufactured units from successive lots will be acceptable. Successfully validating a process may reduce the dependence upon intensive in-process and finished product testing. The FDA Guidelines on General Principles of Process Validation defines process validation as- "establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics "According to EMEA, "Process validation can be defined as documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medical product meeting its predetermined specifications and quality attributes" [2] Considering the case of tablets, Tablets may be swallowed whole or being chewed. Some are dissolved or dispersed in water before administration. Some are put in oral cavity, where the active ingredient is liberated at a predetermined rate. Implants or passeries may also be presented in form of tablet. Tablet may vary in shape and differ greatly in size and weight depending on the amount of medicinal substance and the intended mode of administration.[3]

Objectives of process validation –
• To introduce software verification and validation and to discuss the distinction between them.
• To describe the program inspection process and its role in V & V.
• To explain static analysis as a verification technique.
• To describe the Clean room software development process.[4]

Importance of process validation –
• Government regulation
• Rapid automation
• Improved employee awareness
• Easier maintenance of equipments
• Increased output

• Reduction in quality cost
• Less failures of process thus less complaints
• Process optimization[5]

Types of process validation –

Prospective Validation :

I. Establishing documented evidence prior to process implementation that a system does what it proposed to do based on preplanned protocols.
II. This approach to validation is normally undertaken whenever the process for a new formula (or within a new facility) must be validated before routine pharmaceutical production commences.
III. Validation of a process by this approach often leads to transfer of the manufacturing process from the development function to production.[6]

Retrospective Validation :

I. Retrospective validation is used for facilities, processes, and process controls in operation use that have not undergone a formally documented validation process.
II. Validation of these facilities, processes, and process controls is possible using historical data to provide the necessary documentary evidence that the process is doing what it is believed to do.
III. This type of validation is only acceptable for well-established processes and will be inappropriate where there have been recent changes in the composition of product, operating processes, or equipment.

Concurrent Validation :

I. Concurrent validation is used for establishing documented evidence that a facility and processes do what they purport to do, based on information generated during actual imputation of the process.
II. This approach involves monitoring of critical processing steps and end product testing of current production, to show that the manufacturing process is in a state of control.

Revalidation :

I. Revalidation means repeating the original validation effort or any part of it, and includes investigative review of existing performance data.
II. This approach is essential to maintain the validated status of the plant, equipment, manufacturing processes and computer systems. [7]

Strategy for industrial process validation of solid dosage forms –

The following points gives strategy for process validation:
• The use of different lots of raw materials should be included. i.e., active drug substance and major excipients.
• Batches should be run in succession and on different days and shifts.
• Batches should be manufactured in the equipment and facilities designated for eventual commercial production.
• Critical process variables should be set within their operating ranges and should not exceed their upper and lower control limits during process operation. Output responses should be well within finished product specifications.[8]

Process :

1.Dispensing
2.Sifting
3.Granulation
4.Drying and sizing
5.Lubrication, Compression
6.In process checking, packing, final product analysis and release [9]

Process Overview :

Dispensing :

I. Ensure dispensing booth is clean and line check is given as per Standard operating procedure.
II. Ensure that balance is not due for calibrated. Check for zero error in the balance.
III. Check and ensure that the expire date of product to be released is later than that of batch expiry date.
IV. Check and ensure that the all materials are issued as per Batch Processing Report.

Sifting :

I. Check and record the temperature and relative humidity in processing area i.e. 25 ±20° C & RH 45±5%.
II. Check and ensure visually all the equipment and equipment parts are cleaned.
III. Check and record the integrity of the sieves before and after sifting through out the processing activity.

Granulation :

I. Add and dissolve ingredient into vessel.
II. Add the other ingredients into mixer and mix for 5 minutes using impeller at slow speed.
III. Collect, samples at 3,5 and 7 minutes at 5 different places and analyze it for uniformity in content.
IV. Add granulating solution and homogenize at slow speed for about 10 minutes.
V. Check the Loss of drying in the wet granules.

Drying and sizing :

I. Check and ensure the integrity of the Fluidized bed drying bag.
II. Initially dry the wet granules with air for 10 minutes.
III. Check the Loss of drying of granules; it should not be not more than 1% at 70°C for 15 minutes.
IV. Check and ensure the dried granules are not stored above 25°C before the milling is started.

V. Check and ensure the integrity of the sieves before and after sieving.
VI. Pass the granules through 16 mm mesh sieve, break the oversize granules using mill fitted with 2mm screen.
VII. Collect the granules and analyse their flow properties
VIII. Check the weight of sifted and dried granules.

Lubrications :

I. Perform the pre mixing and final mixing as per Batch process report instruction

II. During the final mixing before i.e., before adding the remaining quantity of the lubricant mix for 15 minutes.

III. Collects sample at 5,10,15 minute's intervals form top, middle, bottom and

IV. Composite and subject it to analysis for assay.

V. After adding the remaining quantity of lubricant mix for 5 minutes.

VI. Collects sample at 3,5,7 minutes interval form top, middle, bottom and composite and subject it to analysis for assay and content uniformity.

VII. Check the weight of the final blend and record.

Compression :

I. Check and ensure the temperature and relative humidity of the compression room is not more than 25°C and Relative Humidity not more than 50%.

II. Check and ensure the compression machine is cleaned.

III. Collect 40 tablets and inspect for Appearance, weight, thickness, friability and hardness every 1 hour.

IV. Tablets weight variation shall be XX mg. hardness shall be (IP) kg/cm2 , thickness.

V. Collect 40 tablets by "Bracketign" i.e. by increasing this speed of the compression machine form the target speed and by reducing from the targeted speed.

VI. Collect 10 tablets during initial, middle and end of the compression process and subjective it to analysis for content uniformity and perform the assay also.

Coating :

I. Check and ensure the coating pan and other equipment's are cleaned.

II. Check and ensure that the tablets is deducted, the speed of the coating pan inlet and exhaust air temperature, spray rate, spray type, temperature of the coating solution.

III. After coating is completed, samples are collected for dissolution testing and weight variation.

Labelling and packing:

I. Check and record the temperature air the heating roller and sealing roller Check and record that the over printing instructions on labels and cartons.

II. Check and verify that price overprinted on label and carton is as per current price list.

III. After ensuring the proper labeling of tablets, check, for correctness of cartons packing for the same.

Finished product analysis and release :

Finished product needs to be analyzed as per in-house specification product released only after predetermined specifications and quality attributes. Needs to be released only after pre-determined specifications As a means of providing a broad overview of these validation criteria, the following checklist/guideline.[10]

Process validation of tablets :

A tablet is a most known solid pharmaceutical dosages form and comprises of a mixture of active substances and suitable excipients. Binders, glidants, lubricants etc are some the popularly used excipients in the tablets. The excipients are used for different purposes in the tabletting; like disintegrants used to enhance the breakdown, glidants used to increase the flow of the powder, flavouring agents to impart different flavours in the tablets. The knowledge of stepwise manufacturing process of any dosages form is a must for validating any process. It helps in determining the
critical areas which need special consideration in terms of causing problems during the process.[11]

Drying :

The type of drying technique (e.g., tray, fluid bed, and microwave) required for the formulation needs to be determined and justified. The type of technique may be dependent on such factors as drug or formulation properties and equipment availability. Changing dryer techniques could affect such tablet properties as hardness, disintegration, dissolution, and stability.

The optimal moisture content of the dried granulation needs to be determined.

i. High moisture content can result in

a) Tablet picking or sticking to tablet punch surfaces and

b) Poor chemical stability as a result of hydrolysis.

ii. An over dried granulation could result in poor hardness and friability.[12]

Dry milling :
The milling operation will reduce the particle size of the dried granulation. The resultant particle size distribution will affect such material properties as flow, compressibility, disintegration, and dissolution. An optimal particle size/size distribution for the formulation will need to be determined. Factors to consider in dry milling are same as that of wet milling.[13]

Lubrication :
Lubricants are added in order to remove the problem of sticking and picking in the tablets.
a) Selection of Lubricant: Grade of the lubricant used and compatibility with other ingredients should be studied thoroughly and then the appropriate one must be chosen.
b) Amount of Lubricant Added: How much lubricant is required? Too much lubricant will form hydrophobic layer on the tablet resulting in dissolution problems.
c) Mixing Time: The optimum mixing time must be decided on proper trial of batches because if not mixed long enough form problems like chipping, capping, etc.[14]

Tablet compression :
Compression is a critical step in the production of a tablet dosage form. As for the compressibility properties of the formulation, it should be examined on an instrumented tablet press. Factors to consider during compression are as follows:
A. Tooling: The shape, size, and concavity of the tooling should be examined based on the formulation properties and commercial specifications.
B. Compression speed: The formulation should be compressed at a wide range of compression speeds to determine the operating range of the compressor.
C.Compression/ejection force: The compression profile for the tablet formulation will need to be determined to establish the optimal compression force to obtain the desired tablet hardness.
The following in-process tests should be examined during the compression stage:
I. Appearance
II. Hardness
III. Tablet weight
IV. Friability
V. Disintegration
VI. Weight uniformity
VII. Tablet Coating[15]

Tablet coating can occur by different techniques (e.g., sugar, film, or compression).

Film coating has been the most common technique over recent years and will be the focus of this section.
Key areas to consider for tablet coating include the following:
a) Tablet Properties: Tablet properties such as hardness, shape, and intagliation (if required) are important to obtain a good film-coated tablet. The tablet needs to be hard enough to withstand the coating process
b) Equipment Type: The type of coater will need to be selected. Conventional or perforated pan and fluid bed coaters are potential options.
c) Coater Load: Having too large a pan load could cause attrition of the tablets because of the overall tablet weight in the coater. In the case of a fluid bed coater, there may not be sufficient airflow to fluidize the tablets.
d) Pan Speed: This will be interrelated to other coating parameters, such as inlet temperature, spray rate, and flow rate.
e) Spray Guns: The number and types of guns should be determined in order to efficiently coat the tablets.
f) Application/Spray Rate: The optimal application/spray rate should be determined. Spraying too fast will cause the tablets to become over wet, resulting in clumping of tablets and possible dissolution of the tablet surface. Spraying too slowly will cause the coating materials to dry prior to adhesion to the tablets. This will result in a rough tablet surface and poor coating efficiency.
g) Tablet Flow: The flow or movement of the tablets in the coater should be examined to ensure proper flow. The addition of baffles may be required to provide adequate movement of tablets for tablet coating.
h) Inlet/Outlet Temperature and Airflow: These parameters are interrelated and should be set to ensure that the atomized coating solution reaches the tablet surface and then is quickly dried.
i) Coating Solution: The concentration and viscosity of the coating solution will need to be determined. The solution will need to be sufficiently diluted in order to spray the material on the tablets.
j) Coating Weight: A minimum and maximum coating weight should be established for the tablet.[16]

II. Conclusion

Validation is a proven assurance of the process efficiency and sturdiness and it is the full fledged quality control tool for the pharmaceutical industries. It eliminates the chances of batch failures as the products are manufactured as per pre optimisation of each manufacturing steps. The conventional process of testing at last stage created much problems in maintain uniformity of each batch but with the introduction of concept of validation, it has been easy to maintain the batch uniformity of the product along with imparting quality in them. This paper summarises the process validation stages of solids, liquids and semisolids which are the most common pharmaceutical dosages form in use.

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