OPTIMIZATION AND VALIDATION PROCESS FOR FORMULATION AND COATING OF TABLET X

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ABSTRACT
The process validation study of X tablets has been carried out on two consecutive batches (Batch 1 and Batch 2) as per process validation protocol. Batches have been manufactured and compiled as per batch manufacturing record. The starting materials used in manufacturing of validation batches has been procured from approved vendors and were analyzed by QC department and approved by QA department. The critical process parameters of manufacturing process have been evaluated with respect to quality attributes of drug product and found to be well within the predefined acceptance criteria. Sampling at various stages of validation batches was carried out as per established sampling plan as mentioned in protocol. All two validation batches comply with the release specifications of drug product and meet the quality attributes of the product. The percentage yields of all three validation batches at various manufacturing stages have been mentioned in relevant section of this report. The observations limits for percentage yield at various stages of manufacturing process of X tablets have been finalized as follows Lubrication 98.0%, Compression 98.0%, Film coating 98.0%, Inspection 98.0%.

Key Points: Validation, QA, QC.

INTRODUCTION
The goal of a quality system is to consistently produce products that are fit for their intended use. During the process validation process parameters are derived from the specifications for the device, component or other entity to be produced by the process. The process is developed in such a way that the required parameters are achieved and it ensures that the
output of the process will consistently meet the required parameters during routine production, the process is validated.

**Need of Process Validation**

There are many reasons, in addition to the regulatory requirements, for validating processes. A manufacturer can assure through careful design of the device, processes, process controls and packaging that all manufactured units will meet specifications and have uniform quality. However, in-process and finished product testing still play an important role in assuring that products meet specifications. A properly validated and controlled process will yield little scrap or rework, resulting in increased output. Consistent conformance to specifications is likely to result in fewer complaints and recalls. Also, when needed, the validation files contain data to support improvements in the process or the development of the next generation of the process.

**What Processes Should Be Validated**

Where process results cannot be fully verified during routine production by inspection and test, the process must be validated according to established procedures. When any of the conditions listed below exist, process validation is the only practical means for assuring that processes will consistently produce devices that meet their predetermined specifications:

- Routine end-product tests have insufficient sensitivity to verify the desired safety and efficacy of the finished devices;
- Clinical or destructive testing would be required to show that the manufacturing process has produced the desired result or product.
- Routine end-product tests do not reveal all variations in safety and efficacy that may occur in the finished devices.
- The process capability is unknown, or it is suspected that the process is barely capable of meeting the device specifications

**Phases of Validation**

The activities relating to validation studies may be classified into three phases:

**Phase 1:** Pre-validation phase or the qualification phase, which 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 forms, equipment qualification, installation qualification, master production documents, operational qualification, process capability.

**Phase 2:** 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 requiring frequent review of all process related documents, including validation audit reports to assure that there have been no changes, deviations, failures, modifications to the production process, and that all SOPs have been followed, including change control procedures.

At this stage the validation team also assures that there have been no changes/ deviations that should have resulted in Requalification and revalidation.

**Planning of the Process Validation Study**
Careful planning of a validation study is essential to ensure that the process is adequately validated. The plan should include design reviews. The plan for the validation study is documented in the validation protocol. Planning for the validation should include the following elements as well as any other relevant issues that must be addressed to conduct the validation study:

- Identification of the process to be validated;
- Identification of device(s) to be manufactured using this process;
- Criteria for a successful study;
- Length and duration of the study;
- Assumptions (shifts, operators, equipment, components);
- Identification of equipment to be used in the process;
- Identification of utilities for the process equipment and quality of the utilities;
- Identification of operators and required operator qualifications;
- Complete description of the process;
- Relevant specifications including those for the product, components, manufacturing materials, the environment, etc;
- Any special controls or conditions to be placed on preceding processes during the validation;
• process parameters to be controlled and monitored, and methods for controlling and monitoring;
• Product characteristics to be monitored and method for monitoring;
• Any subjective criteria used to evaluate the product;
• Definition of what constitutes nonconformance for both measurable and subjective criteria;
• Statistical methods for data collection and analysis;
• Consideration of maintenance and repairs;
• Conditions that may indicate that the process should be revalidated.

The validation plan should also cover the installation and operation qualification of any equipment used in the process, process performance qualification, and product performance qualification.

Validation: Confirmation by examination and provision of objective evidence that the particular requirement for a specific intended use can be consistently fulfilled.

Process validation: Establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications.

Installation qualification: Establishing documented evidence that process equipment and ancillary systems are capable of consistently operating within established limits and tolerances.

Process performance qualification: Establishing documented evidence that the process is effective and reproducible.

Product performance qualification: Establishing documented evidence through appropriate testing that the finished product produced by a specified process (as) meets all release requirements for functionality and safety.

Prospective validation: Validation conducted prior to the distribution of either a new product, or product made under a revised manufacturing process, where the revisions may affect the product's characteristics.

Retrospective validation: Validation of a process for a product already in distribution based upon accumulated production, testing and control data.
**Validation protocol:** A written plan stating how validation will be conducted, including test parameters, product characteristics, production equipment, and decision points on what constitutes acceptable test results.

**Preparation of Validation Protocol**

**Protocol Approval**

Process validation protocol is prepared by QA department. Protocol is checked by QC department, production department and QA department. Validation protocol is reviewed by validation team which is constituted from Production, QC and QA department and it is approved by Head Quality & RA.

- X Tablets is to be manufactured in the manufacturing facility at ISL, GBU Derabassi as per the Master Formulae record and batch manufacturing record derived from same MFR.

**Objective**

To establish documented evidence, which will provide high degree of assurance that specific process and system shall produce a product meeting its predetermined specifications and quality characteristics? To validate and collect sufficient data to establish that manufacturing process of X Tablets will produce the product of its predetermined quality parameters based on validation batches.

At compression composite, various parameters have been checked by QC department and results were found to be within the acceptance limits. All the results have been recorded in observation.

**Table No. 1**

<table>
<thead>
<tr>
<th>Ref QSD</th>
<th>Acceptance Limits</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sr. No.</td>
<td>Test</td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td></td>
<td>White coloured oblong shaped , biconvex, uncoated tablet with breakline on one side and other side plain.</td>
<td>White coloured oblong shaped , biconvex uncoated tablet with breakline on one side and other side</td>
</tr>
<tr>
<td>Identification By HPLC</td>
<td>The retention time of the major peak of the sample solution corresponds to that of the standard solution.</td>
<td>plain</td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Identification By IR</td>
<td>IR absorption spectrum of test sample to be concordant with that of standard spectrum.</td>
<td>plain</td>
</tr>
<tr>
<td>Thickness</td>
<td>3.00± 0.3mm</td>
<td>3.02-3.10mm</td>
</tr>
<tr>
<td>Average Weight</td>
<td>80±.5%</td>
<td>80.50mg</td>
</tr>
<tr>
<td>Uniformity of weight</td>
<td>±7.5% of average wt of tablet</td>
<td>-1.65to1.95%</td>
</tr>
<tr>
<td>Hardness</td>
<td>Between 70-110N</td>
<td>88-112 N</td>
</tr>
<tr>
<td>Friability</td>
<td>NMT 1.0% w/w</td>
<td>0.09%</td>
</tr>
<tr>
<td>Disintegration Time</td>
<td>NMT 15 minutes</td>
<td>1min 2 sec</td>
</tr>
<tr>
<td>Dissolution Test</td>
<td>NLT 80% in 30 minutes</td>
<td>Min. 100.59%</td>
</tr>
<tr>
<td>Water content</td>
<td>NMT 5%</td>
<td>3.77%w/w</td>
</tr>
<tr>
<td>Length</td>
<td>8.00±0.2mm</td>
<td>7.98 - 8.01mm</td>
</tr>
<tr>
<td>Width</td>
<td>4.20±0.2mm</td>
<td>4.16 - 4.21</td>
</tr>
<tr>
<td>Assay by HPLC</td>
<td>Each uncoated tablet contain API NLT 4.75mg and not more than 5.25mg per tablet of average mass</td>
<td>101.92%</td>
</tr>
</tbody>
</table>

**OBSERVATION**

At film coating stage, various parameters have been checked by QC department and results were found to be within the acceptance limits. All the results have been recorded in observation.
Table no. 2

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Test</th>
<th>Acceptance Limits</th>
<th>Result</th>
<th>Batch I</th>
<th>Batch II</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Description</td>
<td>Salmon coloured oblong shaped, biconvex, film coated tablet with breakline on one side and other side plain.</td>
<td>Salmon coloured oblong shaped, biconvex, film coated tablet with breakline on one side and other side plain.</td>
<td>Salmon coloured oblong shaped, biconvex, film coated tablet with breakline on one side and other side plain.</td>
<td>Salmon coloured oblong shaped, biconvex, film coated tablet with breakline on one side and other side plain.</td>
</tr>
<tr>
<td>2.</td>
<td>Identification By HPLC</td>
<td>The retention time of the major peak of the sample solution corresponds to that of the standard solution.</td>
<td>Complies</td>
<td>Complies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Identification By IR</td>
<td>IR absorption spectrum of test sample to be concordant with that of standard spectrum.</td>
<td>Complies</td>
<td>Complies</td>
<td></td>
</tr>
<tr>
<td>Colors</td>
<td>Yellow iron oxide</td>
<td>A light red color develops with white precipitates that turns to yellowish green</td>
<td>Complies</td>
<td>Complies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Red iron oxide</td>
<td>Dark blue coloured precipitates are formed with potassium ferrocyanide test solution.</td>
<td>Complies</td>
<td>Complies</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Thickness</td>
<td>3.00± 0.3mm</td>
<td>3.02-3.10mm</td>
<td>3.01-3.12mm</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Average Weight</td>
<td>82.4mg±.5%</td>
<td>81.49mg</td>
<td>82.54mg</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Uniformity of weight</td>
<td>±7.5% of average wt of tablet</td>
<td>1.96% to1.95%</td>
<td>1.59% to 1.22%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subdivision of tablets A) By mass variation</td>
<td>85% to 115% of the average mass</td>
<td>Min-94.65% Max-106.54%</td>
<td>Min-94.65% Max-106.12%</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>B) By content uniformity</td>
<td>85% to 115% of the average content</td>
<td>Min-102.84% Max-108.61% Avg-106.58%</td>
<td>Min-102.25% Max-106.41% Avg- 104.75%</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>Disintegration Time</td>
<td>NMT 15 minutes</td>
<td>1min 2 sec</td>
<td>0min 56 sec</td>
<td></td>
</tr>
</tbody>
</table>
8. Dissolution Test (in 0.1N HCl) | NLT 80% in 30 minutes | Min. 97.04% Max 104.91% | Avg 101.62% | Min 92.47% Max 10.92% | Avg 96.97%

9. Water content (karl fischer) | NMT 5%w/w | 3.77%w/w | 4.37%w/w |

10. Assay by HPLC Each uncoated tablet contain API | NLT 4.75mg and not more than 5.25mg per tablet of average mass | 101.92% | 98.58%

11. Total impurity By HPLC | NMT 0.1% | 0.01% | 0.01%

**CONCLUSION**

The process validation study of X tablets has been carried out on two consecutive batches (Batch 1 and Batch 2) as per process validation protocol. All above mentioned two validation batches have been manufactured and compiled as per batch manufacturing record. The equipments used in manufacturing of validation batches are as per the list of qualified equipments mentioned in batch manufacturing record and qualification status of the same has been verified and mentioned in validation report.

Analytical instruments used in analysis of validation batches are qualified and calibrated. The same has been verified and mentioned in validation report. The starting materials used in manufacturing of validation batches has been procured from approved vendors and were analyzed by QC department and approved by QA department. The critical process parameters of manufacturing process have been evaluated with respect to quality attributes of drug product and found to be well within the predefined acceptance criteria. Sampling at various stages of validation batches was carried out as per established sampling plan as mentioned in protocol. All samples were analyzed as per established specifications and standard testing procedure. The analytical results of all two validation batches have been found to be well within the acceptance criteria. All two validation batches comply with the release specifications of drug product and meet the quality attributes of the product. The percentage (%) yields of all three validation batches at various manufacturing stages have been mentioned in relevant section of this report. On the basis of observations, limits for percentage (%) yield at various stages of manufacturing process of X tablets have been finalized as follows: Lubrication 98.0% Compression 98.0% Film coating 98.0% Inspection 98.0%
Based on predefined acceptance limit as mentioned in process validation protocol and findings of data and results compiled as per this summary report the manufacturing process of X tablet is considered to be validated for further manufacturing of batches.

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