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Process Performance Qualification, Safety, Global health, Capsules, Critical Process Parameters, Critical Quality Attributes.

Process Performance Qualification and Validation of Prazosin Hydrochloride Capsules USP 1 mg Manufactured at Commercial Scale

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ABSTRACT: **Background**: Process validation is an important part of pharmaceutical quality assurance that gives documented proof of consistency of the manufacturing process in terms of production of products meeting certain pre-defined quality standards. Process Performance Qualification (PPQ) is carried out to confirm reproducibility of the process in commercial scale manufacture.

Objectives: To validate the process of manufacturing of Prazosin Hydrochloride Capsules USP 1 mg by means of PPQ studies. To examine CPPs and CQAs in three consecutive commercial scale batches.

Methods: Three consecutive PPQ batches of Prazosin Hydrochloride Capsules USP 1 mg were manufactured using validated process. Critical stages of the process were controlled, and the samples were subjected to tests for appearance, assay, content uniformity, dissolution, moisture content and microbial limits in accordance with approved specifications.

Results: All three validation batches met pre-defined acceptance criteria. CPPs did not exceed the specified limits during the process. The testing of finished products confirmed their consistent quality, uniformity and appropriate dissolution profile.

Conclusion: The PPQ study proved to be successful in demonstrating that the process of manufacturing of Prazosin Hydrochloride Capsules USP 1 mg is capable of consistently producing the product meeting pre-defined quality requirements.

INTRODUCTION:

Process validation is an important aspect of pharmaceutical quality assurance whereby there is documentation of proof showing that a process reliably yields products which conform to the set specifications1. There is much emphasis on the process validation by the regulatory authorities like the USFDA, EMA, and WHO throughout the lifecycle of the product. Prazosin

Hydrochloride is a selective alpha-1 adrenergic receptor blocking agent which is widely used for the treatment of hypertension2,3. Consistent quality of Prazosin Hydrochloride Capsules can be assured by controlling the manufacturing process.

MATERIALS AND METHODS:

Materials

Prazosin Hydrochloride Polyhydrate was the API used in this research work. The excipients used include Lactose monohydrate, Lactose anhydrous, Microcrystalline cellulose, Colloidal silicon, magnesium stearate.

Equipment used in validation batches

The production process was performed using qualified equipment, such as Vibrio Sifter, High Shear Mixer Granulator (600 L), Bin Blender (4000 L), Capsule Filling Machine (AF-150T), Capsule Sorter, Check Weigher, Metal Detector, and other related material handling equipment. All the equipment and measuring devices were qualified and calibrated prior to performing the validation batches.

METHODOLOGY:

Manufacturing Process

A series of three validation batches on a commercial scale of Prazosin Hydrochloride Capsules USP 1 mg, each producing 4,000,000 capsules, was conducted following the approved Batch Manufacturing Record.

Step I: Dispensing

Bulk raw materials such as Prazosin Hydrochloride Polyhydrate USP, Lactose Monohydrate USP-NF, Microcrystalline Cellulose USP-NF, Anhydrous Lactose USP-NF, Colloidal Silicon Dioxide USP-NF, Magnesium Stearate USP-NF, and hard gelatin empty capsules (Size 2) were dispensed as per the batch manufacturing record.

Step II: Sifting

Prazosin Hydrochloride Polyhydrate USP, Lactose Monohydrate USP-NF, and Microcrystalline Cellulose USP-NF were sifting separately using #30 mesh sieve and were collected in Sub-batches A, B, and C.

Step III: Dry Mixing

The sifted powders were transferred to 600 L High Shear Granulator and were mixed for 10 minutes at slow speed of the impeller and chopper to ensure uniform mixing of the drug substance in the formulation.

Step IV: Intermediate Sifting

The dry mixed mixture was discharged from the granulator and was further passed through a #30 mesh sieve to remove any agglomerates.

Step V: Mixing

Anhydrous Lactose USP-NF, Microcrystalline Cellulose USP-NF, and Colloidal Silicon Dioxide USP-NF were passed through #30 mesh and mixed in 4000 L Blender along with sifted dry blend. The ingredients were mixed for 10 minutes at a speed of 10 rpm.

Step VI: Lubrication

Magnesium Stearate USP-NF was sifted through #40 mesh and then introduced in the blender. The final lubrication was done for 5 minutes at 10 rpm.

Step VII: Encapsulation

The lubricated blend was moved to the area of encapsulation and filled in Size 2 hard gelatin capsules marked with a dark green cap having imprint “019” and light brown body having imprint “novitium” using AF-150T capsule filler.

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Step VIII: Packaging

Filled capsules were packed in high-density polyethylene (HDPE) bottles in 90 count, 100 count, and 1000 count pack sizes.

Dispensing
↓
Sifting(#30Mesh)
↓
Dry Mixing (600 L High Shear Granulator, 10 min)
↓
Intermediate Sifting (#30 Mesh)
↓
Blending (4000 L Blender, 10 min at 10 rpm)
↓
Lubrication (Magnesium Stearate, 5 min at 10 rpm)
↓
Encapsulation (AF-150T Capsule Filling Machine)
↓
Packaging (HDPE Bottles)

Manufacturing Process Flow Diagram

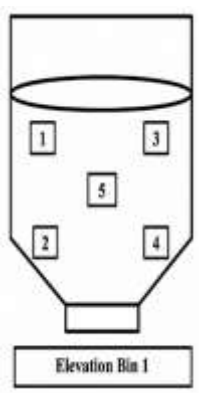
Process Validation Studies

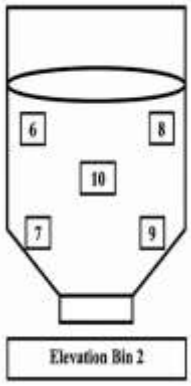
Validation of process has been done by performing PPQ on three batches. CPP and CQA have been identified and monitored during the manufacturing process. The following parameters have been studied according to the approved protocol and specifications: environment, blend uniformity, average capsule weight, weight variation, lock length, stratified uniformity, dissolution, assay, and microbial quality.

Critical process parameter and quality attributes:

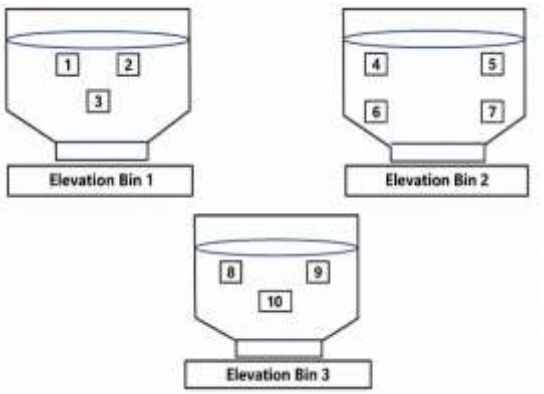
Blend Uniformity Evaluation

Drug Content testing was carried out on samples collected from ten pre-determined sites of the final blend container. Samples from the lubricated blend will be collected into (Either) two 1200L bin blenders with sampling done in triplicate per 1200L bin (Or) three 600L bin blenders with sampling done in triplicate per 600L bin. Blend uniformity was calculated using the % Drug Content and % Relative Standard Deviation (% RSD). Acceptance criteria were such that all individual readings should fall within 90.0-110.0% of label claim with %RSD not more than 5.0%.





Two 1200L Bin Blenders



Three 600L Bin Blenders

Encapsulation and In-Process Testing

Encapsulation was done with in-process control procedures that include capsule descriptions, average weight, individual weight variations, and locking lengths at specific times. Hopper challenges were carried out at 80%, 50%, and 20% levels of the hopper.

Stratified Content Uniformity Sampling

Uniformity of content sample through stratified sampling was done during the process of making capsules according to the standards of ASTM E2709 and ASTM E2810. In this case, three capsules were taken from each of the 40 equally spaced intervals that were provided by the QA department and analysed for uniformity of dosage units by QC. In order to analyze the samples, stratified sampling method was used. The first level of analysis was done on three dosage units from the 20 odd numbered intervals (1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37 and 39). If the result of the first level did not fit the acceptance criteria, second level analysis was conducted on three dosage units from the 20 even numbered intervals (2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, and 40).

Dissolution Profile Study

Dissolution testing was performed to find out how consistent the drug release is in the course of encapsulation process. Sample of 20 capsules was collected from beginning, mid, and end of the encapsulation process. Also, samples combining 20 capsules were collected through the entire process of encapsulation. From the beginning, mid, and end stages (two capsules from each) and from the combination sample (six capsules) dissolution was performed. Dissolution was done for specific periods of time – 5, 10, 15, 20, 30, 45, 60, and 75 minutes.

Evaluation of the Finished Product

The finished capsules were tested for description, identification, loss on drying, dissolution, content uniformity, assay, organic impurities, residual solvents, elemental impurities, and microbiological purity as per USP requirements. The test for dissolution was performed at various time intervals, up to 75 minutes.

Statistical Analysis

The data from the three validated batches were analysed and compared with preset criteria of acceptance. Mean, standard deviation, and percentage relative standard deviation (%RSD) were calculated.

RESULTS:

Environmental conditions

The temperature and relative humidity fell within the specified ranges during production, hence appropriate processing conditions.

Blend Uniformity

From the blend uniformity results, good homogeneity was achieved. The average assays for batch A, B and C were 97.1%, 97.9% and 97.0% respectively. The %RSD was less than 1.0% implying good blending efficiency.

Loss on Drying

The Loss on drying was between 2.2% and 2.4% and thus met the specification of not more than 5.0%.

Table 1. Final Blend Evaluation Results

Parameter	Specification	P25092	P25093	P25094
Description	White to off-white powder	White powder	White powder	White powder
Bulk Density (g/mL)	Informational	0.46	0.47	0.47
Tapped Density (g/mL)	Informational	0.55	0.57	0.60
Loss on Drying (% w/w)	NMT 5.0	2.2	2.4	2.2
Blend Uniformity (%)	90.0–110.0	97.1	97.9	97.0
%RSD	NMT 5.0	1.0	1.0	0.6

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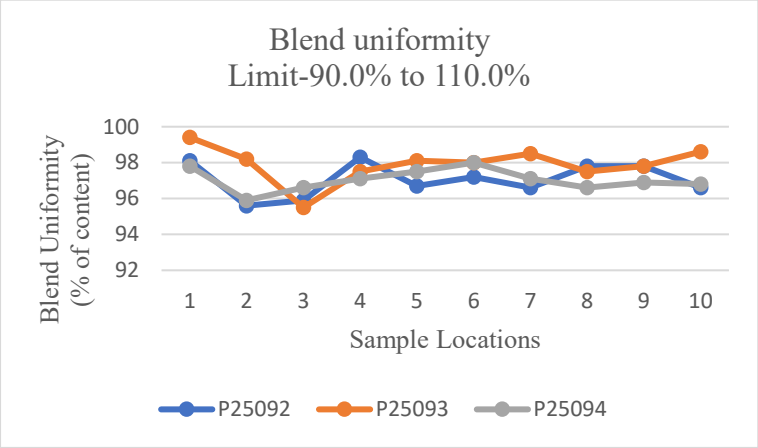


Fig 1: Blend uniformity

Yield Analysis

Accountable and theoretical yields for all validation batches were within acceptable limits, implying that there were no process losses and efficient material handling.

Encapsulation Performance

The mean capsule weights and variations of capsule weights met set specifications during encapsulation. The locking length was kept within the desired limit of 17.10–17.90 mm.

Table 2. Encapsulation Process Evaluation

Parameter	P25092	P25093	P25094	Acceptance Criteria
Average Weight Minimum (mg)	260.29	262.92	261.57	Within Target ±3%
Average Weight Maximum (mg)	269.18	267.80	269.19	Within Target ±3%
Individual Weight Minimum (mg)	251.8	254.2	251.9	Within Target ±5%
Individual Weight Maximum (mg)	276.4	275.0	275.0	Within Target ±5%
Locking Length Minimum (mm)	17.17	17.20	17.17	17.10–17.90
Locking Length Maximum (mm)	17.59	17.56	17.62	17.10–17.90

Uniformity of Stratum Content

The samples obtained through stratified sampling met ASTM E2709 and ASTM E2810 criteria. Average assay percentages varied between 96.5% and 98.3%, but all readings were within acceptable limits. Further testing was unnecessary.

Table 3. Stratified Content Uniformity Results

Parameter	P25092	P25093	P25094
Overall Mean (%)	96.5	98.3	97.5
Between Location SD	1.56	1.49	1.13
Within Location SD	3.00	2.08	2.20

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Lower Acceptance Limit	93.3	91.4	91.0
Upper Acceptance Limit	106.7	108.6	109.0
Result	Pass	Pass	Pass

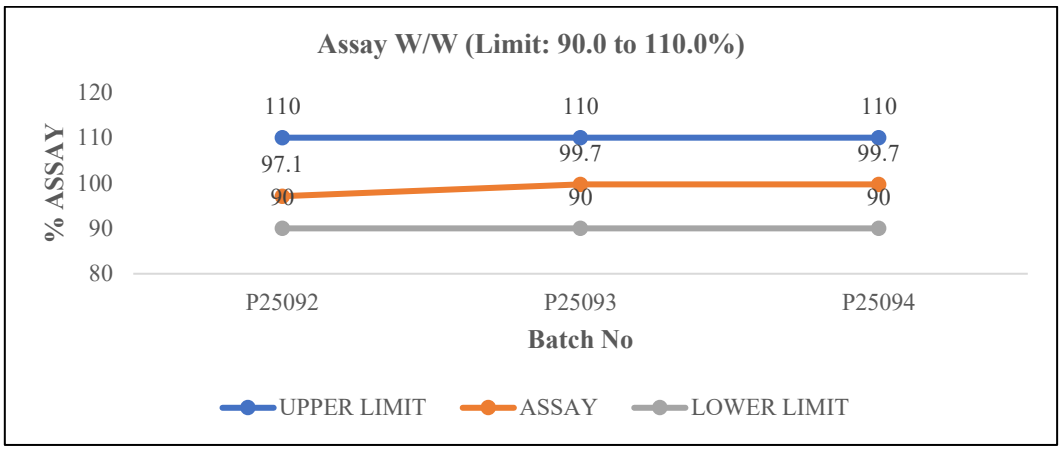


Fig 2: Assay (% W/W)

Dissolution Studies

All the validation batches showed more than 95% drug release in 30 minutes. The dissolution curves indicated uniform release behavior between batches, proving consistency in the process.

Table 4. Dissolution Profile Summary

Batch	Mean Dissolution at 30 min (%)	Mean Dissolution at 45 min (%)	Mean Dissolution at 60 min (%)	Result
P25092	95	95	95	Pass
P25093	100	100	100	Pass
P25094	97	97	97	Pass

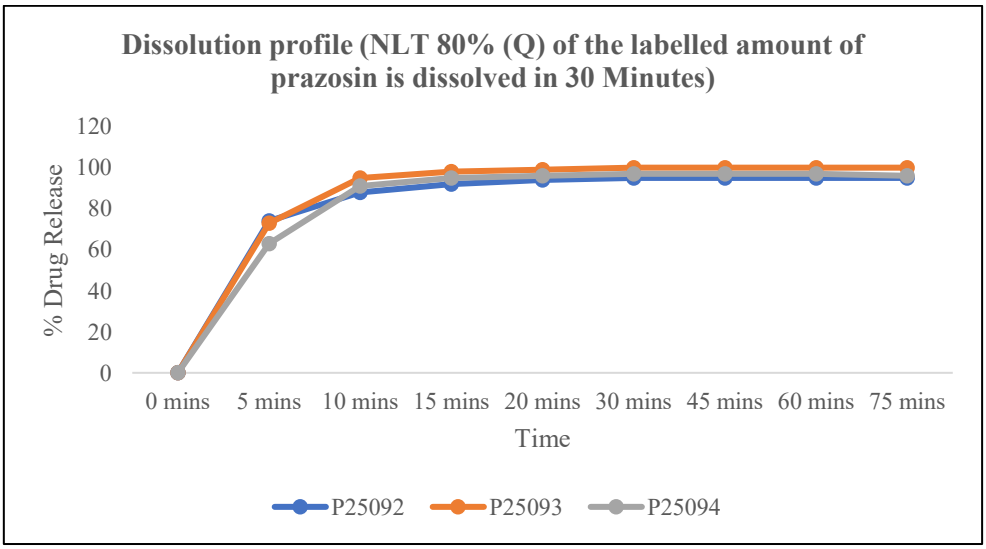


Fig 3: Dissolution profile

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Finished Product Evaluation

Testing conducted for characterization, identification, loss on drying, dissolution, assay, and content uniformity of the finished product met USP requirements. There were no out-of-specification or out-of-trend results throughout validation process.

Table 5. Summary of Finished Product Testing Results for Validation Batches

Parameter	Specification	P25092	P25093	P25094
Description	Conforms to approved specification	Complies	Complies	Complies
Identification (HPLC/PDA)	Conforms	Conforms	Conforms	Conforms
Loss on Drying (%)	NMT 5.0	2.1	2.5	2.1
Dissolution (%)	NLT 80% in 30 min	95	98	97
Content Uniformity (%)	USP <905> Complies	95.6	98.0	97.3
Assay (%)	90.0–110.0	97.1	99.7	99.7
Total Impurities (%)	NMT 1.0	BLQ	0.05	BLQ
Residual Solvents	USP <467> Complies	Complies	Complies	Complies
Elemental Impurities	USP <232>/ICH Q3D Complies	Complies	Complies	Complies
Total aerobic microbial count (TAMC) (cfu/g)	NMT 1000	<10	<10	<10
Total combined yeasts and moulds count (TYMC) (cfu/g)	NMT 100	<10	<10	<10
Escherichia coli	Absent	Absent	Absent	Absent
Overall Result	Meets Specification	Pass	Pass	Pass

NMT: Not More Than; NLT: Not Less Than; BLQ: Below Limit of Quantification.

DISCUSSION:

This report summarizes the observation of process performance qualification batches P25092, P25093 and P25094 of Prazosin Hydrochloride Capsules USP 1 mg as a validation study as per the Protocol No.: PPQP/059/25 with the pre-determined process parameters. The validation batches of Prazosin Hydrochloride Capsules USP 1 mg are executed at Esjay Pharma – Irungattukottai as per the Manufacturing instruction MF#: M-460-1A-2A.

Summary of observation made during execution of validation batches were detailed below:

- The environmental conditions under which Mixing, Blending and Encapsulation were conducted followed the batch record and was found satisfactory.

- The Encapsulation procedures are carried out as per the batch record instructions and all the parameters at the time of manufacturing and Encapsulation/check weighing have been found satisfactory.
- The samples collected during the manufacturing process as per the sampling plan from Protocol No.: PPQP/059/25 for all batches.
- Hopper study has been conducted with 80 %, 50 % and 20 % level (Batch No.: P25092) and the in-process parameters have been found satisfactory.
- Encapsulation Stage: Description, Weight Variation, Individual weight and Locking length parameters have been verified and observed to be within the batch record limit.
- Uniformity of Dosage Unit of stratified sample at the Encapsulation stage have been verified and the test results have been found within the acceptable limits.
- Dissolution Profile of 12 Units have been conducted up to 75 minutes (Intervals: 5, 10, 15, 20, 30, 45, 60 and 75minutes) and the results have been found within the specification limit.
- Finished Product Analysis has been conducted for all tests as per specification of three validation batches and have been found satisfactory and comply with the specification limit.
- It is observed from this study that the process performance qualification of Prazosin Hydrochloride Capsules USP 1mg for a batch size of 4,000,000 Capsules using the proposed machinery has been carried out successfully, and the process was validated as process parameters and Intermediate / Drug Product Critical Quality Attributes are in accordance with standard limits.

Recommendation for further commercial Batches (Critical process parameter)

Based on validation batches, manufacturing batch record for commercial batch shall be prepared to include the following recommendation at Mixing, blending and Encapsulation.

Table 6: Critical process parameter for manufacturing batch record

Stage	**Equipment**	**Parameter**		**Existing**	**Proposed**
Mixing	HSMG 600 L	Dry Mix	Mixing Time (Minutes.)	10	10
			Impeller	Slow	Slow
			Chopper	Slow	Slow
Sifting	Hand Screen	Mesh size		#30	#30
Blending	Bin blender	Capacity (L)		4000	4000
		Speed (RPM)		10	10
		Time (minutes)		10	10
Encapsulation	Capsule Filling Machine (AF – 150 T)	Description		Hard gelatin capsule shell size #2 with dark green colored cap and light brown colored body, imprinted with white ink as 019 on cap and novitium on body, filled with white to off-white powder blend.	
		Capsule Filling Machine Speed		20 – 140 SPM	20 – 140 SPM
		Check weigher speed (CPH)		(20000 CPH – 100000 CPH)	(20000 CPH – 100000 CPH)

CONCLUSION:

Process Performance Qualification for three consecutive commercial batches of Prazosin Hydrochloride Capsules USP 1 mg has been successfully carried out. Critical process parameters and critical quality attributes were within the acceptance criteria set for each parameter. The process was identified to be robust, reproducible and capable of producing consistent high quality capsules. Thus, the process can be validated.

CONFLICT OF INTEREST:

There is no conflict of interest in this study.

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