JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

A REVIEW ON PROCESS VALIDATION OF ORAL SOLID DOSAGE FORM (LOZENGES)

Mr. Kashif Hussain[*1], Mr. Kuldeep Kumar[*2], Sunil Dhanola[*3]
*1-Associate professor Gyani inder singh institute of professional studies, Dehradun.
*2 Associate professor Gyani inder singh institute of professional studies, Dehradun.
*3 Student Gyani inder singh institute of professional studies, Dehradun.

Abstract: The purpose of this work is to perform a study on process validation of Amylmetacresol and 2,4 Di-Chloro Benzyle Alcohol Lozenges that will deliver a process validation approach as a quality assurance aspects. The process validation program shall be examined so that the plan will be designed to the character of the procedure under study. This can be performed by Evaluation and Examination the various critical process parameters and critical quality attributes. Samples from the three consecutive batches of Lozenges are taken as per the sampling plan from different Location in during Manufacturing Process. Every parameter is analyzed as per the specification and all the data are recorded. All the obtained results must comply the specification limits.
Amylmetacresol (AMC) and 2,4-dichlorobenzyl alcohol (DCBA) are mild antiseptic, able to kill bacteria and viruses associated with mouth and throat infections.

Keywords: Process validation, Amylmetacresol and 2, 4 Di-Chloro Benzyle Alcohol Lozenges, critical process parameters, critical quality attributes**.**

INTRODUCTION:

The U.S. Food and Drug Administration (FDA) has proposed guidelines with following definition for *process validatio*n as" The 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 characteristics''.
According to the FDA, assurance of quality is derived from careful and systemic attention to a number of important factors, including selection of quality attributes and material, adequate process, product design & tactical control of the process through in-process and end-product testing.
According to the FDA's C-GMP 21 C.F.R 211.110 " Control procedures shall be establish to *monitor* output & to *validate* performance of the manufacturing processes that may be responsible for causing variability in the characteristics of Inprocess material & the drug
product. Such control procedure shall include, but not limited to the following, where suitable:
1. weight variation
2. Disintegration Time(DT)
3. Proper mixing to assure uniformity and homogeneity

4. Dissolution Time
5. Clarity, Completeness, or pH of solutions, MLT & Assay.

The 1st four items listed above are directly related to the manufacture and validation of solid dosage form. Above Item 1 & 3 are normally associated with variability in the manufacturing process, while above item 2 & 4 are usually subjective by the selection of the ingredients in the product formulation, with respect to content uniformity (item 3), adequacy of mixing to assure uniformity and homogeneity are considered a high-priority concern.
Quality control testing for finished product testing cover three basic steps:
1. Establishment of specifications and performance.
2. Selection of appropriate Method, Equipment, and instrument to ensure that testing of the product meets specification.
3. Testing of the finished product, using validated analytical and testing method to ensure that finished product meets specifications.
With the emergence of the process validation concept, the following 4 additional steps are added:
4. Qualification of the Processing facility/Utility and its equipment
5. Qualification and validation of the Manufacturing process.
6. Auditing, Monitoring, Sampling, of key steps in the process for conformance to Inprocess and Finished product specifications
7. Re-validation when there is a Any significant change in either the product or its manufacturing process.
The main thought of dosage form design is to achieve therapeutic use to a drug included in a formulation which is capable of large scale manufacturing with repeatable product quality, safety and potency. Various processes involved in the development of a drug product into a dosage form are drug Evaluation, lab test, regulatory registration etc. Before releasing the product in the market various product quality Parameter like identity, chemical, physical stability, suitable preservation against microbial contamination if appropriate, strength, quality, purity, uniformity of dose of drug, stability, acceptability to users including prescriber & patient as well as suitable packing, labeling and validation are required. Process validation and process controls are two important key parameters which can ensure the above said parameters in the manufacturing process. In pharmaceutical manufacturing company validation is a primitive tool that supports a company's commitment to quality of the final product. Validation is a tool to quality assurance which provides high degree of assurance that the equipments, system, software; manufacturing process and test method are in a validated state.
Process validation is helps to ensure the final product quality, safety, efficacy, delivery and cost.

Process Validation Stages:

Process validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process validation involves a series of activities taking place over the lifecycle of the product and process.
Process Validation: General Principles and Practices guidance describes process validation activities in three stages.

- **Stage 1 –** Process Design: The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.
- **Stage 2** – Process Qualification: During this stage, the process design is evaluated to determine if the process is 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.

Types of process validation:- There are 4 types

1) Prospective Process Validation
2) Concurrent Process Validation
3) Retrospective Process Validation
4) Process Re-validation

Prospective Process Validation:

In prospective process validation, a preliminary plan called the validation protocol is executed before the process is put into commercial use. The majority validation efforts require some degree of prospective experimentation to generate validation support data. This specific type of process validation is normally carried out in case of introduction of new drug products and their manufacturing processes or introduction new molecule or content. The harmonized process validation strategy should never be undertaken unless and until the following operations and procedures have been found completed satisfactorily:

1. The facilities and equipment which are used during the process validation is to be conducted meet CGMP requirements.
2. The personnel who will be "running" the validation batch have proper knowledge of the process and its predefined requirements.
3. The design criteria, selection criteria, and optimization of the formula have been completed successfully.
4. The qualification trials using 10 times pilot-laboratory batches have been completed, in which the critical processing parameters and critical process variables have been identified, and the transitional operational control limits for each critical test parameter have been provided.
5. Detailed technical information on the product and the manufacturing process has been provided, including documented evidence of product stability.
6. At least one qualification trial of a pilot-production (100x) batch has been made and shows, upon scale-up, that there were no significant deviations from the expected performance of the process.

Concurrent process validation:

Concurrent process validation is done between the routine manufacturing processes. A process where current production batches are used to monitor processing parameters. It gives of the present batch being studied, and offers limited assurance regarding consistency of quality from batch to batch Concurrent Validation may be the practical approach under certain state of affairs.

Retrospective Validation:

The retrospective validation option is chosen for established products whose manufacturing processes are considered stable and when on the basis of economic considerations alone and resource limitations, prospective validation programs cannot be justified. Prior to undertaking retrospective validation, wherein the numerical in-process and/or end-product test data of historic production batches are subjected to statistical analysis, the equipment, facilities and subsystems used in connection with the manufacturing process must be qualified in conformance with CGMP requirements. The basis for retrospective validation is stated in 21 CFR: "Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and shall be derived from previous tolerable process average and process variables calculated where possible and set on by the application of suitable statistical process measures where are appropriate." The concept is also conceded in the FDA's Guidelines on General Principles of Process Validation. Using

Retrospective validation conducted in the following manner:

1. To collect the numerical data from the completed batch and incorporate assay results and values, finish products test results, and in-process results.
2. Categorize these results in a linear order according to batch records.
3. Take data from at least 20–30 batches for analysis.
4. Shorten the data by removing test results from non critical processing steps and delete all unjustified information.
5. Record the data to statistical analysis and evaluate.
6. Make conclusions as to the state of control of the manufacturing procedures based on the analysis of retrospective validation data and results..
7. Prepare and Issue a report of findings (documented evidence).

Retrospective validation needs the preparation of a protocol and reporting of the results for the data review, which leads to a conclusion and recommendation. Batches manufactured for a definite period (minimum of 10 batches).

Process re-validation:

Conditions requiring revalidation study and documentation are listed as follows:

1. Change in a critical raw material and excipient.
2. Change or renewal in a critical change part of the equipment
3. Change in a facility and plant (usually location or site)
4. Notable increase or decrease in batch size
5. Successive batches that failed to meet product and process pre defined specifications.

In some circumstance requalification studies may be required prior to undertaking specific revalidation assignments. The FDA process validation guidelines refers to a quality assurance system in place that requires re-validation whenever there are changes in packaging (assumed to be the primary container-closure system), formulation, equipment or processes (meaning not clear) which could impact on product effectiveness or product characteristics and whenever there are changes in product characteristics. Approved packaging is normally selected after completing package performance qualification testing as well as product compatibility and stability studies. Since in most cases (exceptions: transdermal delivery systems, diagnostic tests, and medical devices) packaging is not intimately involved in the manufacturing process of the product itself, it differs from other factors, such as raw materials.

Benefits of process validation:[7,8]

- Reduction in rejections and reworks
- Increased Outputs
- Reduction in utility costs
- Avoidance of capital expenditures
- Fewer market complaints
- Reduced in-process and finish goods testing
- More rapid and accurate investigations into process deviations
- Easy maintenance of the equipment
- Improved employee awareness of processes
- More rapid automation

Process validation program can be made more effective and efficient through: [9]

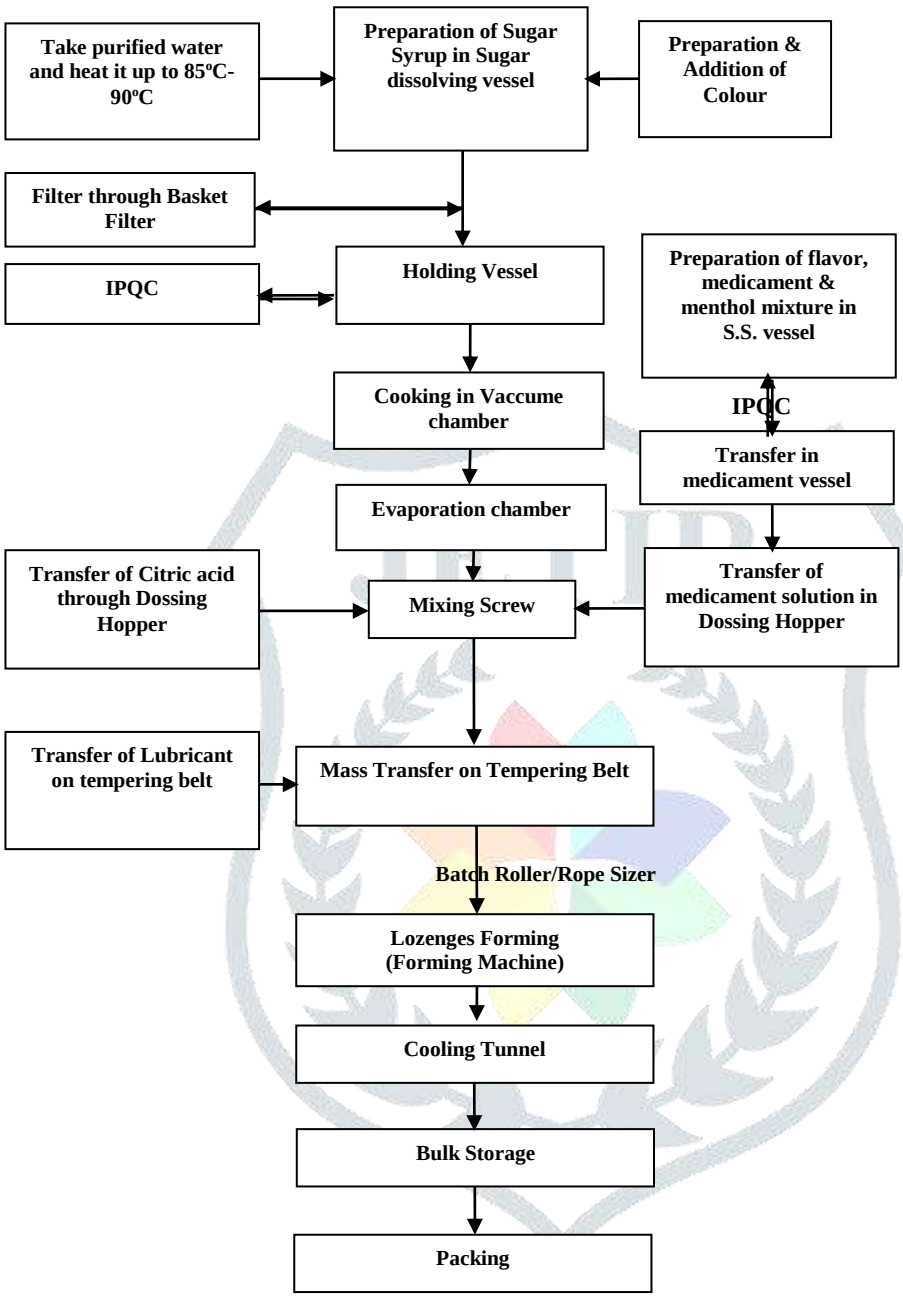
- Good project management team
- Robust scientific knowledge collection, management and archiving

- Uniform collection and assessment of information methods
- Reducing the burden of redundant information gathering
- Use of an integrated team approach
- Appropriately documented Project Plans
- The support of senior management
- Statistical assessment of data

Process Validation Methodology for Lozenges.

- During validation the documentation system, laboratory control, in-process checks shall be evaluated.
- The process validation methodology consists of three basic parts process parameters monitoring, the routine in-process and final product release testing & additional validation sampling and testing.
- The type of validation to be carried out is Concurrent validation.
- The validation exercise for three consecutive batches of production shall be done to assess the process consistency.
- QA department shall take the sample as per validation protocol.
- QC shall analyze all validation samples and raw data shall be recorded/attached with the report. Where applicable the graph and print outs of critical process parameter shall be obtained and attached.
- Process validation data shall be recorded in the process validation Report.

Process Flow Chart of Lozenges :



Sampling Plan: Collect the samples at various intervals at different operations as per the sampling plan mentioned below.

Stage	Test to be performed	Sampling Interval
Manufacturing process	• Average weight • Content of Citric Acid • Content of Amylmetacresol • Content of 2, 4 dichlorobenzyl • alcohol	At an interval of 01 hours up to batch completion
		Lozenges Forming Maximum speed (70 RPM) Minimum speed (55 RPM) Optimum speed (65 RPM)
		Conveyor Belt speed Maximum speed (30 RPM) Minimum speed (18 RPM) Optimum speed (23 RPM)
	Appearance of Lozenges Weight of 20 Lozenges Diameter Thickness	At Start, Middle End
Packing Process	Packing Parameter	Strip Forming at Different Temperature Strip Forming at Different Speed

Conclusion- The process validation have a vital role in pharmaceutical industry to achieve and to maintain the quality efficacy and safety of finished product. There should be a Validation program which is known as validation master plan in Pharmaceutical Industry. The process validation team i.e. quality assurance, production, quality control and engineering should identify the important parameters of the process and product to ensure that the product meats its predetermined quality standards, manufacturing and regulatory requirements.

Reference:-

1. Guideline of general principles of process validation & Centre for drug evaluation and research of FDA.
2. Validation guideline for pharmaceutical dosage forms. Health Canada/Health products and Food Branch Inspectorate guide-0029. www.hc-sc.gc.ca/hpfbdgpsa/inspectorate.
3. Guide to good manufacturing practice for medicinal products. Pharmaceutical inspection convention, pharmaceutical inspection cooperation scheme. www. picscheme.org.
4. Pharmaceutical process validation, an international third edition, revised and expanded- Robert A. Nash and Alfred H. Wachter.
5. Quality Management System-Process Validation Guidence,2nd edition,2004, 1-36.
6. Calnan N, Redmond A, O'neill S. The FDA's draft process validation guidance – A perspective from industry. Pharm Engg., May-June 2009; 10-16
7. Banker GS., and Rhodes C. In Modern pharmaceutics; 4th Edn; marcel dekker Inc., New York, 2007, pp 15,659-665.
8. Jyakhwa U, Joshi D, Chikanbanjar N, "A Review Article on Concurrent Process Validation." Pharmaceutical Sciences.2020; 1(1):48-54.

9. Sandhya C, Bont hagarala B, "Process validation: An essential process in Pharmaceutical industry." Int. J. adv In scientific Res.2015; 1(4):179-182
10. Validation master plan installation and operation qualification non-sterile process validation cleaning validation. Pharmaceutical inspection convention pharmaceutical inspection cooperation scheme. www.picscheme.org