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Pharmaceutical Process Validation Approach for Extended Release Tablets: An Overview

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Abstract Validation is an integral part of quality assurance; it involves the systematic study of systems, facilities and processes aimed at determining whether they perform their intended functions adequately and consistently as specified. A validated process is one which has been demonstrated to provide a high degree of assurance that uniform batches will be produced which meet the required specifications and has therefore been formally approved. Validation in itself does not improve processes but confirms that the processes have been properly developed and are under control. Process validation deepens the understanding of processes; decreases the risk of preventing problems and thus assures the smooth running of the process.

Keywords Prospective Process validation, Extended release tablets, Qualification, Documentation, Sampling, Control Variables

Introduction

Extended-release drug products-

Extended-release products are designed to release their medication in a *controlled* manner, at a predetermined rate, duration, and location to achieve and maintain optimum therapeutic blood levels of drug. These dosage forms allow at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form. Examples of extended-release dosage forms include controlled-release, sustained-release, and long-acting drug products [1].

Process Validation:

The process validation is establishing documented evidence which provides high degree of assurance that a specific process consistently produced a product meeting its predetermined specifications and quality characteristic.

Need of Pharmaceutical Validation

Validation is an integral part of quality assurance; it involves the systematic study of systems, facilities and processes aimed at determining whether they perform their intended functions adequately and consistently as specified. A validated process is one which has been demonstrated to provide a high degree of assurance that uniform batches will be produced which meet the required specifications and has therefore been formally approved. Validation in itself does not improve processes but confirms that the processes have been properly developed and are under control.

- It deepens the understanding of processes; decreases the risk of preventing problems and thus assures the smooth running of the process.
- It decreases the risk of defect costs.
- It decreases the risk of regulatory non- compliance.
- A fully validated process may require less in-process controls and end- product testing.

Process validation should be performed in following conditions:

- Totally new process;
- New equipment;
- Process and equipment which have been altered to suit changing priorities; and
- Process where the end-product test is poor and an unreliable indicator of product quality [2].

Process validation can be used in certain cases:

- Where process results cannot be fully verified during routine production by inspection and test, the process must be validated according to procedures.
- 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.
- Routine end-product tests do not reveal all variations in safety and efficacy that may occur in the finished devices. It is suspected that the process is barely capable of meeting the device specifications [3].

Advantages of Process Validation

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

Basic principle for process validation:

The basic principle for validation may be stated as follows:

1). Installation Qualification (IQ):

Establishing by objective evidence that all key aspects of the process equipment and ancillary system installation adhere to the manufacturer's approved specification and that the recommendation of the supplier of the equipment are suitably considered.

2). Operational Qualification (OQ):

Establishing by objective evidence process control limits and action levels which result in product that all predetermined requirements.

3). Performance Qualification (PQ):

Establishing by objective evidence that the process, under anticipated conditions, consistently produces a product which meets all predetermined requirements.

4). Re–Qualification:

Modification to, or relocation of equipment should follow satisfactory review and authorization of the documented change proposal through the change control procedure. Minor changes or changes having no direct impact on final or in-process product quality should be handled through the documentation system of the preventive maintenance program [6-10].

Approaches to Process Validation:

Process validation involves a series of activities taking place over the lifecycle of the product and process. All the activities of the process validation were divided into three stages as follows:

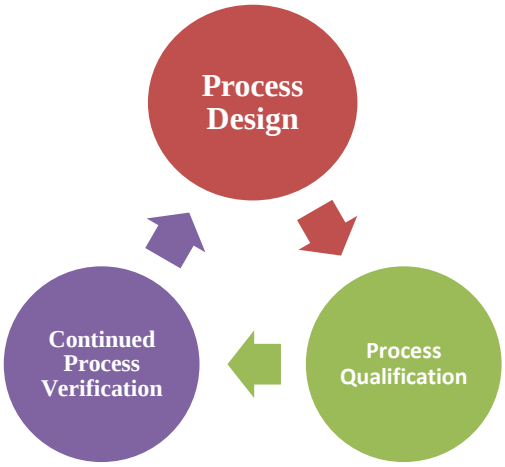

Figure 1: Product Lifecycle

Stage 1: **Process Design**

The commercial manufacturing process defined during this stage based on the knowledge gained through development and scale-up activity.

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 [11-12].

Types of Validation:

1. Prospective validation
2. Concurrent validation
3. Retrospective validation
4. Revalidation

1. Prospective Validation

- It is defined as the established documented evidence that a system does what it purports to do based on a pre-planned protocol.
- This validation usually carried out prior to distribution either of a new product or a product made under a revised manufacturing process. Performed on at least three successive production-sizes (Consecutive batches).

2. Concurrent Validation

- It is similar to prospective, except the operating firm will sell the product during the qualification runs, to the public at its market price, and also similar to retrospective 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.

3. Retrospective Validation

- It is defined as the established documented evidence that a system does what it purports to do on the review and analysis of historical information.
- This is achieved by the review of the historical manufacturing testing data to prove that the process has always remained in control. This type of validation of a process for a product is already in distribution.

4. Revalidation

- Re-validation provides the evidence that changes in a process and/or the process environment that are introduced do not adversely affect process characteristics and product quality.
- Where no significant changes have been made to the validated status, a review with evidence that facilities, systems, equipment and processes meet the prescribed requirements fulfils the need for revalidation [2, 13-14].

Strategy for Industrial Process Validation of Solid Dosage Forms:

The strategy selected for process validation should be simple and straightforward. The following five points gives strategy for process validation-

1) The use of different lots of raw materials should be included. i.e., active drug substance and major excipient.
2) Batches should be run in succession and on different days and shifts (the latter condition, if appropriate).
3) Batches should be manufactured in the equipment and facilities designated for eventual commercial production.
4) Critical process variables should be set within their operating ranges and should not exceed their upper and lower control limits during process operation. Output responses should be well within finished product specifications.
5) Failure to meet the requirements of the validation protocol with respect to process input and output control should be subjected to process requalification and subsequent revalidation [15].

Type of Documentation in Validation Process

1) Validation master plan (VMP)
2) Validation protocol (VP)
3) Validation reports (VR)
4) Standard operating process (SOPs)

1. Validation master plan:

- An approved written plan of objectives and actions stating how and when a company will achieve compliance with the GMP requirements regarding validation.
- VMP is a summary intention document stating the scope of the validation and outlining the methods to be used to establish the performance adequacy [16].

2. Validation protocol:

- Detailed protocols for performing validations are essential to ensure that the process is adequately validated.
- It includes the following :
  - Protocol approval sheet
  - Table of content
  - Objective and Scope
  - Validation team and responsibility
  - Steps for validation and acceptance criteria
  - Evaluation of formulation ingredients & active raw material
  - Manufacturing process flow chart
  - Product & equipment details
  - Critical process parameters
  - In-process specification
  - Sampling procedure and testing plan
  - Revalidation criteria
  - Change control
  - Deviations
  - Stability
  - Report and conclusion [17, 18]

3. Validation reports:

- A written report should be available after completion of the validation. If found acceptable, it should be approved and authorized (signed and dated).
- The report should include at least the following:
  - Title and objective of study.
  - Reference to protocol.

- Details of material.
- Equipment.
- Programme and cycles used.
- Details of procedures and test methods.
- Results (compared with acceptance criteria).
- Recommendations on the limit and criteria to be applied on future basis [19, 20]

4. SOP (Standard Operating Procedure):

- Standard Operating Procedures (SOPs) are issued to specifically instruct employees in areas of responsibility, work instructions, appropriate specifications and required records.
- These outline procedures, must be followed to claim compliance with GMP principles or other statutory rules and regulations.
- The general aspects covered under the SOPs are the Preparation and maintenance of work area like washing and sterilization, decontamination and testing area.
- Even the work done in the laboratory were documented, for example, the laboratory operations involving the receipt of reagents, standards, preparation of reagents, labeling and storage, test procedures, reference material, identification, handling, storage and use deviations, errors. Even the details of the equipments and their maintenance were also involved [21-22].

Materials and Methods

Table 1: Equipments used during manufacturing of validation batch

S. No.	Processing stage	Processing Equipments/Instruments
1.	Weight verification	Weighing balance
2.	Sifting	Mechanical sifter equipped with # 20 & # 40 sieve
3.	Dry mixing	Rapid mixer granulator (100 L)
4.	Granulation	Rapid mixer granulator (100 L)
5.	Drying	Fluidized bed dryer (60 kg)
6.	Sifting & milling	Mechanical sifter equipped with # 20 sieve Multi-mill equipped with 1.5 mm & 1.00 mm screen
7.	Pre- lubrication & lubrication	Conta-blender & bin (150 L)
8.	Compression	Tablet press (45 station double rotary machine)
9.	De-duster	De-dusting units
10.	Metal detection	Metal detectors
11.	Coating suspension preparation	Mechanical stirrer
12.	Coating	Coating pan (24”)
13.	Imprinting of tablets	Printing machine- Tamprint 60
14.	Inspection of tablets	Inspection machine

Table 2: Equipments used during in-process testing of validation

S. No.	Test	Processing Instruments
1.	Weight verification	Weighing balance / Smart test 50
2.	Thickness verification	Vernier caliper / Smart test 50
3.	Hardness testing	Hardness tester / Smart test 50
4.	Friability testing	Friability tester
5.	Disintegration time	Disintegration test apparatus
6.	Loss on drying	Halogen moisture balance

Process flow diagram:

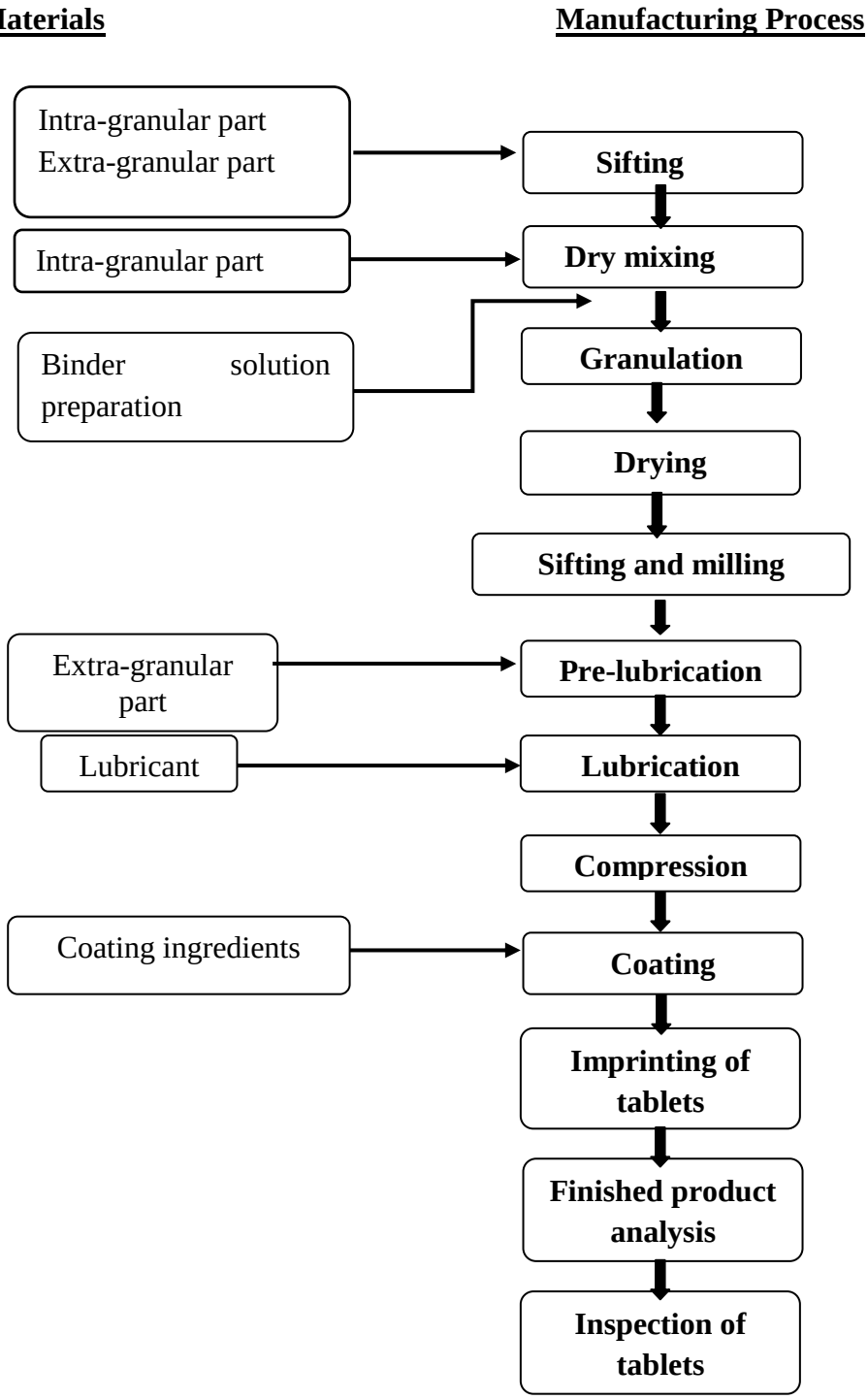

Figure 2: Manufacturing Process Flow Chart

Table 3: Sampling testing plan

Processing Time	No. of samples	Quantity of samples	Test to be performed
1. Dry mixing Stage			
After completion of dry mixing	02 x 05 = 10 samples (Figure 3)	67.50 to 202.50 mg	*
2. Drying Stage			
After completion of drying	01 x 05 = 5 samples	Approx. 5 g collected each from front, rear, left, right & centre of bowl & tested individually	Loss on drying by Halogen moisture balance at 105° C.
3. Lubrication			
After completion of lubrication process	03** x 11 = 33 samples (Figure 4.1)	170 to 510 mg	Uniformity of blend
	01 sample (composite sample) (Figure 4.2)	Take a composite sample from 5 different locations (About 150 g)	Description, water content, assay, bulk density, tapped density, particle size (by sieve analysis)
After unloading – In SS bin	02*** x 11 = 22 (Figure 4.1)	170 to 510 mg	***
After unloading – In IPC	02*** x 5 = 10 (Figure5)		
4. Compression Stage			
Different speed at optimum hardness	• Slow speed 01 sample • Optimum speed 01 sample • High speed 01 sample (01 x 03 = 03 samples from LHS & RHS)	20 tablets	Appearance, average weight of 20 tablets & uniformity of weight
		10 tablets	Thickness, Hardness
		Take tablets equivalent to 6.5 gm.	Friability
		03$ x 10 = 30 tablets	Uniformity of dosage units (By content uniformity)
Different hardness at optimum speed	• Low hardness 01 sample • Optimum hardness 01 sample • High hardness 01 sample (01 x 03 = 03 samples from LHS & RHS)	20 tablets	Appearance, average weight of 20 tablets & uniformity of weight
		10 tablets	Thickness, Hardness
		Take tablets equivalent to 6.5 gm.	Friability test
		03@ x 06 = 18 tablets	Dissolution (At low, optimum and high hardness)
Hopper challenge study	• Full hopper 01 sample • Half hopper 01 sample • Quarter hopper 01 sample (01 x 03 = 03 samples from LHS & RHS)	20 tablets	Appearance, average weight of 20 tablets & uniformity of weight
		10 tablets	Thickness, Hardness
		Take tablets equivalent to 6.5 gm.	Friability test
		03$ x 10 = 30 tablets	Uniformity of dosage units (By content uniformity)
First & last round of tablets during compression	• Immediately after start of compression 01 sample • Before stoppage of compression 01 sample 1 x 02 = 02 samples from LHS & RHS)	20 tablets	Appearance, average weight of 20 tablets & uniformity of weight
		10 tablets	Thickness, Hardness
		Take tablets equivalent to 6.5 gm.	Friability test
		03$ x 10 = 30 tablets	Uniformity of dosage units (By content uniformity)
Stages of	• Initial stage	20 tablets	Appearance, average weight of 20 tablets

compression at optimum speed & optimum hardness	01 sample • Middle stage 01 sample • End stage 01 sample (01 x 03 = 03 samples from LHS & RHS)		& uniformity of weight
		10 tablets	Thickness, Hardness
		Take tablets equivalent to 6.5 gm.	Friability test
		3** x 20 = 60 tablets	Assay
		03$ x 10 = 30 tablets	Uniformity of dosage units (By content uniformity)
5. Coating Stage			
Completion of coating of each lot	01 sample	Composite 50 tablets from front, rear, left, right & center of pan	Description, average weight

* Sampling shall be performed in duplicate and shall be kept as reserve sample. If any discrepancy observed in the results of lubricated sample, use the reserve sample as a part of investigation.

** Sampling shall be performed in triplicate. One set of sample shall be submitted for QC analysis and other 2 sets shall be kept as reserve samples.

*** Sampling from IPC/SS bin shall be performed in duplicate and shall be kept as reserve sample.

$ Sampling shall be performed in triplicate. One set of 10 tablets from each stage shall be submitted for QC analysis and other 2 sets shall be kept as reserve samples. Result of one set sample should pass "readily pass criteria" and if result does not meet criteria, reserve samples shall be used as part of investigation which should pass "marginally pass criteria".

@ Sampling shall be performed in triplicate for each hardness challenge (low, optimum and high hardness). One set of sample shall be submitted for QC analysis and other 2 sets shall be kept as reserve samples.

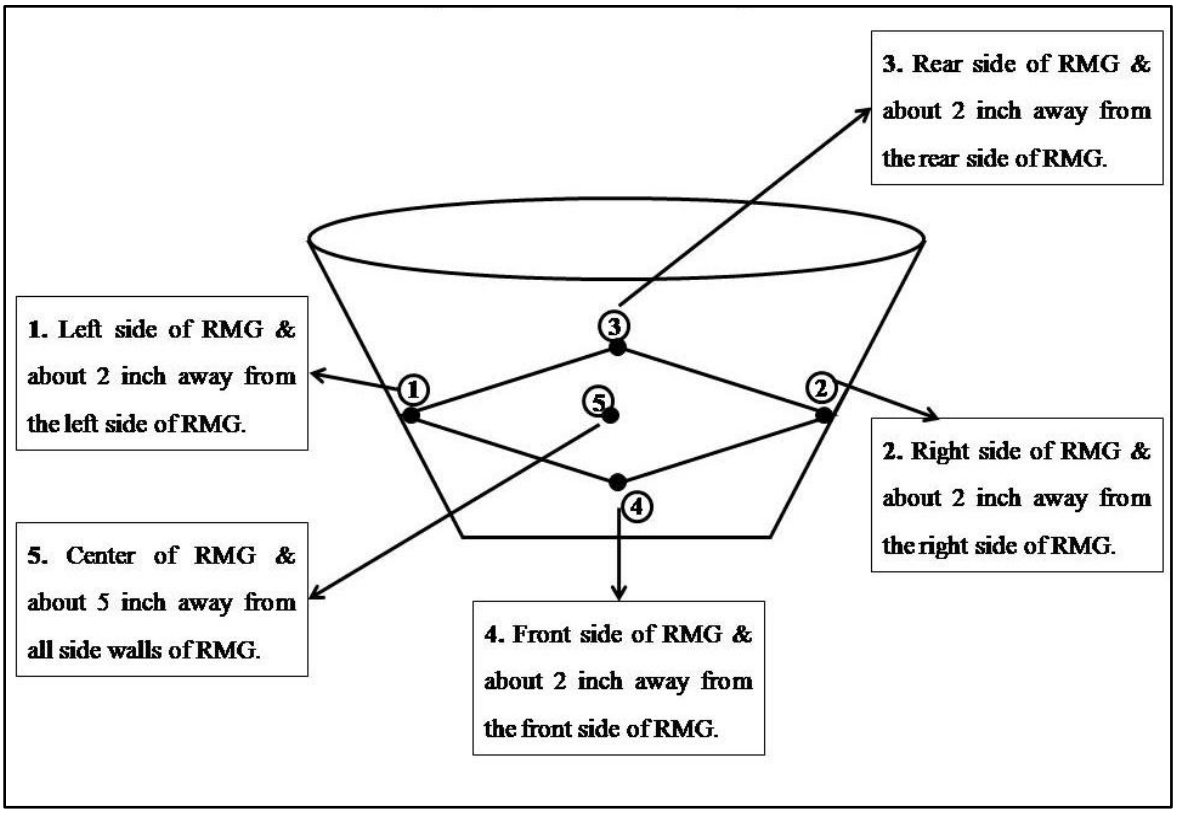

Figure 3: Sampling points from Rapid Mixer Grinder

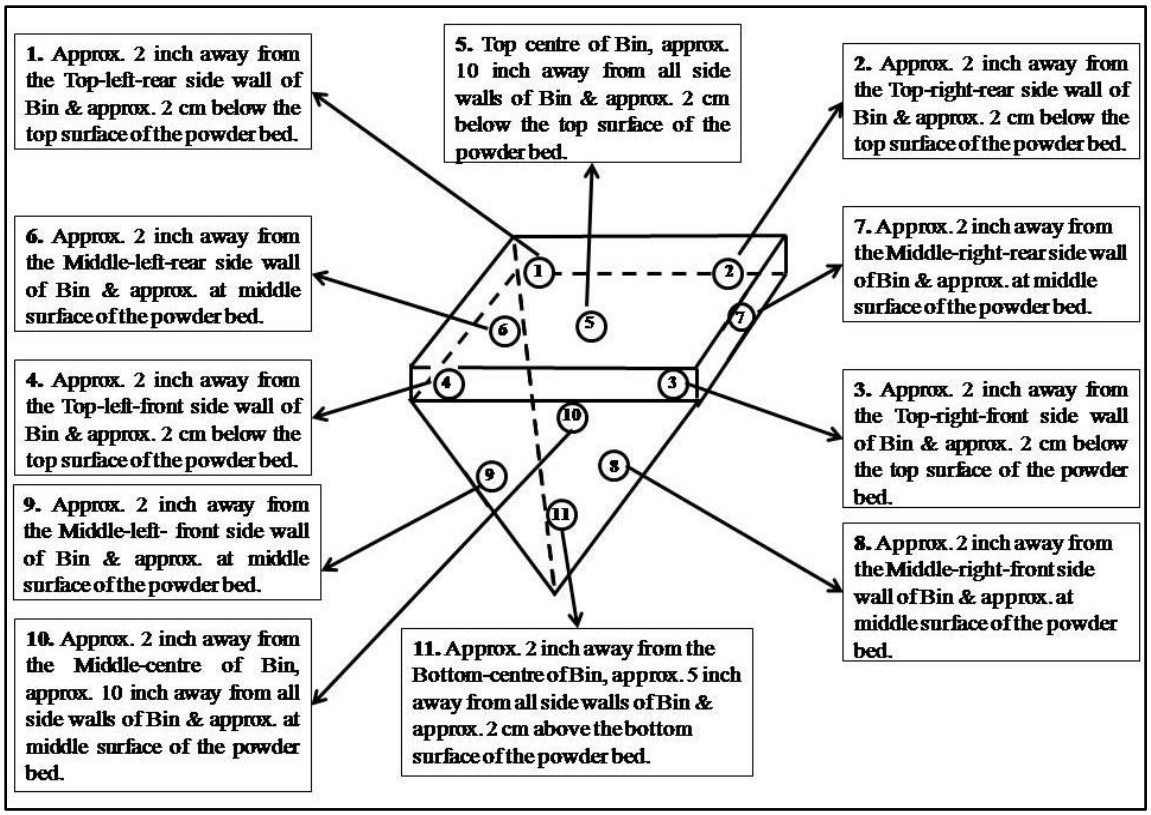

Figure 4a: Sampling points from conta blender

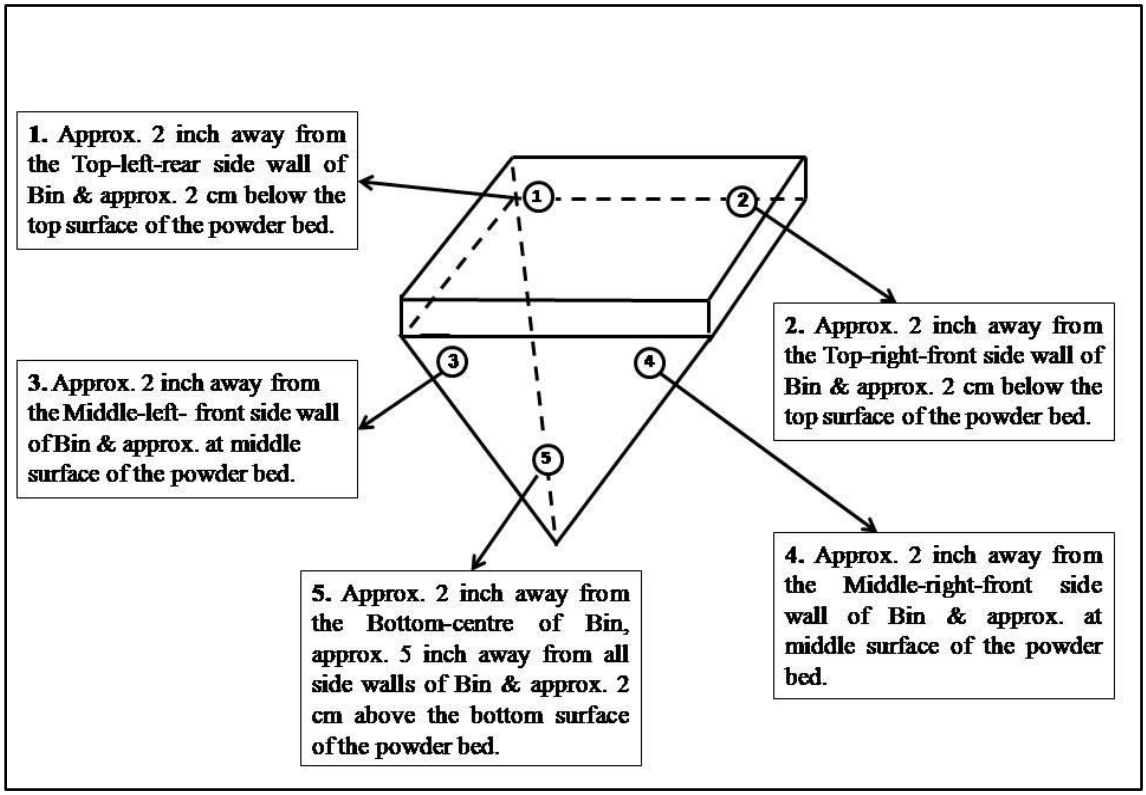

Figure 4b: Sampling points from conta blender

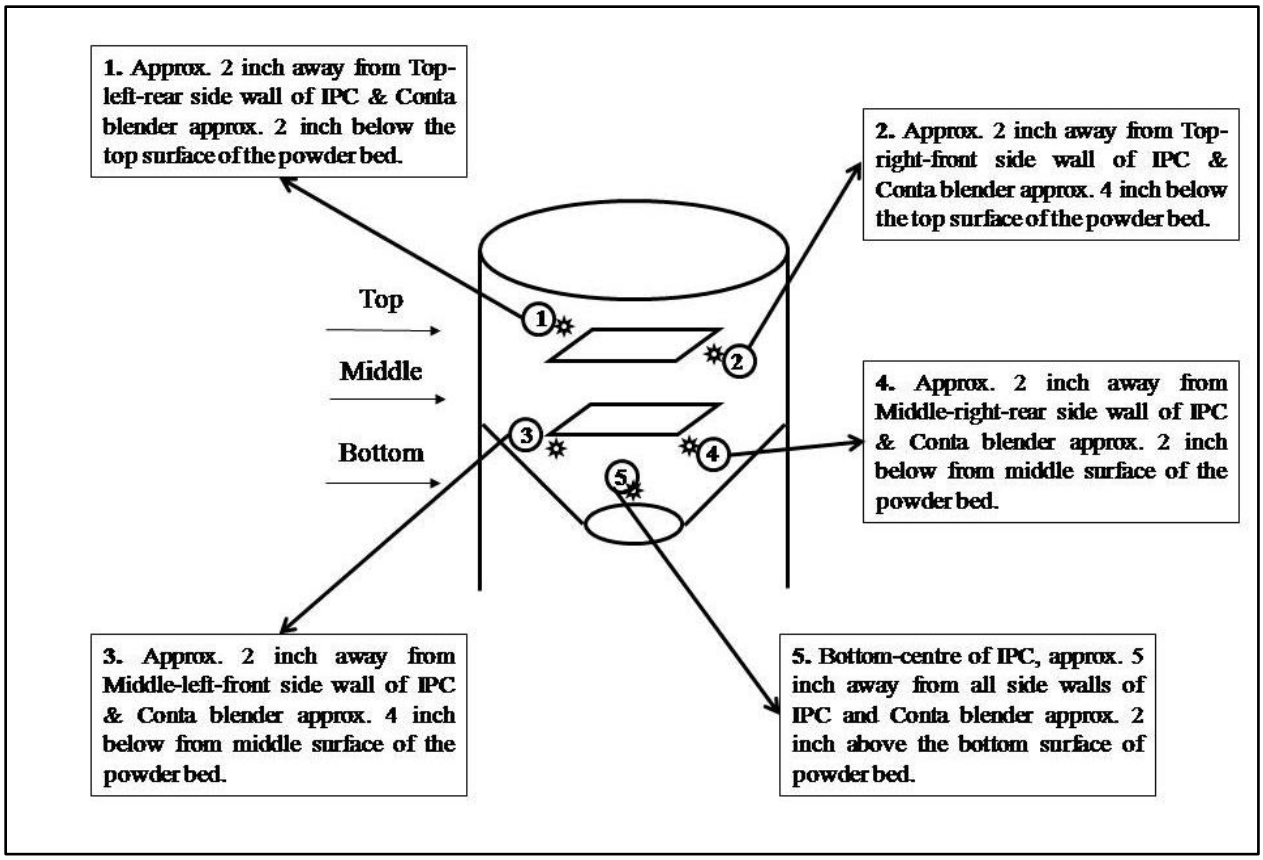

Figure 5: Sampling points from Intermediate Product Container

Conclusion

Process validation is an accurate and reliable method to ensure that the drug product will meet standards for quality, purity, identity, strength, effectiveness, stability, evaluation safety and efficacy. Pharmaceutical process validation is the most important and recognized parameters of cGMP, hence one of the important steps in achieving and maintaining the quality of the final product. Process validation and process control provide a certain assurance of batch uniformity and integrity of the product manufactured.

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