

Process Validation of Rabeprazole Sodium Tablets (Rabi 20)

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Abstract: 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”. Validation establishes that the process equipment has the capability of operating within required parameters. Validation in itself does not improve only processes but also confirms that processes have been properly developed and are within control. According to Indian Pharmacopoeia, Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage forms prepared by compressing a drugs or a mixture of drugs with or without diluents. The validation study provides the accuracy, sensitivity, specificity and reproducibility of the test methods employed by the firms, shall be established and documented. Thus the validation is an essential part of the quality assurance.

Keywords: Process Validation, GMP, specifications, consistent, documented.

1. Introduction

The main purpose of all pharmaceutical industries is to made quality products consistently in lowest feasible cost. Validation plays a very important role in quality assurance and productivity improvement. Process validation establishes the flexibility and constraints in the manufacturing process controls in the fulfillment of desirable character in the drug product while preventing undesirable attributes. The concept of validation was first proposed by two Food and Drug Administration officials, Ted Byers and Bud Loftus in the mid 1970's in order to improve the quality of pharmaceuticals.

2. Objective of process validation

- To minimize variation between different batches.
- To provide a high degree of assurance of quality of the product.
- To reduce the risk of defect costs and regulatory noncompliance.
- To ensure the consistency of the manufacturing operation and reproducibility of the process.
- To demonstrate the robustness of the process.
- A fully validated process may require less in-process controls and end product testing.
- To ensure the existence of all necessary quality assurance

system within organization.

A. Advantages of process validation

1. It is simple process and moisture sensitive , heat sensitive products can also be processed.
2. Expanded real time monitoring and adjustment of process.
3. Decreases the risk of preventing problems and thus ensure the smooth running of the process.
4. Enhanced ability to statistically evaluate process performance and product variables e.g. individuals; mean; range; control limits.
5. Enhanced data and evaluation capabilities and increased confidence about process reproducibility and product quality.
6. Improved ability to set target parameters and control limits for routine production, correlating with validation results.
7. Enhanced reporting capability.

FDA guidelines “general principle of validation”

“Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification and quality attributes.” Validation is the most important and recognized parameters of cGMP. According to the FDA's current Good Manufacturing Practices (cGMP) control procedure shall be established to monitor output and to validate performance of the manufacturing processes that drug products be produced with a high degree of assurance of meeting all the attributes they are intended to possess.

3. Types of validation

1. *Prospective Process Validation:* It is defined as the establishing documented evidence that a process does what it intend to do based on a pre-planned protocol. This validation usually carried out prior to distribution either of a new product or a product made under a continuous revised manufacturing process performed on at least three consecutive successive production batches.
2. *Concurrent Process Validation:* It is similar to the prospective, except the operating firm will sell the product during the qualification runs, to the public as its market price. This validation involves in process monitoring of critical processing steps and product testing. This helps to

generate and documented evidence to show that the production process is in a good state of control with quality characteristics.

3. *Retrospective Process Validation*: Retrospective validation is defined as the establishment of documented evidence that a system does what it intend to do on review and analysis of previous historical data. The sources of such data are production, QA and QC records. The issues to be addressed here are changes to process, equipment, specification and other relevant changes in the past. Retrospective validation is only acceptable for well-established processes and will be inappropriate where there have been recent changes in composition of the product, equipment or operating procedures.
4. *Revalidation*: It is the repetition of a validation process or a part of it. This is carried out when there is any change or replacement in formulation, batch size and in the case of sequential batches that do not meet it's product specifications, equipment plan or site location, and is also carried out at specific time intervals in case of no changes.

4. Strategy for validation of methods

There are following strategy for process validation:

- Making of process flow charts and Identification of critical process variables.
- Selection two consecutive batches having same batch size & manufacturing formula.
- The Failure to meet the requirements of the Validation protocol with respect to process input and output control should be subjected to process prequalification and subsequent.
- Revalidation following a thorough analysis of process data and formal discussion by the validation team.
- Document validation experiment and results in the validation report.
- Batch manufacturing record, in process and finished product specification, other related documents to BMR and specifications, Related SOPs and Batch packing record all documents are necessary for process validation.
- Preparing process validation protocol.
- Develop SOPs for executing the method routinely.
- Execution of validation protocol.
- Monitoring process validation batches.
- Doing in process testing during manufacturing.

A. Type of documentation in validation process

Validation: Type of documentation

- Validation master plan (VMP)
- Validation protocol (VP)
- Validation reports (VR)
- Standard operating process (SOPs)

Validation master plan

An approved written plan of objectives and actions stating how and when a company will achieve compliance with the GMP requirements regarding validation. MP 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 provides an overview of the entire validation operation, its organizational structure, it's content and planning. The main elements of its being the list/ inventory of the items 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's summary and conditions of Validation Protocol.

Process validation protocol

- Protocol approval sheet
- Table of content
- Objective and Scope
- Validation team and responsibility
- Steps for validation and acceptance criteria
- Process validation plan
- Evaluation of formulation ingredients
- Evaluation of active raw material
- Evaluation of equipment
- Responsibility
- Manufacturing process flow chart
- Product details
- Equipment detail
- Critical process parameters
- In-process specification
- Sampling procedure and testing plan
- Revalidation criteria
- Change control
- Deviations
- Stability
- Conclusion
- Report and conclusion

Validation reports:

- 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:
 - Title and objective of study.
 - Reference to protocol.
 - Details of material.
 - Equipment.
 - Programmes and cycles used.
 - Details of procedures and test methods.
 - Results (compared with acceptance criteria).
 - Recommendations on the limit and criteria to be applied on future basis.

SOP (Standard Operating Procedure): Standard Operating

Procedures (SOPs) are issued to instruct employees in areas of responsibility, appropriate specifications, work instructions and required records. These outline procedures must be followed to claim the 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, testing and decontamination. Even the work done in the laboratory were documented, for example, the laboratory operations involving the receipt of reagents, , test procedure, preparation of reagents, reference material, identification, standards, labelling and storage handling, storage and use deviations, errors. Even the details of the equipment's and their maintenance were also involved.

B. Steps of process validation of solid dosage form (tablets)

- Raw material
- Dispensing
- Movement of raw material to production area
- Wet granulation (Blending + Mixing)
- Drying
- Compression
- In process test
- Finished product testing
- Packaging

C. Different types of analysis during process

- Description [Physical Observation]
- Moisture Content
- Content uniformity

D. Process validation of non-sterile dosage forms

1) Mixing or Blending

Mixing or blending time

- Drug uniformity
- Mixing or blending technique: Diffusion (tumble),
- Mixing or blending speed
- Excipient uniformity
- Lubricant:
- Color
- Equipment capacity/load

2) Wet Granulation

- Amount of binder solution/granulating solvent
- Binder solution/granulating solvent addition rate
- Binder addition
- Binder concentration
- Mixing time
- Granulation end point

3) Wet Milling

- Mill speed
- Feed rate
- Equipment size and capacity
- Screen size

4) Drying

- Inlet/outlet temperature

- Airflow
- Moisture uniformity

5) Milling

- Mill speed
- Feed rate
- Mill type
- Screen size

6) Lubrication

- Mixing time
- Selection of lubricant
- Amount of lubricant added

7) Tablet Compression

- Tooling
- Compression speed
- Compression/ejection force

8) In-process tests

1. Moisture content of "dried granulation"
2. Granulation particle size distribution
3. Blend uniformity
4. Individual tablet/capsule weight
5. Disintegration
6. Impurity profile
7. Tablet hardness
8. Tablet thickness

9) Finished product tests

- Appearance
- Tablet hardness
- Tablet friability
- Assay Content uniformity
- Impurity profile

E. Introduction to Rabeprazole sodium

Rabeprazole sodium is the class of proton pump inhibitors of an antiulcer drug. It is a prodrug - in the acid environment of the parietal cells which turns into active sulphenamide form. Rabeprazole inhibits the H⁺, K⁺ATPase of the coating gastric cells and dose-dependent oppresses basal and stimulated gastric acid secretion.

Rabeprazole sodium possess properties of both bases and acids, making it an amphoteric.

5. Conclusion

It is establishing documented evidence that a process does what it purports to do, based on information generated during actual implementation of the process. In process monitoring of critical processing steps and end product testing of current production is involved in concurrent validation. Validation is the art of designing and practicing the designed steps alongside with the documentation. Solid dosage forms include tablets and capsules. Validation and quality assurance will go hand in hand, ensuring the through quality for the products. Hence, an emphasis made on to review that gives a detailed, overview of validation concept of designing, organizing and conducting validation trials. Despite the ongoing development of more

sophisticated solid drug delivery system, tablets are still by far the most prevalent solid dosage form.

References

- [1] Metformin hydrochloride tablet dosage form, International Journal of Pharmatech Research, 2010, 2(3), 1673-1678.
- [2] S. Prabhu Lakshamana, T.N.K. Suriyaprakash, K. Ruckmani, R. Thirumurugan, Concepts of process validation in solid dosage form (Tablet), Scholarena, 2014, 1(1), 1-12.
- [3] Paruchuri R, Trivedi S, Pavuluri G, Prasanthi B and Kumar S. Process Validation of Finasteride Tablets. International Journal of Pharmaceutical, Chemical and Biological Sciences, 2012; 2(1): 11-28.
- [4] Nash RA, Wachter HA. Pharmaceutical Process Validation. Third Edition, Marcel Dekker Inc., New York: 2003, 159-80.
- [5] Armbruster D, Feldsien T. Applying HACCP to Pharmaceutical Process
- [6] S. Rohokale, V. M Jadhav, V.J. Kadam, Studies in Prospective Process Validation of Validation Pharmaceutical Technology. October 2000; 24(10):170 -178.
- [7] Sharma A, Saini S. Process Validation of Solid Dosage Form: A Review. International Journal of Research in Pharmacy and Science, 2013; 3(2):12-30.
- [8] Herbert A. Lieberman, Leon Lachman, Joseph B. Schwartz, Pharmaceutical Dosage Forms Tablets. Second edition, volume 3. Marcel Dekker. Inc, New York, 1990, 417-447.
- [9] Thaduvai R, Rao B. S. S, Jeybaskaran M. Process Validation of Pantoprazole 40mg Tablets. The Pharma Innovation, 2012; 1: 47-62.
- [10] Parida R. Overview of Pharmaceutical Validation and Process Controls in Drug Development. Pelagia Research Library, 2010; 1(1): 11-19.
- [11] Kaur G, Rana AC, Bala R, Seth N. An Overview: The Role of Process Validation in Pharmaceutical Industry. International Research Journal of Pharmacy, 2012; 3(1): 25-27.
- [12] Kumar S. Pharmaceutical process validation: A CGMP concept. Pharma tutor, 2011; 1-9.
- [13] Kathiresan K, Sreenu VS, Moorthi C, Reddy B, Kumar B, Reddy M, Yellamula P, Manavalan R. Cleaning Validation of Acetaminophen Tablets. International Journal of Chemical Environmental and Pharmaceutical research, 2010; 3(3): 503-506.
- [14] Himanshu, Pahuja S. A Review on Pharmaceutical Process Validation. International Journal of Pharmacy, 2012; 3(7): 56-58.
- [15] Chows S. Pharmaceutical validation and process control in drug development. Drug Information Journal, 1997; 31: 1195-1201.
- [16] US FDA, (1987) General principles of validation, Rockville, MD, Center for Drug Evaluation and Research (CDER).
- [17] Good Manufacturing Practices for Pharmaceutical Products. WHO Expert Committee on Specifications for Pharmaceutical Preparations (1992).32nd Report, WHO Technical Report Series no.823. Geneva: WHO, 14-96.
- [18] A WHO guide to GMP (1997); Requirements, part 2: Validation.
- [19] Kumar S, Chakraborty GS, Kumar P, yadav AS, Seth AK, Yadav YC, Jain G. Process validation of Azifast 500 mg tablet. Journal of Advances in Pharmacy and Healthcare Research, 2011; 1(2): 3-9.
- [20] Pandita R., Rana AC, Seth N. Introduction and general overview of pharmaceutical process validation: review. International Research Journal of Pharmacy. 2012; 3(6): 60-64.
- [21] Sharma S, Khurana G, Gupta R. A Review on Pharmaceutical Validation and Its Implication. Indian J. Pharm. Biol. Res. 2013; 1 (3): 100-104.
- [22] Paruchuri R, Trivedi S, Pavuluri G, Prasanthi B and Kumar S. Process Validation of Finasteride Tablets. International Journal of Pharmaceutical, Chemical and Biological Sciences, 2012; 2(1): 11-28.
- [23] Armbruster D, Feldsien T. Applying HACCP to Pharmaceutical Process Validation Pharmaceutical Technology. October 2000; 24(10):170 -178.
- [24] Nash RA, Wachter HA. Pharmaceutical Process Validation. Third Edition, Marcel Dekker Inc., New York: 2003, 159-80.
- [25] Sharma A, Saini S. Process Validation of Solid Dosage Form: A Review. International Journal of Research in Pharmacy and Science, 2013; 3(2):12-30.
- [26] Herbert A. Lieberman, Leon Lachman, Joseph B. Schwartz, Pharmaceutical Dosage Forms Tablets. Second edition, volume 3. Marcel Dekker. Inc, New York, 1990, 417-447.
- [27] Thaduvai R, Rao BS. S, Jeybaskaran M. Process Validation of Pantoprazole 40mg Tablets. The Pharma Innovation, 2012; 1: 47-62.
- [28] Parida R. Overview of Pharmaceutical Validation and Process Controls in Drug Development. Pelagia Research Library, 2010; 1(1): 11-19.
- [29] Kaur G, Rana AC, Bala R, Seth N. An Overview: The Role of Process Validation in Pharmaceutical Industry. International Research Journal of Pharmacy, 2012; 3(1): 25-27.
- [30] Kumar S. Pharmaceutical process validation: A CGMP concept. Pharma tutor, 2011; 1-9.
- [31] Kathiresan K, Sreenu VS, Moorthi C, Reddy B, Kumar B, Reddy M, Yellamula P, Manavalan R. Cleaning Validation of Acetaminophen Tablets. International Journal of Chemical Environmental and Pharmaceutical research, 2010; 3(3): 503-506.
- [32] Himanshu, Pahuja S. A Review on Pharmaceutical Process Validation. International Journal of Pharmacy, 2012; 3(7): 56-58.
- [33] Chows S. Pharmaceutical validation and process control in drug development. Drug Information Journal, 1997; 31: 1195-1201.
- [34] US FDA, (1987) General principles of validation, Rockville, MD, Center for Drug Evaluation and Research (CDER).
- [35] Tandel MJ, Kumar J, Dedania R, Vadalia KR. Process Validation of Pyrazinamide Tablets: Review. International Journal of Advances in Pharmacy, Biology and Chemistry. 2012; 1(3): 342-353.
- [36] Nandhakumar L, Dharmamoorthy G, kumar RS, Chandrasekaran S. An Overview of Pharmaceutical Validation: Quality Assurance View Point. International Journal of Research in Pharmacy and Chemistry, 2011; 1(4): 1003-1014.
- [37] Paruchuri R, Trivedi S, Pavuluri G, Prasanthi B and Kumar S. Process Validation of Finasteride Tablets. International Journal of Pharmaceutical, Chemical and Biological Sciences, 2012; 2(1): 11-28.