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A REVIEW ON PROCESS VALIDATION OF SOLID DOSAGE FORM (TABLET)

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Abstract

Drugs have a significant role in treating a variety of ailments in the medical field. Drugs must therefore be produced to obtain a consistent therapeutic response at the highest levels of quality. End-product testing by itself does not ensure the product's quality. A well-designed system will offer a high level of assurance that each action, procedure, and modification has been thoroughly examined before being put into effect. The most frequently used word in medication research, production, and finished product specification is "validation." Process validation is a key element of the quality assurance system employed by pharmaceutical producers since it is essential to the safety and quality of drug products. The most important factor in ensuring the identity, power, purity, safety, efficacy, and sustaining the quality of the end product is process validation. Process validation highlights the importance of objective measurements, statistical tools, and analyses; it also emphasises knowledge and detection; it establishes flexibility; it controls variability in the attainment of desirable attributes; and it provides assurance on consistency of quality and productivity throughout a product's life cycle by preventing undesirable properties. The current article provides an introduction to validation, a summary of process validation, and information on its significance in the production of solid dosage forms.

Keywords: Tablet, Validation, Process Validation, Solid Dosage Form

1. INTRODUCTION

Every time a product is taken into consideration, quality is an absolute requirement. Therefore, pharmaceuticals must be produced to achieve a predictable therapeutic response to a drug included in a formulation that can be produced on a wide scale with the highest level of reproducibility. These days, one of the most well-known, frequently talked, and cherished topics in the pharmaceutical sector is validation.[1,2,3]To have the product approved for commercialization, it is a crucial success component. The first and most important justification for process validation is a regulatory obligation for nearly every process in the global health care sector, including pharmaceuticals, biologics, and medical

devices.[4,5]Regulatory agencies in different nations all around the world demand that the firm validate its production procedures. Reduced sample size and intervals are easily justified once a process or product has undergone systematic validation since they yield a quantifiable return on the validation effort.[6,7,8]One of the biggest problems with the application of validation in the pharmaceutical sector, aside from utility systems, is that this is hardly ever realised. More advanced drug delivery systems are now available on the market, although tablets are still by far the most used solid dosage form worldwide.[9,10]

1.1 VALIDATION

A scientific investigation of quality assurance known as validation verifies the systems, equipment, manufacturing procedures, software, and testing techniques that have an impact on a product's efficacy, safety, and quality.[11,12] The outcome of validation studies is:

- to demonstrate that the machinery, system, and process consistently carry out their intended functions. (The process is controlled, in other words.)
- to establish suitable process control, determine the process variables and acceptable limits for these variables.[13,14,15]

"Establishing documented proof that offers a high degree of assurance that a certain system, related equipment, and process consistently fulfil the approved requirements and generate goods meeting preset quality criteria" is the definition of process validation.[16,17]

1.2 ELEMENTS OF VALIDATION

The validation procedures are carried out in accordance with documented protocols that have already been authorised. By carrying out Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ) in accordance with the established protocols, the facility, utilities, significant production equipment, and laboratory instruments should be qualified. The user department may develop the protocol, or the vendor may provide it. It is preferred that qualified professionals from within or outside the company qualify the equipment and instruments.[18,19]

1.2.1 Design Qualification (DQ): The DQ aims to establish that the facility, system, or equipment is developed in conformity with Good Manufacturing Practice (GMP) standards and user requirements. With the supplier's input, a protocol for design needs and technical specifications should be created, and a report should be created for it.[20,21]

1.2.2 Installation Qualification (IQ): When the equipment is delivered to the facility, it is initially examined to make sure it meets the design and technical criteria. The Engineering Department confirms that the components and equipment are provided in line with the requirements stated in (DQ). The equipment is subsequently moved to its designated spot and placed in accordance with the equipment floor plan. The following activities make up the IQ process.[22,23]

1.2.3 Operational Qualification (OQ): During operational qualification, written proof is produced to show that every component of the apparatus operates in accordance with its design parameters.[24]

1.2.4 Performance Qualification (PQ): Performance qualification is the final stage of qualification, which demonstrates that how the equipment/system will perform when challenged under simulated or actual production conditions. A series of tests are designed to demonstrate that the equipment / system is capable to perform consistently and meet required specifications under routine production operations.[25,26]

1.3 Principles of Process validation

Process validation is defined as "establishing documented evidence which provides a high degree of assurance that a specific system, related equipment and process consistently meet the approved specifications and produce products meeting predetermined quality attributes.[27,28]

1.3.1 Process validation: Process validation is a basic factor for drug product safety and quality and thus a fundamental component of the quality assurance system used by pharmaceutical manufacturers. The basic principle of Quality Assurance is that a drug should be produced that is fit for its intended use. Effective Process Validation contributes significantly to assure the drug quality; this principle incorporates the understanding that the following conditions exist:

1. Prospective validation
2. Concurrent validation
3. Retrospective validation
4. Revalidation

1.3.1.1 Prospective validation: Prospective validation is carried out during the development stage of a product and it is required for new manufacturing formulae or methods of preparation where the latter are adopted. The purpose is to ensure that the defined process, using the materials and equipment specified, should be shown to yield a product that is consistently of the required quality and quantity what it is proposed to do based on the preplanned protocols. In this phase the extent to which deviations from the chosen processing parameters can influence in the product quality is also be evaluated. In general the final batch size should not be more than 10 times the batch size of the representative development batches. The process should include identification and evaluation of individual steps, identification of critical situations, design of trial plans and set of priorities, performance of trials, recording of results, assessment and evaluation of observed results. If the results are unsatisfactory then the processes are modified and improved until acceptable results are obtained. This is essential to limit the risk and errors that may occur on production scale.[29,30,31]

1.3.1.2 Retrospective validation: Retrospective validation is based on a review of historical manufacturing and testing data, and the analysis of accumulated results from past production to assess the consistency of a process. It is assumed that the composition, procedures and equipment remained unchanged.

During retrospective validation results of in-process and final control tests are evaluated. A total of 10-25 batches (or more), manufactured over a period of 12 months, is used for reviewing the results, to provide a statistically significant picture. Quality control charts could be used when performing retrospective validation. Failure investigations should however, be performed separately. All difficulties and failures recorded are analyzed to determine limits of process parameters and product-related problems. These should include rejections, complaints and returns. As

retrospective validation is not considered to be a quality assurance measure it should not be applied to new processes or products.[32,33,34]

1.3.1.3 Concurrent validation: Concurrent validation is carried out during normal production. This method of validation can only be successful if the development stage has resulted in a proper understanding of the fundamentals of the process. It is carried out during normal production of products intended for sale. It should involve close and intensive monitoring of the steps and critical points for at least first three production scale batches. The in-process control results are used to provide some of the evidence required for validation but these are no substitute for validation. Validation in the production unit mainly comprises of the determination and evaluation of the process parameters of the facilities applied for the scale-up to final batch size. The control of all critical process parameters, the results of the in-process controls, final controls and stability tests should prove the suitability of the important individual steps of a procedure.[35,36,37]

1.3.1.4 Revalidation: In general Revalidation is exploratory review the current performance of the validation effect to confirm the validated status of the facilities, systems, equipments, manufacturing processes, software and testing.[38]

1.4 Approaches in Process Validation

1.4.1 Process Design: The goal of this stage is to design a process suitable for routine commercial manufacturing that can consistently deliver a product that meets its quality attributes

1.4.2 Process Qualification: This stage has two elements: (1) design of the facility and qualification of the equipment and utilities and (2) process performance qualification (PPQ).

1.4.3 Continued Process Verification: The goal of the third validation stage is continual assurance that the process remains in a state of control (the validated state) during commercial manufacture.[39,40]

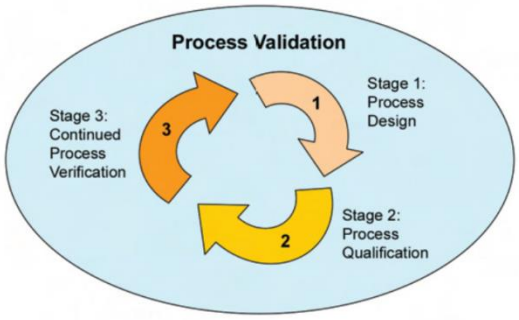

Figure 1. Process validation

1.5 Process Validation of Solid Dosage Forms

• The use of different lots of raw materials should be included. i.e., active drug substanceand 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 withintheir operating ranges and should not exceedtheir upper and lower control limits duringprocess operation. Output responses should bewell within finished product specifications.[41,42]

1.6 Guidelines for process validation of tablets

There are several important reasons for validating a product and /or process.

• Manufacturers are required by law to confirmto GMP regulations.

• Good business dictates that a manufacture avoid the possibility of rejected or recalled batches.

• Validation helps to ensure product uniformity,reproducibility and quality.[43,44]

1.7 Process validation for solid dosage forms

The critical parameters considered during the process validation of tablets are

1. Mixing or Blending
2. Granulation
3. Wet milling
4. Drying
5. Milling
6. Compression
7. Coating

1.8 Tablet Coating

Tablets may be coated for various reasons.

- Stability
- Taste masking
- Controlled release
- Product identification
- Aesthetics
- Safety–material handling

Tablet coating can occur by different techniques. Film coating has been the most common technique over recent years and will be the focus of this section.[45,46]

Key areas to consider for tablet coating include the following:

A. Tablet properties: Tablet properties such as hardness,shape, and intagliation are important toobtain a good film-coated tablet. The tablet needs to behard enough to withstand the coating process. If tabletattrition occurs, the tablets will have a rough surface appearance. For shape, a round tablet will be easier to coat than tablets will multiple sides or edges because of the uniformity of the surface. For intagliated tablets, the intagliation style and depth should be developed to prevent fill-in or chipping of the intagliation.[47,48]

B. Equipment type: The type of coater will need to beselected. Conventional or perforated pan and fluid bedcoaters are potential options.

C. Coater load: Having too large a pan load could causeattrition of the tablets because of the overall tablet weightin the coater. In the case of a fluid bed coater, there maynot be sufficient airflow to fluidize the tablets.

D. Pan speed: This will beinterrelated to other coating parameters, such as inlettemperature, spray rate, and flow rate.[49,50]

E. Spray guns: The number and types of guns should bedetermined in order to efficiently coat the tablets. Thespray nozzles should be sized properly to ensure even

distribution over the tablet bed and to prevent clogging ofthe nozzles. The location and angle of the spray gun(s)should be positioned to get adequate coverage. Having

the guns positioned too close together can lead to aportion of the tablets to be over wet.[51,52]

F. Application/spray rate: The optimal application/sprayrate should be determined. Spraying too fast will causethe 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 todry prior to adhesion to the tablets. This will result in arough tablet surface and poor coating efficiency.

G. Tablet flow: The flow or movement of the tablets in thecoater should be examined to ensure proper flow. Thereshould be sufficient tablet bed movement

to ensure evendistribution of the coating solution onto the tablets. Theaddition of baffles may be required to provide adequatemovement of tablets for tablet coating.[53,54]

H. Inlet/outlet temperature and airflow: These parametersare interrelated and should be set to ensure that theatomized coating solution reaches the tablet surface and

then is quickly dried.

I. Coating solution: The concentration and viscosity of thecoating solution will need to be determined. The solutionwill need to be sufficiently diluted in order to spray the

material on the tablets. The concentration of the coatingsolution will also determine the amount and volume ofsolution to be applied to the tablets. The stability of thecoating solution should be investigated to establish itsshelf life.

J. Coating weight: A minimum and maximum coatingweight should be established for the tablet. Sufficientcoating material should be applied to the tablets to

provide a uniform appearance; however, it should not begreat enough to cause fill-in of the intagliation.[55,56]

K. Residual solvent level: If solvents are used for tabletcoating, the residual solvent level will need to bedetermined. Appearance testing of the tablets is criticalduring the coating operation.

1.9 Process Optimization

During the early stages of process development, parameter target value and tolerance limits are based on good scientific rationale and experience knowledge gained from the earlier and pilot scale studies.[57,58]

During product and process development both the inputs and outputs of the process are studied. The purpose of the study is to determine the critical parameters and attributes for the process, the tolerance for those parameters and how best to control the various experimental and analytical techniques used for the process characterization.

In subsequent product development the parameters and attribute of the process are characteristics to determine the critical parameter of the process, the tolerance limit of the process, and how best to control them. Controllable parameters may be parameters that are adjustable like drying time and temperature. At other time it may be desirable to fix a parameter by specifically setting one value and not testing around the variability. A cause-and-effect relationship may be established for parameters and desired attributes. Critical quality attributes are dissolution, assay, blend and tablet uniformity and stability.[59,60]

1.10 Critical process parameters of Solid dosage form

Blending: Blend time, rotation rate, agitator speed, room temperature, humidity.

Dry granulation (Roller compaction): Roll speed, feed screw speeds, roll force/pressure, roll separation/gap, room temperature/ humidity.

Milling: Impeller speed, feed rate, room temp, humidity.

Fluid bed granulation: Granulation fluid mixing time, fluid mixing speed, fluid amount, fluid addition rate, fluid temperature, spray nozzle air volume, bed mixing time, supply air flow rate, dew point, product bed temperature, exhaust air temperature, filter shaking intervals.

Wet granulation: Granulation fluid mixing time, fluid mixing speed, fluid amount, fluid addition rate, fluid temperature, spray nozzle air volume, drug and

wet mixing time, impeller speed, chopper speed, power consumption.[61,62]

Cabinet drying: Supply air temperature, drying time, final moisture content

Fluid bed drier: Supply air flow rate, temperature, product bed temperature, exhaust air temperature, filter shaking intervals, final moisture content.

Compression: Tablet weight, turrent speed, main compression force, pre compression force, feeder speed, upper punch entry, room temperature, humidity.

Coating: Coating suspension mixing time, mixing speed, amount, spray rate, atomization, pressure, pan rotation speed, pre heat time, supply air flow rate, temperature, product bed temperature, exhaust air temperature.[63,64,65]

2. CONCLUSION

Nowadays Validation is the art of designing and practicing the designed steps together with the documentation in pharmaceutical industry. Validation itself does not improve processes but confirms that the processes have been properly developed and are under control in achieving, maintaining the quality of the final product.[66,67] Application of validation principles will ensure to maintain quality, consistency and reproducibility in product manufacturing process and safety of the pharmaceutical products required from regulatory agencies across the world. The multidisciplinary validation team must identify, study the product and process characteristics and incorporate the important required validation key parameters to ensure that that product will meet all quality, manufacturing, and regulatory requirements.[68,69] Process validation in solid dosage form is a systematic approach in identifying, measuring, evaluating, documenting and re-evaluating the critical steps in the pharmaceutical solid dosage form manufacturing process with control to assure consistency in the quality of final product. From this review we can conclude that the pharmaceutical process validation and process controls are important steps in manufacturing of solid dosage form with consistent to meet the regulatory required standard such as identity, strength, quality, purity and stability in the final solid dosage form.[70,71]

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