WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.421
Volume 8, Issue 2, 1208-1233 Review Article ISSN 2278 – 4357

A REVIEW ON PROCESS VALIDATION: STANDARDIZATION OF HERBAL TABLET FORMULATION

Anil M. Sawant[1]*, Sultan A. Mulla[1], Devyani V. Pisal[1], Sachin S. Mali[2], Dipak P. Mali[1], Durgacharan A. Bhagwat[1]

[1]Department of Pharmacetical Quality Assurance, Bharati Vidyapeeth College of Pharmacy, Near Chitranagari, Kolhapur, 416 013, Maharashtra, India.

[2]Department of Pharmaceutics, Y. D. Mane Institute of Pharmacy, Kagal, 416 216, Maharashtra, India.

Article Received on
17 Dec. 2018,

Revised on 08 Jan. 2019,
Accepted on 29 Jan. 2019

DOI: 10.20959/wjpps20192-12557

***Corresponding Author**

1. Anil M. Sawant
Department of Pharmaceutics, Bharati Vidyapeeth College of Pharmacy, Kolhapur.

2. Sachin S. Mali
Department of Pharmaceutics, Y. D. Mane Institute of Pharmacy, Kagal.

ABSTRACT

Validation is a concept that is fundamental to GMP and any quality assurance programme. Validation of the individual stage of the process is called process validation. Process is developed in such way that the required parameters achieved and it ensures that the output of process will consistently meet the required parameters during routing production. This concept is applied in pharmaceutical industry, but not that much deeply applied in herbal industry. The use of herbal medicine is the oldest form of healthcare. About 80% of the world's population has belief in traditional medicine, particularly herbal drugs for their primary healthcare. India has a rich tradition of herbal medicine as evident from Ayurveda. As growing public interest in use of herbal medicines, it is necessary to development of modern and objective standards for evaluating quality of herbal medicines. So that it is a need process validation in manufacturing of herbal drugs for control the quality of herbal drugs. The reasons for doing process validation in herbal manufacturing industry are manufacturers are required by law to confirm to GMP regulations, good business dictates that a manufacturer avoids the possibility of rejected or recalled batches, process validation helps to ensure product uniformity, reproducibility, quality and to make process economical.

KEYWORDS: Process validation, Standardization, IPQC, Quality assurance, Herbal formulation, etc.

INTRODUCTION

USFDA defines validation as: "**Validation** is 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. [1]According to European commission: Validation is defined as "Action providing in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually lead to the expected results.[1] 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.[7] Process validation generally has four types: Prospective process validation, concurrent process validation, retrospective process validation and revalidation. Prospective validation is defined as the establishment of documented evidence that a system does what it purports to do based on a pre planned protocol. This validation is usually carried out prior to the introduction of new drugs and their manufacturing process. This approach to validation is normally under taken whenever new formula, process or facility must be validated before routine pharmaceutical formulation commences. In fact validation of process by this approach often leads to transfer of the manufacturing process from the development function to product. The objective of prospective validation is to prove or demonstrate that the process will work in accordance with a predefined validation protocol prepared for pilot product trails. Concurrent process validation is similar to the prospective validation. 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 state of control. This study can be carried out on commercial batches. Retrospective validation is defined as the establishment of documented evidence that a system does what it purports to do on review and analysis of past experience of production on the condition that composition, procedures, and equipment remain unchanged & historical information. The sources of such data are production, QA and QC records. The issues to be addressed here are changes to equipment, process, specification and other relevant changes in the past. Revalidation 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, equipment or site location, batch size and in the case of sequential batches that do not meet product specifications. In case of no changes revalidation shall be carried out at specific time intervals.[1]

Need of process validation

Validation is the overall expression for a sequence of activities in order to demonstrate and document that a specific product can be reliably manufactured by the designed process, usually, depending on the complexity of today's pharmaceutical products, the manufacturer must ensure. Quality cannot be adequately assured merely by in-process and finished product inspection or testing so the firms should employ objective measures (e.g. validation) wherever feasible and meaningful to achieve adequate assurance.Quality, Safety and Effectiveness must be designed and built in to the product, quality cannot be inspected or tested in the finished products and each step of the manufacturing process must be controlled to maximize the probability that the finished product meets all quality and design specifications.To confirm the process design as capable of reproducible commercial manufacturing, Risk/Worst Case assessment. To provide ongoing assurance that the process remains in a state of control during routine production through quality procedures and continuous improvement initiatives, Quantitatively determine the variability of a process and its control, The variability within and between batches can be evaluated to determine the inner and intra-batch variability. Lack of written documentary evidence on clinical efficacy. TM- more particularly Ayurveda is essentially a highly customized and individualized medicine. Transformation into a generalized and commercial system has adversely affected the system .Lack of consistency in quality in batch to batch production of products. Lack of a well defined and well orchestrated SOP, so as validation is very important.

Herbal medicines, includes herbs, herbal materials, herbal preparation and finished herbal products. Herbal medicines are used very commonly in various health practices or therapies of Traditional Medicines like Chinese medicines, Ayurveda, Unani, Naturopathy, Osteopathy, and Homeopathy .The medicinal plants are important sources for pharmaceutical manufacturing. Medicinal plants and herbal medicines account for a significant percentage of the pharmaceutical market. As the side effects of synthetic medicines have started getting more apparent, more emphasis is given to prepare formulations from herbs. The herbal medicines however, suffer from lack of standardization parameters. The main limitation is the lack of standardization of raw materials of processing methods and the final products, dosage formulation and the non-existence of criteria for quality control. It is necessary to introduce measure on the regulation of herbal medicines to ensure quality, safety, efficacy of herbal medicines by using modern techniques, applying suitable standards and GMP.[2,6]

Standardization of herbal medicines is the process of prescribing a set of standards or inherent characteristics, constant parameters, definitive qualitative and quantitative values that carry an assurance of quality, efficacy, safety, and reproducibility. It is the process of developing and agreeing upon technical standards. Standardization is a tool in quality control process. Standardization of herbal products can be divided into two categories, first, an active constituent's extract, where the biochemical principles are known and have therapeutic values and second, a marker extract, where the active principle is not known and a characteristic compound is used as marker to assess the presence of other therapeutic biochemical compounds. Standardization has limitations because only isolated compounds are considered, ignoring the whole constituents of the herb, which may have synergistic or buffering activities to reduce the side effects.

Why to Validate the Processes: There are many reasons, in addition to the regulatory requirements, for validating processes. A manufacturer can assure through careful design of the device and packaging, careful design and validation of processes, and process controls, that there is a high probability that all manufactured units will meet specifications and have uniform quality. The dependence on intensive in-process and finished device testing can be reduced. 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 [10]. 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.

Approach to Process Validation: For purposes of this guidance, 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. This guidance describes process validation activities in three stages.[22]

• 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.

This guidance describes activities typical of each stage, but in practice, some activities might occur in multiple stages. Before any batch from the process is commercially distributed for use by consumers, a manufacturer should have gained a high degree of assurance in the performance of the manufacturing process such that it will consistently produce APIs and drug products meeting those attributes relating to identity, strength, quality, purity, and potency. The assurance should be obtained from objective information and data from laboratory-, pilot-, and/or commercialscale studies. Information and data should demonstrate that the commercial manufacturing process is capable of consistently producing acceptable quality products within commercial manufacturing conditions.[V]

A successful validation program depends upon information and knowledge from product and process development. This knowledge and understanding is the basis for establishing an approach to control of the manufacturing process that results in products with the desired quality attributes.

Manufacturers should

• Understand the sources of variation

• Detect the presence and degree of variation

• Understand the impact of variation on the process and ultimately on product attributes

• Control the variation in a manner commensurate with the risk it represents to the process and product.

Each manufacturer should judge whether it has gained sufficient understanding to provide a high degree of assurance in its manufacturing process to justify commercial distribution of the product. Focusing exclusively on qualification efforts without also understanding the manufacturing process and associated variations may not lead to adequate assurance of quality. After establishing and confirming the process, manufacturers must maintain the process in a state of control over the life of the process, even as materials, equipment, production environment, personnel, and manufacturing procedures change.[9] Manufacturers should use ongoing programs to collect and analyze product and process data to evaluate the state of control of the process. These programs may identify process or product problems or opportunities for process improvements that can be evaluated and implemented through some

of the activities described in Stages 1 and 2. Manufacturers of legacy products can take advantage of the knowledge gained from the original process development and qualification work as well as manufacturing experience to continually improve their processes. Implementation of the recommendations in this guidance for legacy products and processes would likely begin with the activities described in Stage 3.[22]

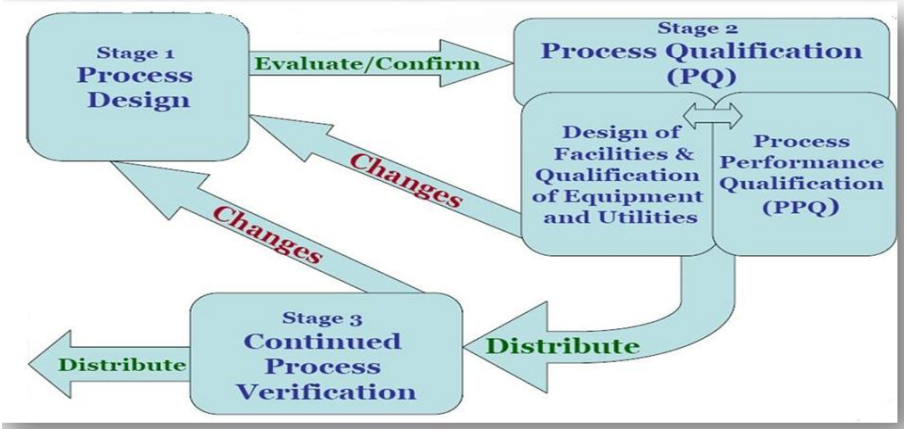

Figure 1: Approach to Process Validation.

Responsible authorities for validation: The validation working party is convened to define progress, coordinate and ultimately, approve the entire effort, including all of the documentation generated. The working party would usually include the following staff members, preferably those with a good insight into the company's operation.

- Head of quality assurance
- Head of engineering
- Validation manager
- Production manager

Table No 1: Responsible Authorities for Validation

Department /Designation	Responsibility
Manager Production	Responsible for manufacturing of batches and review of protocol and report.
Manager QC	Responsible for analysis of samples collected
Executive QC	Responsible for samples collection and submission to QC
Manager Maintenance	Providing utilities and engineering support
Executive Production	Responsible for preparation of protocol and manufacturing of validation batches
Manager QA	Responsible for protocol authorization and preparation of summary report.

Types of Validation

1. Analytical Validation

Analytical validation is an evaluation of product quality attributes through testing, to demonstrate reliability is maintained throughout the product life cycle and that the precision, accuracy, purity, strength, specification has not been compromised.

2. Equipment Validation: Equipment validation is divided in to Design Qualification(DQ), Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ). IQ documents specific static attributes of a facility or item to prove that the installation of unit has been correctly performed. An OQ is the ensuring that the equipment can deliver operating ranges as specified in purchase order. PQ is concerned with proving that the process being investigated works as it is supposed to do.

Validation Protocol: A written plan stating how validation will be conducted, including test parameters, product characteristics, production and packaging equipment, and decision points on what constitutes acceptable test results. This document should give details of critical steps of the manufacturing process that should be measured, the allowable range of variability and the manner in which the system will be tested.

The validation protocol provides a synopsis of what is hoped to be accomplished. The protocol should list the selected process and control parameters, state the number of batches to be included in the study, and specify how the data, once assembled, will be treated for relevance. The date of approval by the validation team should also be noted. In the case where a protocol is altered or modified after its approval, appropriate reasoning for such a change must be documented.[22]

The validation protocol should be numbered, signed and dated, and should contain as a minimum the following information

1. Title
2. Objective & Scope
3. Responsibility
4. Protocol Approval
5. Validation Team
6. Product Composition
7. Process Flow Chart

8. Manufacturing Process
9. Review of Equipments / Utilities
10. Review of Raw Materials and Packing Materials
11. Review of Analytical and Batch Manufacturing Records
12. Review of Batch Quantities for Validation (Raw Materials)
13. Review of Batch Quantities for Validation (Packing Materials)
15. Review of Process Parameters
16. Validation Procedure
17. Sampling Location
18. Documentation
19. Acceptance Criteria
20. Summary
21. Conclusion

Validation Master Plan[7,22]

A validation master plan is a document that summarizes the company's overall philosophy, intentions and approaches to be used for establishing performance adequacy. The validation master plan should be agreed upon by management Validation in general requires meticulous preparation and careful planning of the various steps in the process. In addition, all work should be carried out in a structured way according to formally authorized standard operating procedures. All observations must be documented and where possible must be recorded as actual numerical results.[V,G]

The validation master plan should provide an overview of the entire validation operation, its organizational structure, its content and planning. The main elements include the list/inventory of the items to be validated and planning schedule. All validation activities relating to critical technical operations, relevant to product and process controls within a firm should be included in the validation master plan. It should comprise all prospective, concurrent and retrospective validations as well as re-validation. The validation master plan should be a summary document and should therefore be brief, concise and clear. It should not repeat information documented elsewhere but should refer to existing documents such as policy documents, SOP's and validation protocols and reports.

The format and content should include

- Introduction: validation policy, scope, location and schedule
- Organizational structure: personnel responsibilities
- Plant/ process /product description: rational for inclusions or exclusions and extent of validation
- Specific process considerations that are critical and those requiring extra attention
- List of products/ processes/ systems to be validated, summarized in a matrix format, validation approach
- Re-validation activities, actual status and future planning
- Key acceptance criteria
- Documentation format
- Reference to the required SOP's.

Types of Process Validation[22]

1 Prospective process validation: This is performed for all new equipments, products, and processes. It is proactive approach of documenting the design, specifications and performance before the system is operational.

2. Concurrent validation: Concurrent validation is used for establishing documented evidence that a facility and processes do what they purport to do, based on information generated during actual imputation of the process. This approach involves monitoring of critical processing steps and end product testing of current production, to show that the manufacturing process is in a state of control.

3. Retrospective Process Validation: In some cases a product may have been on the market without sufficient premarket process validation. In these cases, it may be possible to validate, in some measure, the adequacy of the process by examination of accumulated test data on the product and records of the manufacturing procedures used.

4. Revalidation

Revalidation means repeating the original validation effort or any part of it, and includes investigative review of existing performance data. This approach is essential to maintain the validated status of the plant, equipment, manufacturing processes and computer systems. Possible reasons for starting the revalidation process include.

- The transfer of a product from one plant to another
- Changes to the product, the plant, the manufacturing process, the cleaning process, or other changes that could affect product quality
- The necessity of periodic checking of the validation results
- Significant (usually order of magnitude) increase or decrease in batch size.
- Sequential batches that fail to meet product and process specifications.
- The scope of revalidation procedures depends on the extent of the changes and the effect upon the product.

Regulations[22]

Validation is considered to be integral part of GMPs, compliance with validation requirements is necessary for obtaining approval to manufacture and to introduce new products in market. The FDA's cGMP refers to the concept of the validation in both sections, 21 CFR 210 and 211. 21 CFR 211.100 states: "There shall be written procedure for production and process control design to assure that the drug product have the identity, purity, strength, and quality they purport or are represented possess.

Importance of Process Validation

- Quality: customer- patient satisfaction. It has been built in to product.
- Understanding system, equipment, process: Process improvement, rapid failure investigation, increase employee awareness.
- Cost reduction:

- Reduce rejects and rewards.
- Reduce testing of raw materials, bulk formulations, and finished product.
- Longer equipment life due to operating the equipment as per manufacturer's specifications and the establishing of cost effective preventing maintenance schedules.

Process Validation Sequence[22]

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. The activities relating to validation studies may be classified into three stages.

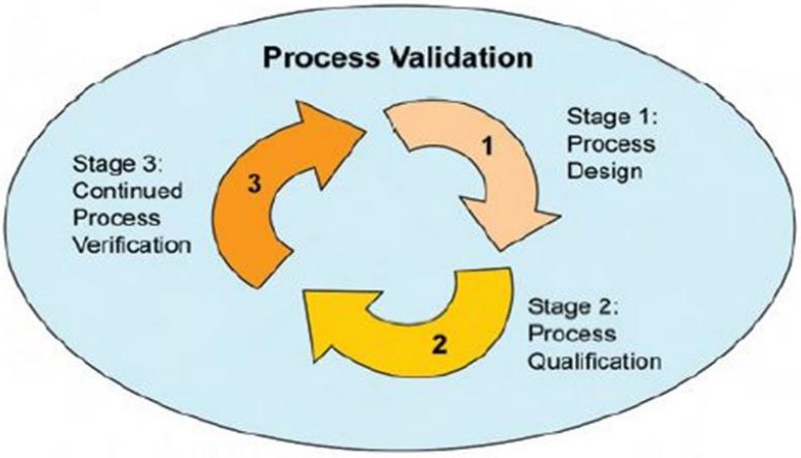

Figure. 2: Process Validation Stages.

Stage 1 – Process Design: Focusing exclusively on qualification efforts without also understanding the manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities. It 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. Also this is the stage in which the establishment of a strategy for process control is taking place using accumulation knowledge and understanding of the process.

Stage 2 – Process Qualification: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing. It confirms that all established limits of the critical Process Parameters are valid and that satisfactory products can be produced even under "worst case" conditions. GMP compliant procedures must be followed in this stage and successful completion of this stage is necessary before commercial distribution of a product.

There are two aspect of process qualification

a) Design of facilities and qualification of equipment and utilities

- Proper design of manufacturing facility is desired under the 21 CFR part 211, subpart C, of the CGMP regulation on Buildings and Facilities.
- Activities performed to assure proper facility design and that the equipment and utilities are suitable for their intended use and perform properly.

b) Process Performance qualification

"Criteria and process performance indicators that allow for a science and risk-based decision about the ability of the process to consistently produce quality products".

- Part of the planning for stage 2 involves defining performance criteria and deciding what data to collect when, how much data, and appropriate analysis of the data.
- Likely consist of planned comparisons and evaluations of some combination of process measures as well as in-process and trial product attributes.
- Manufacturer must scientifically determine suitable criteria and justify it.
- Objective measures, where possible.
- May be possible to leverage earlier study data if relevant to the commercial scale.

Stage 3 – Continued Process Verification

Ongoing assurance is gained during routine production that the process remains in a state of control. The validation maintenance stage requires 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.

Herbal Medicines[15]

The World Health Organization (WHO) defined ''herbal medicine'' as: a plantderived material or preparation with therapeutic or other human health benefits which contains either raw or processed ingredients from one or more plants.

Herbal medicines can be classified into three groups

1. Herbal materials (raw or processed herbal materials, e.g. powder, slice),
2. Traditional herbal products (decoctions, tablets, pills or capsules containing crude herbal materials or crude extracts),
3. Standardized herbal products (formulations containing standardized extracts or purified substances.

Standardization of Herbal Medicines[18]

This involves adjusting the herbal drug preparation to a defined content of a constituent or a group of substances with known therapeutic activity by adding excipients or by mixing herbal drugs or herbal drug preparations.

Need of Process Validation in Herbal[7,19,20]

The validation of herbal products is a major public health concern. In this regard, there is no control by the government agencies, despite the existence of certain guidelines in some individual countries and those outlined by the WHO. If the herbal products are marketed as therapeutic agents, and irrespective of whether the products really have any positive effects to cure and reduce the severity of the disease, it is necessary to ensure scientific validation and periodic monitoring of the quality and efficacy.

This concept of validation is getting well applied to manufacturing of synthetic drugs from long time back. But this concept is not that much deeply or methodically studied and applied for the manufacturing of herbal drugs. All international regulations like USFDA, MCC, MHRA, TGA etc. shows the applicability of validation to pharmaceutical manufacturing but no one regulation except WHO applies the validation concept to manufacturing of herbal drugs. WHO also emphasize on very little part of validation. Therefore introduction of scientific validation would control the production of impure and adulterated herbal product.

Validation Model[22]**:** There is simple and mostly used validation model for manufacturing of synthetic drugs.This model is applied to for manufacturing of herbal drugs. Generally this model is straightforward that means starting from input and ends to output. But in case of validation one has to go in reverse direction. First of all to identify and define which type of quality product required i.e. product has its own identity, strength, safety, purity and efficacy. This model is also applicable to herbal manufacturing industry.

- Identity - having specific shape, packing
- Strength - having specific strength (500mg/tablet, strip of 10 tablets having 500mg/tablet etc.)
- Safety - safe for both i.e. persons who are engaged in the manufacturing and the persons who are going to take that tablet.
- Purity - shows purity (99.9% pure) Efficacy - it shows the desired therapeutic efficacy.
- After deciding the required output, the processes and its parameter are defined,
- Mixing - how much time is required for mixing?
- Granulation - which type of granulation (Wet or Dry) for how much time?
- Compression - how much pressure and for how much of time is required?
- Packing - which type of packing?

Process flow in Product Manufacturing

1. Process Description
2. Raw Material Dispensing
3. Raw Material Quantity Verification
4. Sifting
5. Dry Mixing
6. Granulation
7. Drying
8. Mixing of Lubricant
9. Compression
10. Packaging.

Standardization Methods for raw Materials

1. Physical

- Moisture content
- Ash value
- Extractive value
- Foreign matter

2. Chemical

- Chromatographic analysis

3. Botanical

- Macroscopic
- Microscopic

1. Physical method

a. Moisture content-check the content of moisture using moisture balance.

b. Ash value: To determine ash content, the plant material is burnt and the residual ash is measured as total and acid-insoluble ash. Total ash is the measure of the total amount of material left after burning and includes ash derived from the part of the plant itself and acid-insoluble ash. The latter is the residue obtained after boiling the total ash with dilute hydrochloric acid, and burning the remaining insoluble matter. The second procedure measures the amount of silica present, especially in the form of sand and siliceous earth (AOAC, 2005).[6]

Figure. 3: Ash value.

c. Determination of extractive values

i) Determination of water-soluble extractive: 2.5 g of test sample was weighed and then macerated with 50 ml of water in a closed flask for twenty-four hours, shaked frequently during six hours and allowing standing for eighteen hours. It was filtered rapidly, taking precautions against the loss of solvent. 25 ml of the filtrate was taken and evaporated to dryness in a tarred flat bottomed shallow dish at 105˚C, to constant weight and weighed the percentage of water soluble extractive was calculated with reference to the air dried sample.

ii) Determination of alcohol-soluble extractive: Procedure for water soluble extractive was followed for the determination of alcohol soluble extractive but 90% ethanol was used instead of water.

iii) Determination of chloroform soluble extractive: Procedure for chloroform soluble extractive was followed for the determination of chloroform soluble extractive but chloroform was used instead of water.

d) Foreign matter

Weigh a sample of herbal material, taking the quantity indicated above unless otherwise specified in the test procedures for the herbal material concerned. Spread it in a thin layer and sort the foreign matter into groups either by visual inspection, using a magnifying lens (6× or 10×), or with the help of a suitable sieve, according to the requirements for the specific herbal material. Sift the remainder of the sample through a No. 250 sieve; dust is regarded as mineral admixture. Weigh the portions of this sorted foreign matter to within 0.05 g. Calculate the content of each group in grams per 100 g of air-dried sample. For some herbal materials where the foreign matter may closely resemble the material itself, it may be necessary to take a pooled sample of the herbal material and apply a critical test-either

chemical, physical or by microscopy. The proportion of foreign matter is calculated from the sum of the portions that fail to respond to the test.[21]

2. Chemical

- Chromatographic analysis

❖ Thin-layer chromatography.

Thin-layer chromatography is particularly valuable for the qualitative determination of small amounts of impurities. The principles of thin-layer chromatography and application of the technique in pharmaceutical analysis are described in The international pharmacopoeia . As it is effective and easy to perform, and the equipment required is inexpensive, the technique is frequently used for evaluating herbal materials and their preparations.[21]

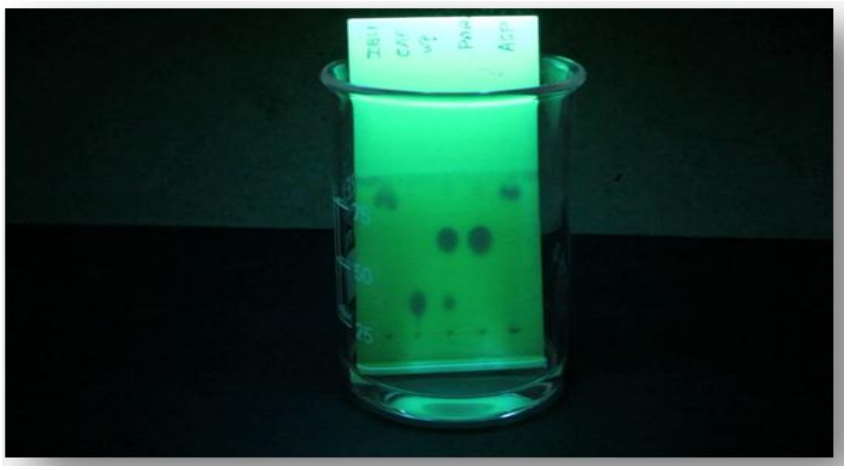

Figure. 4: Thin-layer chromatography.

The following parameters should be determined on the basis of published pharmacopoeial monographs or established experimentally for the analysis of each individual herbal material:

- Type of adsorbent and method of activation (if no information on the latter can be obtained, heat at 110 °C for 30 minutes).
- Method of preparation and concentration of the test and reference solutions.
- Volume of the solutions to be applied on the plate
- Mobile phase and the distance of migration.
- Drying conditions (including temperature) and method of detection.
- For the spots obtained: number and approximate position (or the Rf values if necessary).
- fluorescence and colour.

3) Botanical

❖ **Macroscopic and microscopic examination:** Herbal materials are categorized according to sensory, macroscopic and microscopic characteristics. An examination to determine these characteristics is the first step towards establishing the identity and the degree of purity of such materials, and should be carried out before any further tests are undertaken. Wherever possible, authentic specimens of the material in question and samples of pharmacopoeial quality should be available to serve as a reference.

Visual inspection provides the simplest and quickest means by which to establish identity, purity and — possibly — quality. If a sample is found to be significantly different from the specifications in terms of colour, consistency, odour or taste, it is considered as not fulfilling the requirements. However, judgement must be exercised when considering odour and taste, owing to variability in assessment from person to person or by the same person at different times.

Macroscopic identity of herbal materials is based on shape, size, colour, surface characteristics, texture, fracture characteristics and appearance of the cut surface. However, since these characteristics are judged subjectively and substitutes or adulterants may closely resemble the genuine material, it is often necessary to substantiate the findings by microscopy and/or physicochemical analysis. Microscopic inspection of herbal materials is indispensable for the identification of broken or powdered materials; the specimen may have to be treated with chemical reagents. An examination by microscopy alone cannot always provide complete identification, though when used in association with other analytical methods it can frequently supply invaluable supporting evidence.

Stages of Manufacturing Process

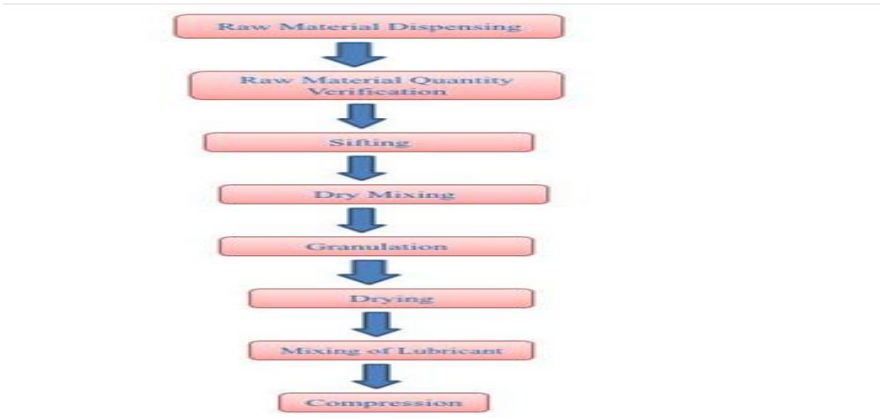

Figure. 5: Stages of Manufacturing Process.

A. Sifting: The material were sifted through 40 mesh S.S. sieve fitted to turbo-sifter and collected it in RMG.

B. Dry Mixing: The dry-mixing step involves mixing of active ingredients with other additives using Rapid Mixer Granulator (RMG). Mixing speed and mixing time are the critical variables. Mixing speed is kept constant, mixing time shall be studied to validate dry mixing step. In dry mixing stage 3 batches like I, II and III are considered for validation. Dry mixing results of all the batches are well within the acceptance criteria.

Parameters

1. Time of mixing
2. Agitator speed

C. Binding: The mixer was started and added slowly the binder solution into RMG within 1to 3 minutes by keeping impeller at “slow” speed and chopper "off”. Mix for 2 minutes by keeping chopper and impeller at “slow” speed. Stop the Rapid mixer granulator and scrap the contents from the sidewalls of bowl and blades with S.S. scrapper. Again start the mixer and mix up to 1 minute by keeping impeller and chopper at “Fast” speed, till granulation end point is reached to get required consistency of dough mass. The ammeter reading of impeller and chopper at granulation end was recorded. Repeat this same procedure for the second lot.

D. Wet Milling: Pass the wet mass through conical mill using 16.0 mm screen. Collect the milled granules in to FBD bowl.

E. Drying: The 1st FBD bowl containing wet granules was placed under the retarding chamber and fitted it to the retarding chamber by operating the control panel. Initially air-dry the wet mass in the fluid bed dryer. Then further the dried at inlet air temperature of 60-65°C. Check the LOD when outlet temperature reaches around 40°CAfter drying sift the granules through # 20 sieves using vibratory sifter .After sifting and sizing load the granules in octagonal blender.

F. Lubrication: Load the granules in octagonal blender. Add all lubricants previously weight andsifted mix for 10 minute at slow speed.

G. Compression: The compression was performed on rotary compression machine as per specifications.

Critical Process Parameters Considered for Validation

Table No. 2: Critical Process Parameters Considered For Validation.

Sr. No.	Process Stage	Sampling Frequency	Controlled Parameter	Tests	Rationale
1	Dry mixing	At end of mixing	Mixing time, Speed	Bulk density, Tapped density, Angle of Repose	To ensure proper Mixing
2	Drying	At end of mixing	Inlet temperature	Percent LOD	To get desired Moisture content in Granules
3	Lubrication	At end of Blending	Time, Speed	Bulk density, Tapped density, Angle of Repose	To obtain final blend for compression
4	Compression	Start, Middle, end	Machine speed, compression force	Appearance, Thickness, Hardness, Friability, Disintegration time	To meet the Desired specification

Sampling Procedure at Different Stages: Process Validation was performed on the three consecutive batches of formulation tablets. The experimental study followed the validation protocol for execution of actual validation studies.The execution includes each and every step and procedure studied or reviewed right from the beginning of the process validation, i.e. monitoring of the critical process parameters, and collection of the data from the in-process and validation sample analysis for the final compilation.

a. Dry mixing

1. Add all material previously weighed and sifted, sequentially in RMG & mix for8 min. at slow speed.

2. Sample were Withdrawn from 6 different locations top left (Sample No. 1), top right (Sample No. 2), top middle (Sample No. 3), bottom left (Sample No.

4), bottom middle (Sample No. 5) & bottom right (Sample No. 6) as shown in below diagram from RMG after 8 min. mixing interval.

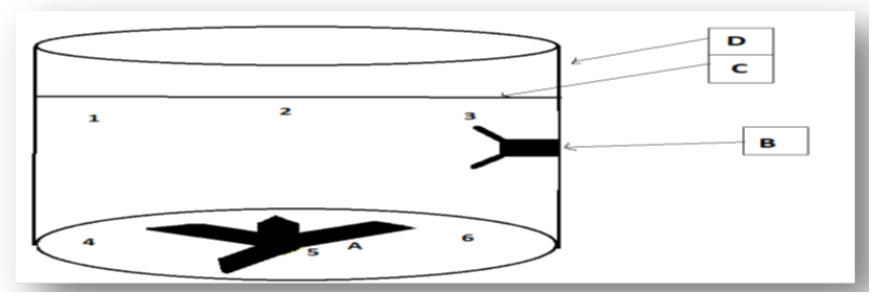

Figure. 6: Sampling location (locations from 1 to 6).

A: Impeller, B: Chopper, C: Powder Bed, D: Bowl of FBD.

Sampling and testing plan of dry mixing

1. Stage-. Dry mixing
2. Sample Location-From RMG after 8minutes of mixing of API and excipients in RMG draw 6-point sample
3. Sample Size-100mg from each point /after 08 minutes dry mixing
4. Test-Assay on each Sample of blend uniformity.

b. Drying: Three samples were collected from upper, middle and lower layer of FBD.

Drying Sampling and testing plan

1. Stage-Drying.
2. Sampling Location-From FBD bowl draw 3 samples(upper, middle and lower layer).
3. Sample quantity-2.0g from each location.
4. Test-LOD.
5. Acceptance limit-LOD should be in the range of 1.0%to 2.0% w/w.

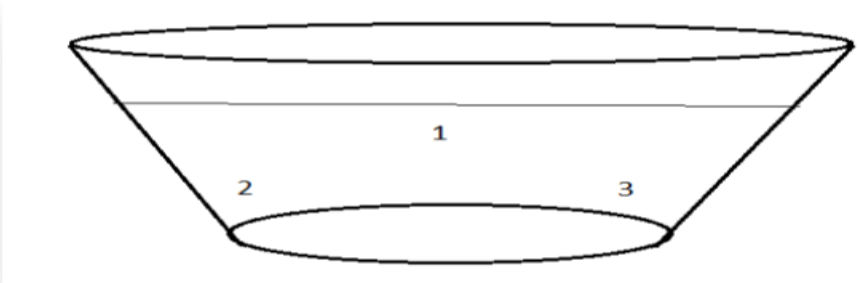

Figure. 7: Sampling diagram of FBD (Location from1 to 3).

Fixed parameters for drying

1.Inlet air temperature at end of drying (0C) – limit 60-64

2.Outlet temperature at end of drying (0C) –limit 40-45

2.Total Drying time (Minutes)-

c. Lubrication: Lubricants were added to powder blend, till the free flowing powder was produced. Samples were collected from different positions of blender as shown in Fig. Each sample was collected in butter paper at different interval of time.The samples were subjected for further tests i.e. tapped and bulk density, angle of repose. Acceptance criterion was free flowing powder blend.

Sampling and testing plan of Lubrication

1. Stage-Lubrication

2. Sample Location-Approximately150 g of the Lubricated bulk blend to be sampled for physical characterization

3. Sample Quantity-Approximately150 g of the Lubricated bulk blend

4. Test-

1. Bulk density and tapped density

2. Carr's Index

3. Hausner's ratio

4. Angle of repose.

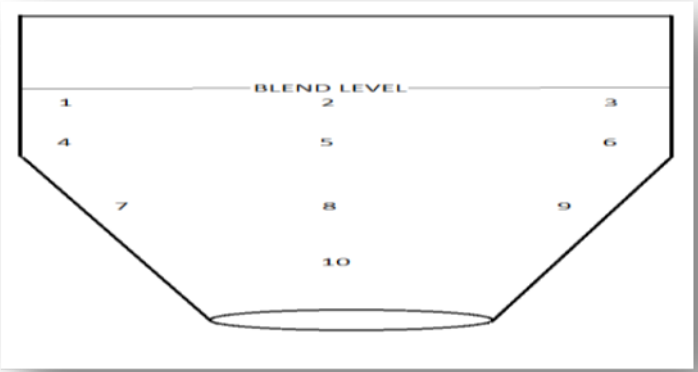

Figure. 8: Sampling plan diagrams of lubrication.

Bulk Density

Method: The powder sample under tests was screened through sieve no. 18 and the sample equivalent to 25 g was accurately weighed and filled in 100 ml graduated cylinder and the powder was leveled and the unsettled volume, *(Vo)* was noted. The bulk density was calculated in g/cm3 by the formula,

Bulk density* (ρo) = *M/V o (1)

Where *M* is Mass of powder taken and *Vo* is Apparent unstirred volume.

Tapped Density

Method: The powder sample under test was screened through sieve no. 18 and the weight of sample equivalent to 25 g was filled in 100 ml graduated cylinder. The tapped density was achieved by mechanical tapping a cylinder containing powder. The tapped density was calculated in g/cm3 by the formula,

Tapped density* (ρt) = *M/V f (2)

Where *M* is weight of sample powder and *Vf* is tapped volume.

Carr's Index (Compressibility Index)

The bulk density and tapped density were measured and Compressibility index was calculated using the formula, ***Carr's Index= ρt− ρo/ ρt X 100 (3)***

Where ρt is tapped density and ρo is bulk density.

Hausner's Ratio

Tapped density and bulk density were measured and Hausner's Ratio was calculated by using the formula.

Hausner's Ratio= ρt / ρo (4)

Where ρt is tapped density and ρo is bulk density.

d. Compression

Compression involves consistent flow of lubricated granules from hopper to die where it is being compressed to form a tablet. Compression was carried out as per batch manufacturing record. Samples were collected from initial, middle andend stage of compression cycle for testing of physical parameters. The fixed parameters and specification during compression, sampling andtesting plan for compression, physical parameter and acceptance criteria for compression are given.

Fixed Parameters and Specifications during Compression-

1. No. of punches- 45
2.Variables considered -Compression speed
3.Compression machine- Double rotary Compression Machine
4.Upper Punch- 12 mm
5. Lower Punch -12 mm
6. Die- 12 mm

Sampling and Testing Plan for Compression-

1. Sample Location- Initial, middle and end of the operation.
2. Sample –Size-200tablets
3. Test –

a.. Description

b. Average wt

c. Uniformity of wt

d. Disintegration test

e. Friability

f. Hardness

e. Thickness.

Acceptance Criteria- Physical parameters to comply limits as per BMR.

Physical parameters and testing procedure

Various physical parameters and their testing procedure for compression are given as

1. Average weight and uniformity of weight of tablets: Selected 20 tablets randomly from the pooled sample.Weighed 20 tablets individually calculated the average weight and weight variation. Average weight =wt of 20 tab/20

2. Hardness: Selected 05 tablets randomly from the pooled sample and measured the hardness by using Monsanto hardness tester and noted the reading.

3. Thickness: Selected 05 tablets randomly from the pooled sample and measured the thickness, length and width of tablet using calibrated verniercalliper noted the reading directly from screen.

4. Friability: Selected 20 tablets randomly from the pooled sample and measured the Friability by using friabilator.

Formula: Percent Friablility = 1-W3/W2 X 100

W3 = W1 – W2, W1 – Initial weight of 20 tablets, W2 – Final weight of 20 tablets.

5. Disintegration time: Disintegration test performed on 6 tablets. Placed one tablet in each of six tubes of the basket, and operated the apparatus using water maintained at 37±2 °C as the immersion fluid. Recorded the disintegration of each tablet at the end of 15 min, lift the basket from the fluid and observed the tablet. All the tablets should be disintegrated.

5. Analysis of Garcini Tablet

A simple UV spectrophotometric method was developed for the estimation of Garciniaindica in Garcini tablet.

Instruments: Absorbance measurements was made on Shimadzu 1800 UV/Visible spectrophotometer with a pair of matched quartz cells of 1 cm width, Shimadzu AUW 220D balance used for weighing, and ultra sonicator of Quality instruments was used sonicating the drug and sample solution.

Preparation of standard stock solution

The standard stock solutions of marker were prepared by dissolving 10 mg of each drug in ethanol and final volume was adjusted with same solvent in 10 mL of volumetric flask to get a solution containing 1000 µg/mL of drug.

Calibration Curve: Aliquots of working stock solution of were prepared with distilled water to get concentration in range of 100- 200 µg/mL. The absorbances of resulting solutions were measured at λmax 222nm. A calibration curve as concentration vs. absorbance was constructed to study the Beer-Lambert's Law and regression equation.

Sample preparation: 20 tablets were weighed and powdered. From that 15.25mg of powder was weighed and transferred into a 10 mL volumetric flask and extracted with 10 mL of ethanol by sonication for 20 min. Then solution was filtered through Whatmann No.1 filter paper to obtain a clear solution. Filtrate diluted up to 10mL with ethanol. Withdraw the 1mL sample from above solution and diluted with distilled water up to 10mL. Measure the absorbance of resulting solution at λmax 222nm.

Analytical results of finished products

Tests and Specifications Results

1. Description
2. Average weight (g)
3. Uniformity of Weight of Tablets (g)
4. Thickness (mm)
5. Hardness Kg/cm
6. Length (mm)
7. Width (mm)

CONCLUSION

Process validation of herbal formulation tablets was conducted for a batch which included the validation of critical steps of manufacturing such as blending, mixing, drying and

compression .If you applied this process validation protocol then final product will be quality product. In process validation was found to be critical steps will be find out, so as quality of product will be maintain. The concurrent process validation of tablet formulation has been performed for three batches (batch I, batch II, batch III) and all the parameters and results were find within the acceptance limit. Based on the results of the validation data for three batches, it was concluded that the manufacturing process used for formulation of herbal tablet formulation will consistently producing the product meeting its predetermined specifications and quality attributes.

REFERENCES

1. Desai, L., & Oza, J. Prospective process validation of polyherbal cough syrup formulation, 2012; 2(4): 225–231.
2. Patel, V., Patel, N., & Patel, P. Review on Quality Safety and Legislation for Herbal Products. International Journal of Research in Ayurveda & Pharmacy, 2011; 2(5): 1486–1489. Retrieved from http://www.ijrap.net/admin/php/uploads/639_pdf.pdf.
3. Gandhi, A. J., Sharma, S., Baranwal, V. K., & Bedarkar, P. Industrial approach of process validation of Bharjana (frying) process WSR to, 2016; (4): 172–177.
4. Himanshu, & Sonia, P. A Review on Pharmaceutical Process Validation. International Research Journal of Pharmacy, 2012; 3(7): 56–58.
5. Partha, G., Kumar, G. A., Rahul, S., Chandrakant, K., Elfiyani, R., Amalia, A., Gohel, A. Standardization of marketed Ayurvedic formulation, Balaguloochyadi kashayam-physicochemical, microbial evaluation and ephedrine content. International Food Research Journal, 2017; 9(3): S1–S4. https://doi.org/10.5530/jyp.2017.
6. Kunle. (2012). Standardization of herbal medicines - A review. International Journal of Biodiversity and Conservation, 4(3), 101–112. https://doi.org/10.5897/IJBC11.163.
7. Desai, S. R., Disouza, J. I., & Shirwadkar, B. B. Process validation: An approach for herbal tablet standardization. International Journal of Pharmacognosy and Phytochemical Research, 2016; 8(2): 313–320.
8. Yadav, N. P., & Dixit, V. K. Recent Approaches in Herbal Drug Standardization Herbal drug standardization. International Journal of Integrative Biology, 2008; 2(3): 195-203.
9. Guidance, D. (2008). Guidance for Industry Process Validation : General Principles and Practices Guidance for Industry Process Validation : General Principles and Practices. Federal Register, (November).

10. Thaduvai, R., Rao, B. S. S., & Jeybaskaran, M. Process Validation of Pantoprazole 40mg Tablets. The Pharma Innovation, 2012; 1(5): 47–62. Retrieved from http://www.thepharmajournal.com/vol1Issue5/Issue_july_2012/4.4.pdf.
11. WHO. (2013). Validation of Production Processes for Vaccines for WHO Prequalification- Compliance Expectations. Vaccine Quality and Regulations (VQR). Retrieved from http://www.who.int/immunization_standards/vaccine_quality/validation_guide_july2013.pdf.
12. Zöllner, T., & Schwarz, M. Herbal reference standards: Applications, definitions and regulatory requirements. Brazilian Journal of Pharmacognosy, 2013; 23(1): 1-21. https://doi.org/10.1590/S0102-695X2012005000144.
13. Kumar, S. B., & Kumar, V. (2009). An Overview of Herbal Medicine. Int. J. Ph. Sci Int. J.Ph.Sci., 2009; 1(11): 1-201. Retrieved from www.ijps.info.
14. Patil, S. G., Wagh, A. S., Pawara, R. C., & Ambore, S. M. Standard Tools for Evaluation of Herbal Drugs: An Overview. The Pharma Innovation-Journal, 2013; 2(9): 2–7. Retrieved from www.thepharmajournal.com.
15. Rose, N., Kamta, E., Namdeo, P., & Samal, P. K. Standardization Strategies for Herbal Drugs-An Overview Macrosc. Research J. Pharm. and Tech., 2008; 1(4): 310–312.
16. Bele, A. A., & Khale, A. Standardization of Herbal Drugs : an Overview. International Research Journal of Pharmacy, 2011; 2(12): 56–60.
17. Kunle. Standardization of herbal medicines - A review. International Journal of Biodiversity and Conservation, 2012; 4(3): 101-112. https://doi.org/10.5897/IJBC11.163.
18. Bele, A. A., & Khale, A. Standardization of Herbal Drugs : an Overview. International Research Journal of Pharmacy, 2011; 2(12): 56–60.
19. W. H. O. (2011). Quality control methods for herbal materials. World Health Organization, Geneva, Switzerland, pp 187. https://doi.org/ISBN 978 92 4 150073 9.
20. Services, H. (2011). Guidance for Industry Process Validation : General Principles and Practices Guidance for Industry Process Validation : General Principles and Practices. Quality, (January), 22.
21. Sachin S. Mali et.al, An overview: Quality control and standardization of herbals. Int J Life sci Biomed Res., 2015; 1: 11-20.
22. Sachin S. Mali et.al, Pharmacovigilance Towards Safety Approach For Ayurvedic Drugs: A Narrative Overview. ejpmr, 2016; 3(1): 180-186.