Original Article

Process Validation Of Softgelatin Capsule In Pharmaceutical Industry

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Abstract

Process validation is the collection of data from the process design stage to commercial production that offers scientific evidence that a process is capable of reliably producing high-quality products.

The validation study for Ibuprofen Capsules 400 mg was conducted by taking into account critical process parameters at various stages of manufacturing process such as Fill preparation, gel preparation, encapsulation, drying, wiping, sorting, and inspection are all included.

The analytical results obtained for three consecutive process validation batches manufactured in accordance with approved BMR/BPR were documented in a controlled manner in accordance with the company's policies.The report is reviewed, conclusions are drawn, and the report is finally signed by the head of the quality department.The validated resultsof the three batchesshow that the manufacturing process of Ibuprofen Capsules 400 mg is capable of delivering quality product and ensuring that the process is under control during routine production.

Key Words: Process validation, Ibuprofen capsules, Critical Process Parameters, Process Design, Quality system.

I. INTRODUCTION:

The Food and Drug Administration (FDA) closely monitors the pharmaceutical industry's quality standards. The Current Good Manufacturing Practices (CGMPs) regulation for human medicines is the primary regulatory norm for assuring pharmaceutical quality that every batch of the medications they take will adhere to quality standards, ensuring their safety and efficacy. [1]

Title: Food and Drugs;	**Chapter1: FDA Department of health and human services** **Subpart C Subpart F Subpart H Subpart J**
General, part 211-Current Good Manufacturing Practice for Finished Pharmaceuticals	

Production and process control 211.110 sampling and testing of in-process material and drug products and 211.113 control of microbiological contamination.
Part 820-Quality System Regulation
820.100(b) deals with (Corrective Action and Preventive Action)

Fig 1: GMP regulations

Validation Under EU Regulation:

Documented evidence that the process performs effectively and reproducibly within established parameters to produce a product meeting its predetermined specifications and quality[2]

Validation Under PIC/S:

According to Annex 15 the principles of qualification & validation of the PIC/S is given under document PIC/S PI 006-3: Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation & Cleaning Validation can assist with the interpretation and the implementation." [3]

PHASES OF VALIDATION:

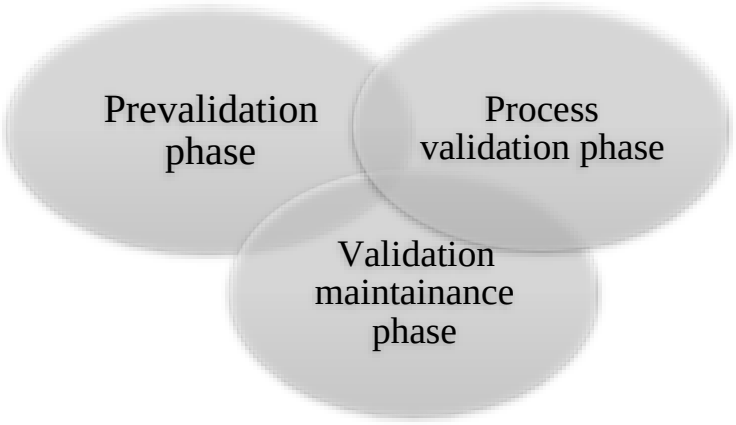


Fig 2: Phases of Validation Phase-1 (Pre –Validation Phase / Qualification Phase)

It encompasses all aspects of product development, formulation, pilot batch studies, scale-up studies, technology transfer to commercial scale batches, establishing stability conditions, and storage and handling of in-process and completed dosage forms.

Phase-2 (Process Validation Phase / Process Qualification Phase)

Its purpose is to ensure that all set critical process parameter limits are valid and that satisfactory goods can be generated even in the worst-case scenario.

Phase-3(Validation Maintenance Phase)

It necessitates a regular evaluation of all process-related documentation, including validation audit reports, to ensure that no changes, deviations, failures, or notifications have occurred in the production process, and that all modifications and sops, including change control, have been followed. [5]

STAGES OF VALIDATION:

Fig 3: Stages of Validation

Stage 1: Process Design

The goal of this stage is to design a process suitable for commercial manufacturing based on the knowledge gained through development and pilot scale that can consistently produce a product that meet its quality attributes.

Stage 2:Process Qualification

During this stage process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

Stage 3: Continued Process Verification

To achieve this purpose, a system for identifying unplanned deviations from the process as envisaged is required.Compliance with CGMP regulations.The data gathered should show thatCritical Quality Attributes are being monitored properly throughout the process.Relevant process trends and quality of incoming material, in-process and finished product should be included in the data collected.[6,7]

TYPES OF PROCESS VALIDATION:

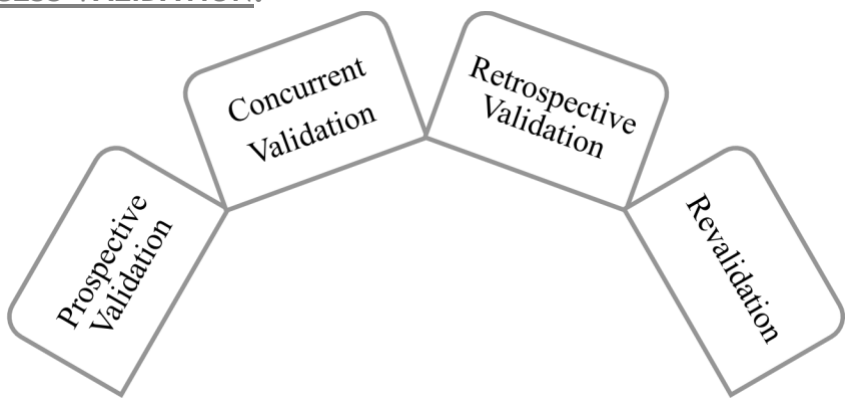


Fig 4: Types of Validation

I. Prospective Validation

Establishing documented evidence that a system accomplishes based on pre-planned protocols prior to process implementation. This method of validation is typically used if a new formula (or a new facility) needs to be tested before routine pharmaceutical manufacture begin.

II. Concurrent Validation

Concurrent validation is a method of establishing documented evidence that a facility and its processes perform what they claim to do, based on data collected during the process' real execution.

III. Retrospective Validation

Historical data can be used to validate these, providing the essential written evidence that a process is under control. As a result, this method of validation is only applicable for well-established processes and is ineffective for recent modifications such as product composition.

IV. Revalidation

Revalidation involves repeating all or part of the initial validation work. It entails looking into existing performance data. This strategy is required to keep a manufacturing plant validated – Equipment, Manufacturing methods & Information technology system.[8]

DEVIATION IN PROCESS VALIDATION:

Deviations from written procedures (or) any other approved documents, such as specifications, analytical procedures, or batch processing records, need to be thoroughly explored and dealt with. [14]

SYSTEMS FOR HANDLING DEVIATIONS:

Deviation permits quality improvement, yield improvement, improves Good Manufacturing Practices, safety reasons, market needs, regulatory compliance, or any other particular cause. Department heads identify deviations, which must be reviewed with Quality Assurance (QA) before the deviation is carried out. The department head must complete the form in accordance with the guidelines' structure, adding suggestions, comments, and a recommended time period for the deviation, then signed and forwarded to QA.

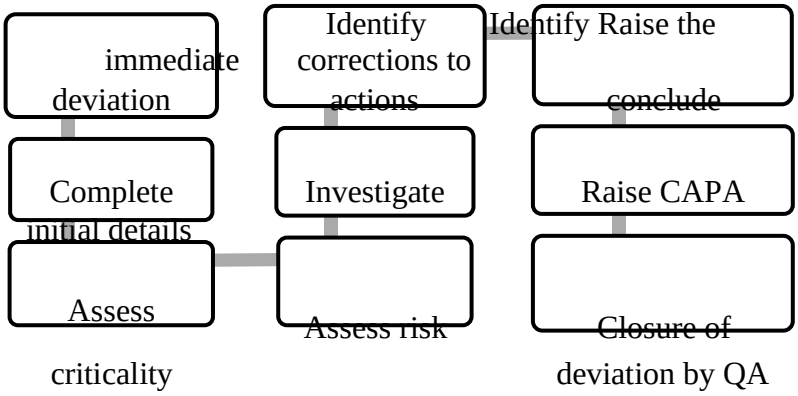


Fig 5: Overall flow for Deviation

Documents used in validation process:

Validation protocol: Procedures, test methods, equipment handling, requirements, acceptance criteria, report, and approval are all included in a written statement to conduct the validation process Protocol approval, Objective, Scope, Reason for Validation, Revalidation criteria, Responsibilities, Reference documents, Procedure, Deviations, Conclusions, Report and Approval should all be included.

Validation report: The approved validation technique, tabular or graphical findings, process monitoring (CPP, CQA), and all analytical results of validation batches should all be included in the validation report.

Validation master plan: It is a written, approved plan of objectives and action that outlines how and when a company will comply with GMP validation standards.

Standard operating procedures: Employees are given SOPs to teach them about their responsibilities and job instructions, and they must follow these processes in order to claim conformity with GMP principles and standards.[9, 10]

II. METHODOLOGY:

1. CAPSULE FILL PREPARATION:

Check the weight and A.R. No's ingredients against the formula record.Addall ingredients in a fill mixing tank and mix well at the appropriate RPM.Filter the above fill obtained through suitable mesh and collect it over the product fill holding tank.Intimate QA for in-process sampling for analysis.Label the capsule fill holding tank properly and close it tightly.Transfer the capsule fill to fill staging area.

(**Test to be done by QC:** Description, pH, Wt/ml and Assay)

2. CAPSULE SHELL PREPARATION:

Check the name, weight, raw material code and A.R. No's of all the ingredients.Allow the hot water circulation in gelatin melting tank jacket at temperature of 80°C to 90°C.Transfer all theingredients into the gelatin melting tank until creamy mixture is formed.Apply vacuum for 20 to 30 minutes at 600 to 700 mm of Hg and remove extra quantity of purified water, which is added in the capsule shell preparation. Take out a small quantity of gelatin mass and examine for the presence of air bubbles and homogeneity of gelatin mass. If air bubble is observed continue the vacuum till satisfactory gelatin mass is obtained.Inform QA to draw sample for in process analysis.[11,12]

(Test to be done by QC: Description, Loss on drying and Viscosity)

3. ENCAPSULATION:

As the gelatin ribbons travel between the die rolls, precisely measured amounts of the liquid fill matrix are injected from the wedge device. Here, the application of heat and pressure is used to seal the two soft gelatin capsule halves together. By raising edges around each die on the rollers, the capsules are automatically cleaved from the gel ribbon.

4. DRYING:

Collect the capsules from tumble drier and spread it in trays then stack in trolleys and keep in capsules drying area. Check the hardness (Hardness Limit: 8 – 9 N).

5. CAPSULE WIPING:

Load NMT 60 kg of dried capsules in wiping pan. Take 100 % IPA in a bowl, soak with sufficient of lint free wiping cloth and place them inside the wiping pan as per the Quantity.

6. SORTING AND METAL DETECTION:

Pour the capsules in hopper and start the vibrator. Allow the capsules to pass through the metal detector and adjust the sensitivity control such that it gets adequately detected.

7. CAPSULE PRINTING:

Allow the capsules to pass through the printing roller and adjust the printing roller for smooth and fine printing over the capsules. [13-15]

8. CAPSULE INSPECTION:

Remove Under Size Capsules, Over Size Capsules, Inspect for Leakers, Twins & De-Shaped.

9. BULK CAPSULE STORAGE:

Maximum permissible weight of capsule allowed to store in a poly bag is 8.0 kg and label it properly. **(Test to be Done by QC:** As per Bulk Product Specification)

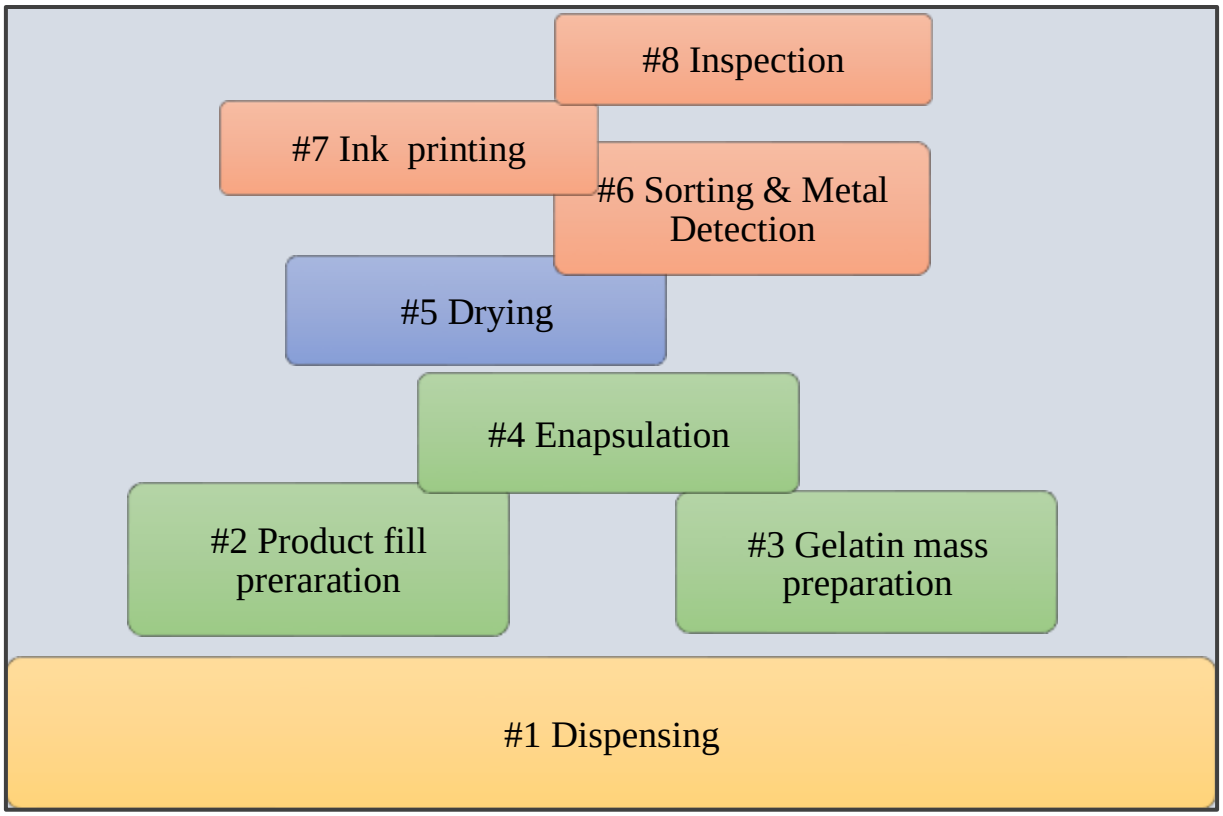
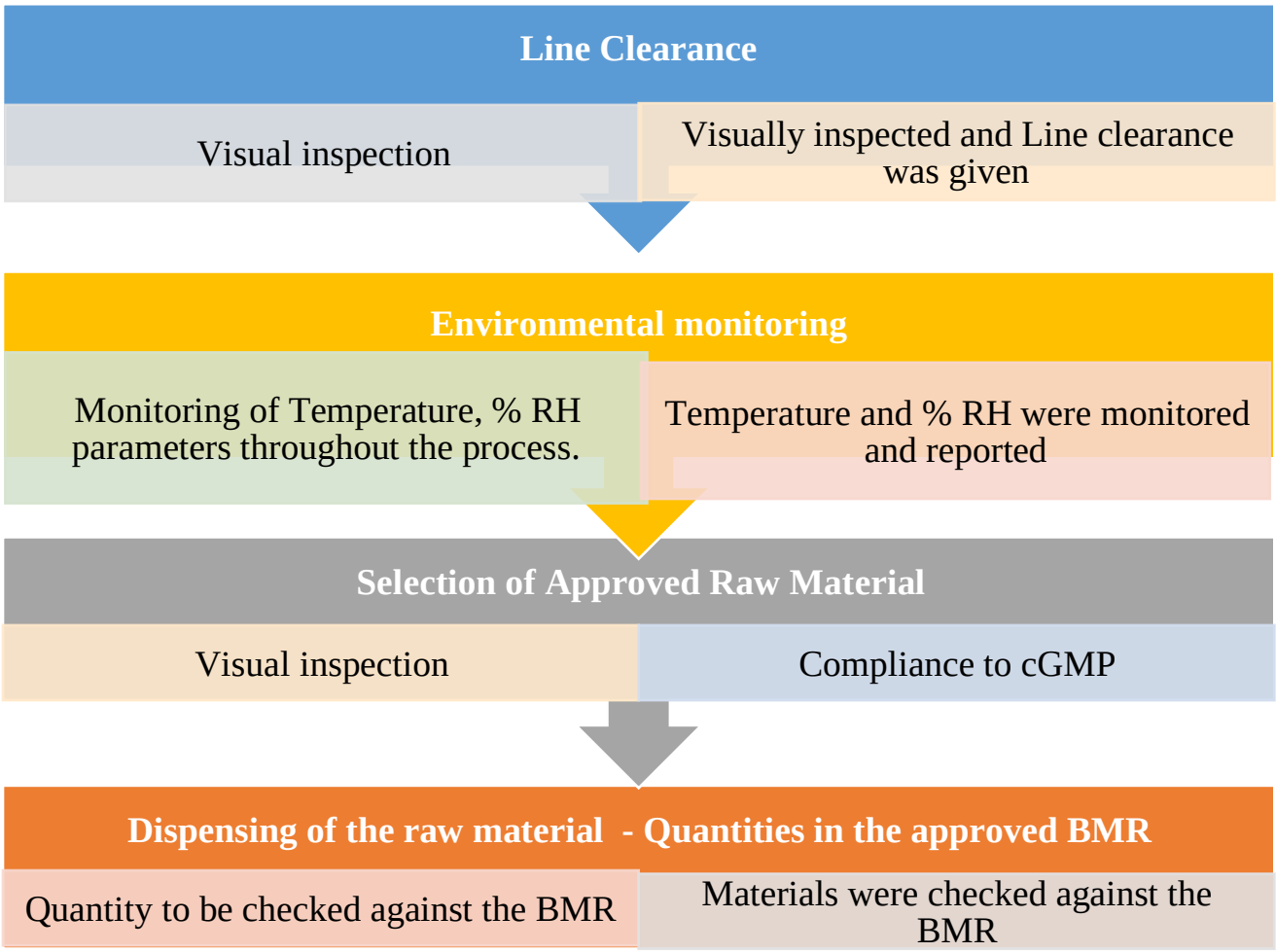


Fig 6: Soft Gelatin Capsule Manufacturing Flow

III. RESULT & DISCUSSION:

Control # 1 DISPENSING

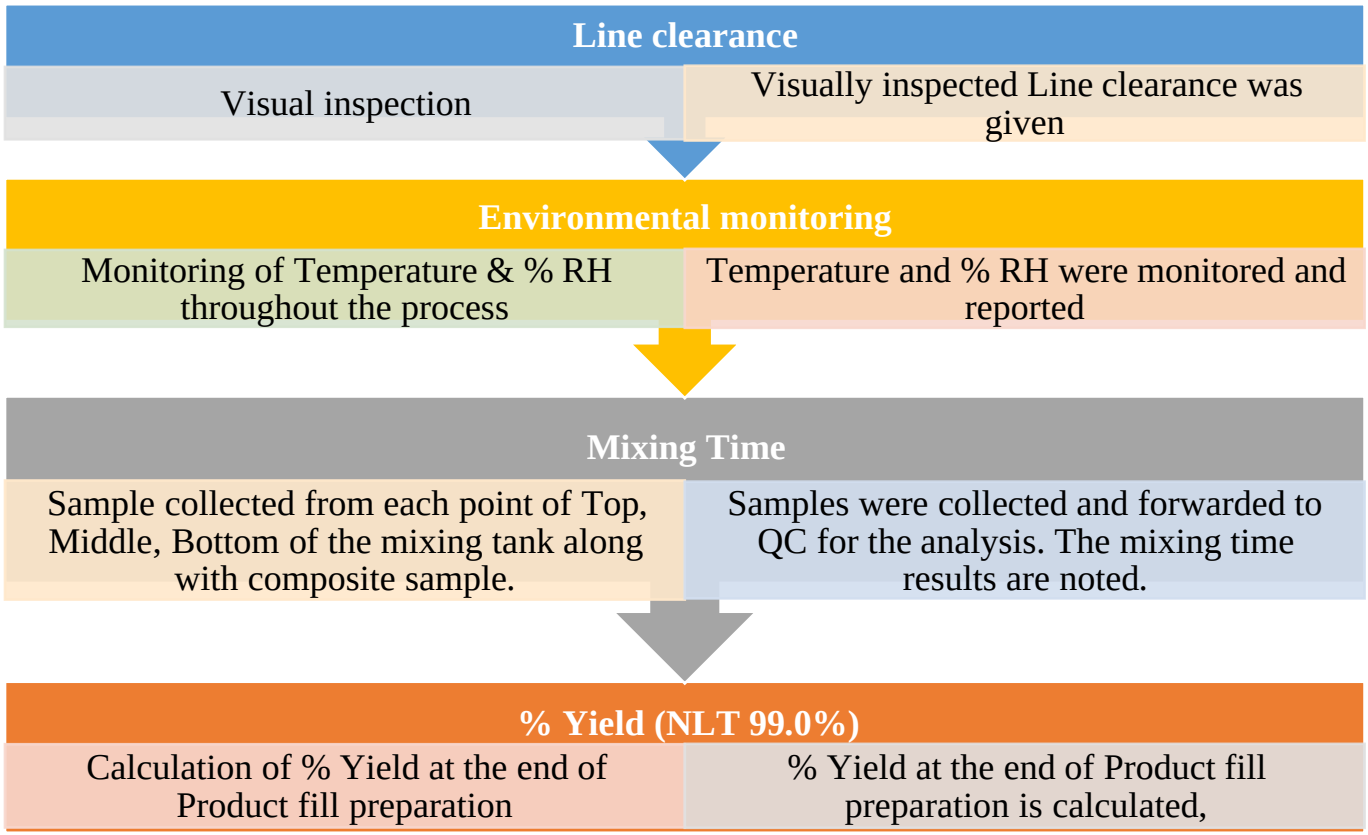
Fig7: Control variable for Dispensing



Control #2 PRODUCTS FILL PREPARATION (MEDICAMENT)

Carried out the manufacturing of the Fill Preparation as per the Procedure given in the Batch Manufacturing Record. On Completion of Manufacturing, Sample was withdrawn as per the SOP

Fig8: Control variable for capsule fill preparation

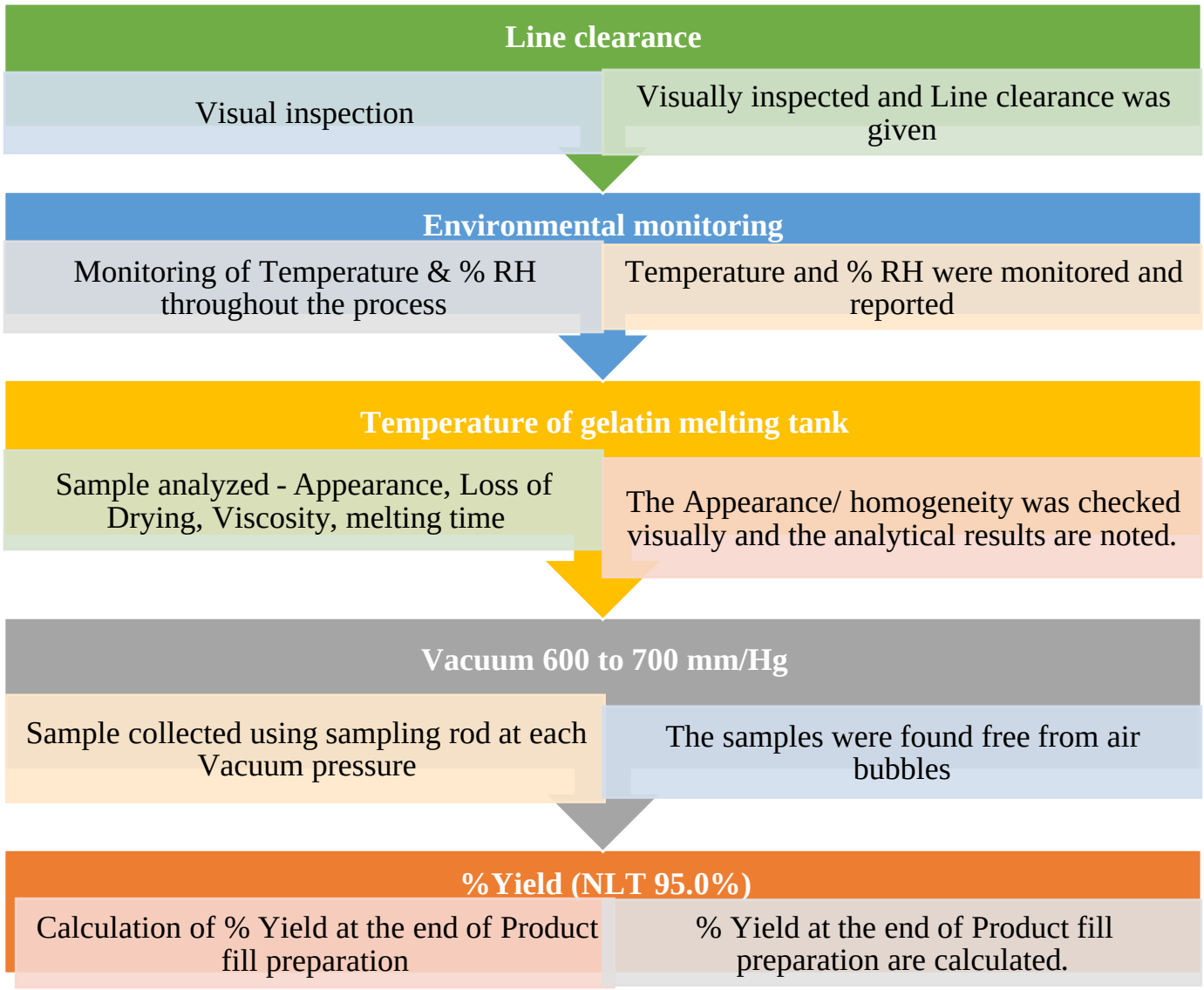


The analytical results of Assay, Microbial results and % yield calculated for all the three batches are within the specification limit; it can be concluded that the process is in a state of control.

Control # 3 CAPSULE SHELL PREPARATION

The manufacturing of the Shell mass is carried out as per the Procedure given in the Batch Manufacturing Record. On Completion of Shell mass Manufacturing, samples were collected from the bottom discharge valve of the Gelatin Melting Tank and carried out the tests as per in process QC Specification.[16]

Fig 9: Control variable for capsule shell preparation

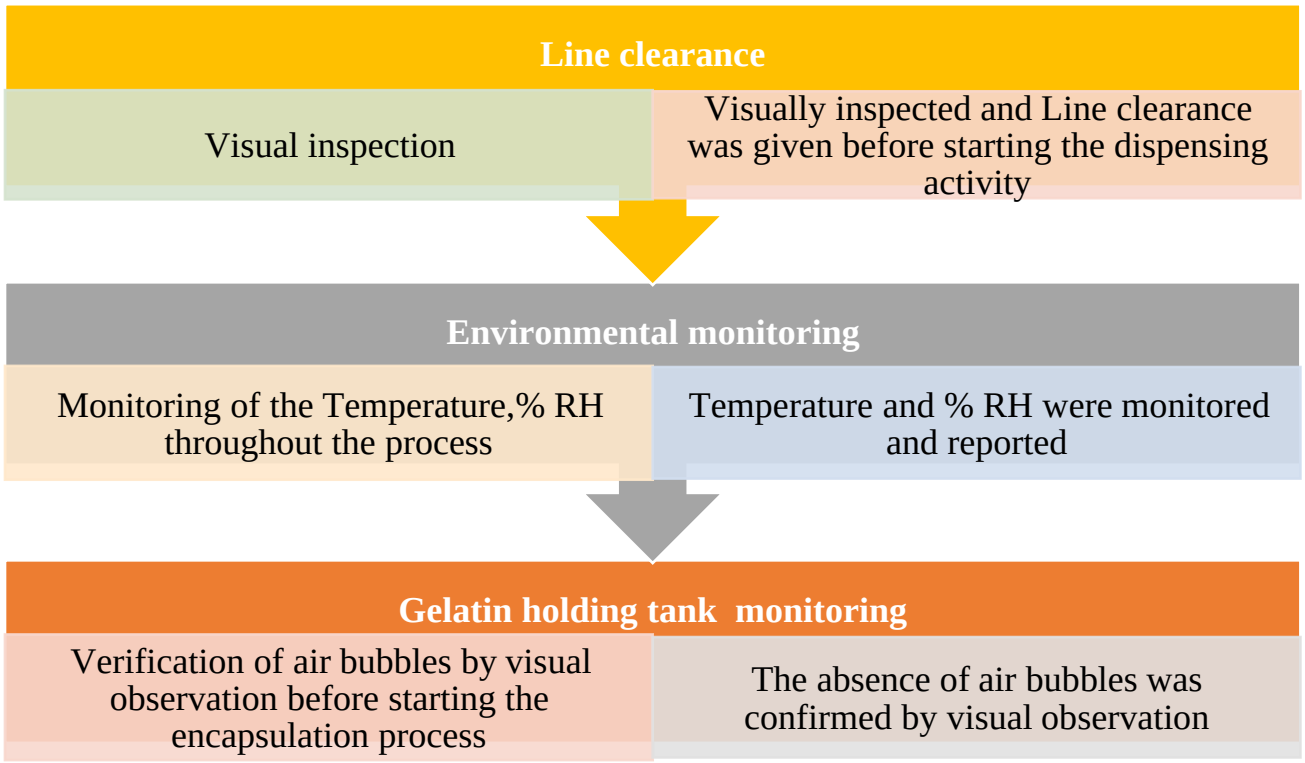


The analytical results of Viscosity and LOD of all the three batches are found satisfactory and well within the specification limit. The air bubbles are effectively removed by applying the Vacuum in between 600 and 700 mm/Hg. Hence, it can be concluded that the melting temperature can be fixed as 70°C ± 5°C. and Vacuum can be fixed as 600 and 700 mm/Hg for routine production batches.

Control #4 ENCAPSULATION

All the samples were collected as per the approved protocol and sent to Quality Control department for chemical Analysis.

Fig 10: Control variable for encapsulation stage

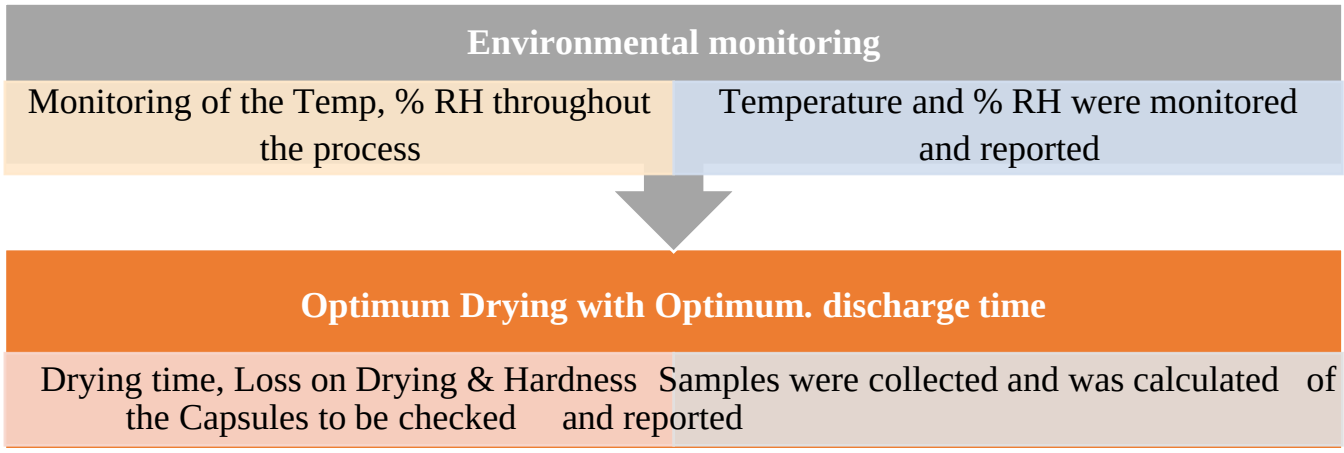


The analytical results obtained for all the three batches at encapsulation stages are well within the predefined specification. Hence it can be concluded that the Encapsulation process is in a state of control and same can be followed during routine manufacturing.[17]

Control # 5: Drying

The capsules from the tumble drier were collected and spreaded them onto the trays and stacked the trays on the trolleys and note the time of Initiation of Drying.The capsules are dried in the drying room at NMT 25ºC and RH 20±5 %

Fig 11:Control variable for Drying stage

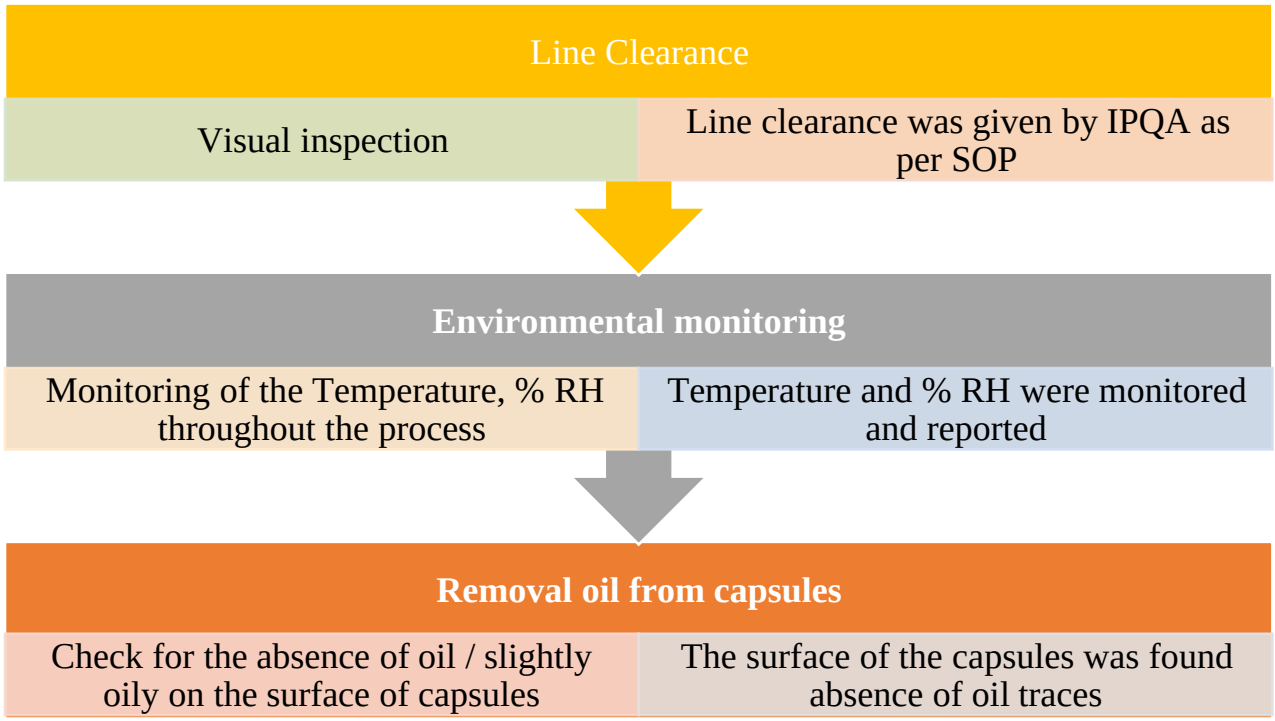


The Loss on drying and Hardness values of all the three batches shows that, the drying of capsules will be effective to attain proper LOD & Hardness values if the capsules are dried between 36 to 40 hours. However, hardness is the critical to conclude completion of drying of capsules.

Control # 6: Wiping

Took 25 kg of dried capsules with sufficient quantity (4 – 5) nos. lint free cloth and placed the cloths in wiping pan for 15 minutes. Removed the lint free cloth from pan. Added fresh (6) nos. lint free wiping cloth and continued the polishing for 15 minutes and checked the capsules for the dryness of oil.[18]

Fig12:Control variable for wiping stage



During verification of capsules of all the three batches after wiping, there are no oil traces found capsules and residual solvent IPA traces found with a Limit. Hence, it can be concluded that the wiping process is in a state of control and the same method can be followed during routine manufacturing.

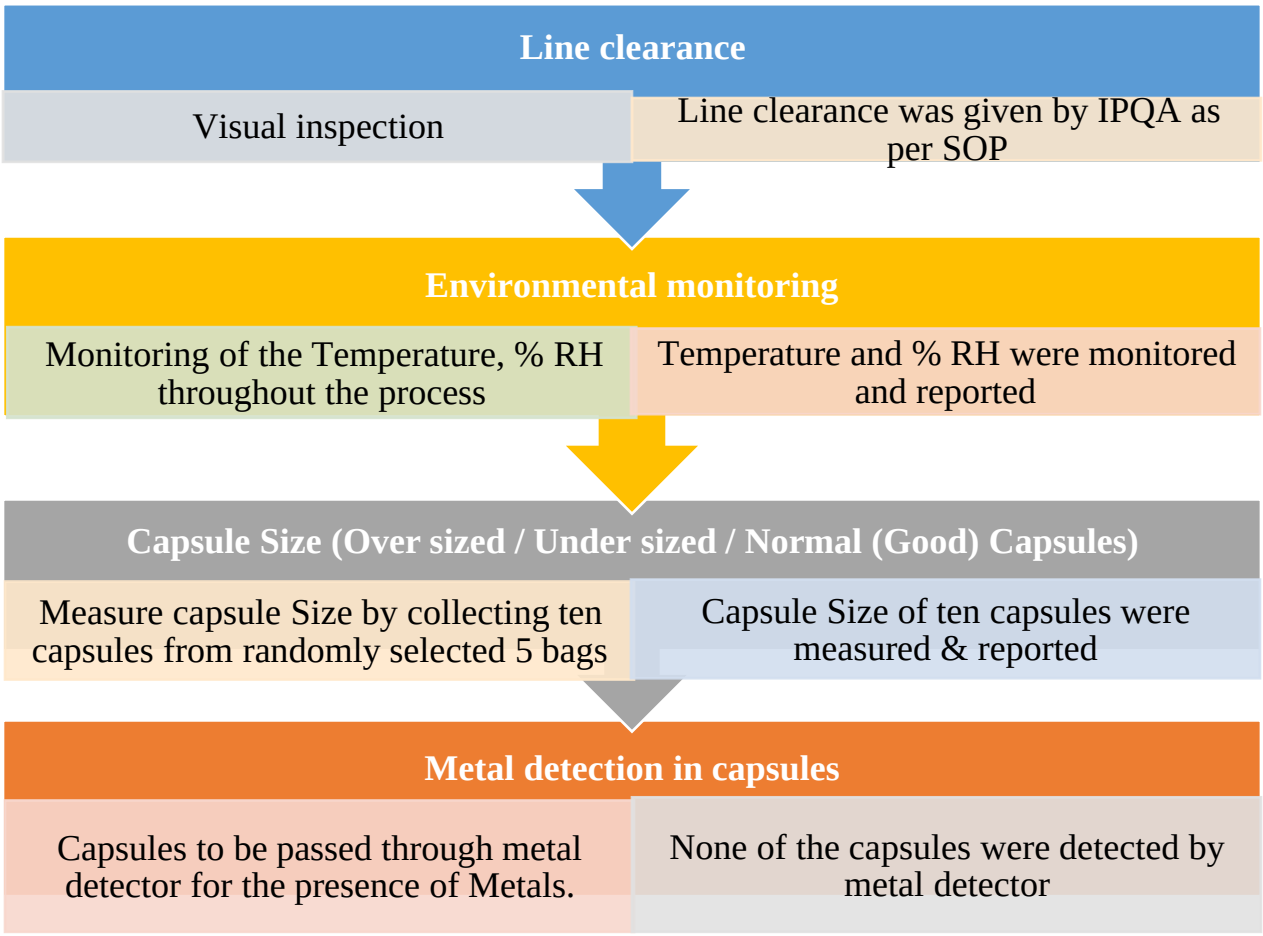
Based on the data obtained during wiping study of the capsules, the followings are included.

1. No oil traces on the capsules after wiping.
2. The capsules are free from traces of residual solvent.

Control # 7: SORTING

Loaded the wiped capsules in the Sorting Machine. Measured the size of the capsules using vernier caliper as per the procedure given in approved BMR.

Fig13: Control variable for Sorting stage

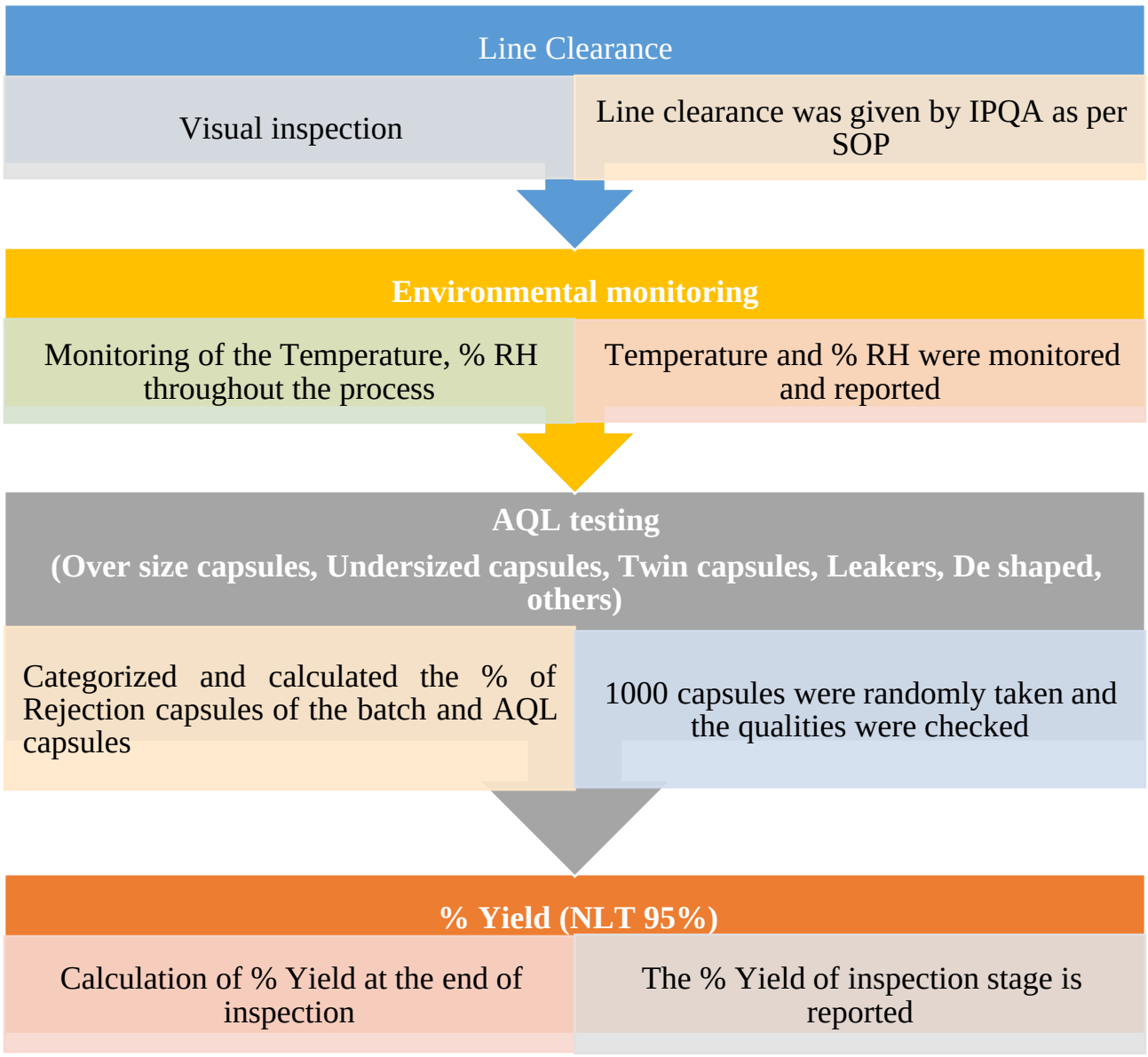


The measurement of capsule size and the metal detection process was found satisfactory. This shows that the process is in a state of control during sorting / metal detection.[19]

Control # 8 Inspection

Remove Under Size Capsules, Over Size Capsules, Inspect for Leakers, Twins & De-Shaped

Fig 14: Control variable for inspection stage



The analytical results of Inspection stage is found satisfactory and within the specification limit. The AQL testing and rejection shows that the process is in a state of control

IV. CONCLUSION:

In this present study, process validation of soft gelatin capsules ofwas framed.The validation was done at the various stages of manufacturing such as Gel, fill preparation, Encapsulation, Drying, Wiping, Sorting, Printing and Inspection.If three batches were validated and found to be within the specification limits; the entire process will in state of control.As the entire three batches data is in control, the product obtained will meetsss its requirements and quality attributes.

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