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PROCESS VALIDATION OF ANTI-HYPERTENSIVE DRUG: PROPRANOLOL HYDROCHLORIDE USP 10 MG TABLETS

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ABSTRACT

Validation is a very crucial step involved in achieving and maintaining the quality of any drug products. The main objective of my research is to study the process validation of propranolol hydrochloride USP 10 mg. The study untaken here provides the assurance that the manufacturing procedure is suitable for intended purpose and the product consistently meets predetermined specifications and quality attributes, as per specified master formula record. It give the detailed information of various steps involved in the validation like sifting, mixing, granulation, sizing, compression, and analyses of final finished products. During this process all the critical control parameters are observed such as uniformity in blend, bulk density, tapped density, flow property, uniformity of content, uniformity of dosage unit, average weight, thickness, hardness, friability, disintegration time, dissolution test, and assay. After all the results and discussion it can be said that this manufacturing process is capable of producing the product consistently of its quality attributes and meeting its predetermined specification. Hence the process is validated and can be used for routine manufacturing of propranolol Hydrochloride 10 mg tablet USP.

Keywords: Propranolol Hydrochloride, Validation, Process Validation, Prospective Validation, Concurrent Validation, Retrospective Validation, Revalidation.

INTRODUCTION

Development of the drug product is a long process which covers many steps including discovery of drug, testing in laboratory, preclinical studies in animals, clinical trials in human, registration by the regulatory bodies and their approval. Facilities involved and processes controlled during drug development have a great effect on the quality. Hence even after regulatory approval, to further improve the efficacy and safety of the drug product, regulatory agencies necessitate the manufacturer to examine its drug product for identity, strength, quality, purity and stability before release the drug product for commercial use. To implement this, pharmaceutical validation becomes crucial step. The concept of validation had its foremost formal appearance in United States in 1978 but the origin of validation in the healthcare industry is after the failure of the process in terminal sterilization in the early 1970s.

Validation

Validation is an extremely diverse and a complex area of regulatory concern, impacting all area of pharmaceutical, medical devices, and biologic research, manufacturing, and clinical testing.

Definition of validation

In 2011 [1],

"A process validation is defined as the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products"

Types of Validation: [2]

There are different types of validation:

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Analytical Validation:

The Code of Federal Regulations (CFR) explicitly states that "the accuracy, sensitivity, specificity, and reproducibility of test methods which were employed by the firm shall be established and documented." It is the evaluation of product quality characteristics through testing, to show consistency is being continued throughout the product life phase and that the accuracy, precision, purity, strength and specification have not been compromised.

Equipment Validation:

Validation of equipment's is also termed as Qualification. Equipment Validation is divided into Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ).

Computer System Validation [3]:

It includes computers, which straightway control system or process or collect data. It contains the qualification of all software and hardware, which has an influence, direct or indirect, on the quality of product. The validation approach to programmable logic controller (PLC) hardware and personal computers (PCs) is similar.

Cleaning validation

Cleaning validation is a documented process that shows the effectiveness and uniformity in cleaning pharmaceutical production equipment. Validations of equipment cleaning procedures are primarily used in pharmaceutical industries to prevent cross contamination and adulteration of drug products hence is critically important.

Process Validation:

"It is an established documented evidence which provides a high degree of assurance that a specific process (such as the manufacture of pharmaceutical dosage forms) will consistently produce a product meeting its predetermined specifications and quality characteristics". It is divided into different types as follows:

1. Prospective validation
2. Concurrent validation
3. Retrospective validation
4. Re-validation

Elements of validation [4]

Design Qualification (DQ):

The DQ is intended to specify that the equipment, system or facility is designed in accordance with the necessities of the user and Good Manufacturing Practice (GMP) guidelines.

Installation Qualification (IQ):

Upon advent of the equipment in the plant, it is first tested to ensure that the equipment is supplied as per the design requirements/technical terms. The Engineering Division confirms that the equipment and components are supplied in accord with the terms mentioned in (DQ). Installation Qualification is considered completed only afterwards the equipment has been correctly installed; all the above said parameters are confirmed and documented as per the approved IQ protocol.

Operational Qualification (OQ):

During Operational Qualification documented evidence are made to establish that all parts of the equipment work within their specifications and operational parameters.

Performance Qualification (PQ):

It is the final stage of qualification, which shows, how the equipment/system will perform when tested under simulated or actual production conditions.

Process Validation Definition [5]

According to US FDA

In 1987,

"Process validation is establishing documented evidence which provides a high degree of assurance that a specific process (such as the manufacture of pharmaceutical dosage forms) will consistently produce a product meeting its predetermined specifications and quality characteristics".

In 2008,

"Process Validation is defined as the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products".

In 2011,

"The revised guidance also provides recommendations that reflect some of the goals of FDA's initiative entities "Pharmaceuticals CGMPs for the 21st century – A Risk-Based Approach," particularly with regards to the use of technological advances in pharmaceutical manufacturing, as well as implementation of modern risk management and quality tools and concepts"

Types of Process Validation [6]

Prospective validation:

This validation is normally conducted prior to the introduction of new drugs and their manufacturing process. This approach to validation is generally undertaken whenever a new formula, process or facility must be validated before routine pharmaceutical formulation initiates. During the product development phase the production process should be broken down into individual

steps. A series of experimentations should be designed to define the criticality of these factors. Each of the experimental series should be preplanned and completely documented in an authorized protocol. Master batch documents can only be prepared after the identification of all the critical parameters involved in the process and setting of the machines, specifications of the components and environmental conditions have been determined. It is normally considered acceptable only if the three consecutive batches/runs are within the finally agreed parameters, which is able to produce the products of the quality desired. This would constitute a proper validation of the process. It is a authorization on the commercial three batches before marketing.

Retrospective validation:

This method is selected for those products for whom the manufacturing processes are ascertained to be stable and when prospective validation cannot alone justify the process based on the economic considerations and resource limitations. Before commission of the retrospective validation, wherein the numerical in-process and/or end-product test data of historic production batches are exposed to statistical analysis, the equipment, facilities and subsystems used in connection with the manufacturing process must be qualified in accordance with CGMP requirements.

It may be conducted in the following manner:

1. Collect all the mathematical data from the batches completed, record and include assay values, end-product test results, and in-process data.
2. Arrange these data in a chronological order according to batch manufacturing data, using a spreadsheet format.
3. Take account of data from at least the last 20–30 batches manufactured for analysis. If the number of batches is less than 20, then include all manufactured batches and commit to obtain the required number for analysis.
4. Fit the data by eliminating test results from noncritical processing steps.
5. Give the subsequent data for statistical analysis and evaluation.
6. Take out the conclusions as to the state of control of the manufacturing process based on the analysis of retrospective validation data.
7. Prepare a report of your findings (documented evidence).

Concurrent validation:

In-process monitoring of critical processing steps and end-product analysis of current production can give documented evidence to prove that the manufacturing process is in a controlled state. It is similar to prospective, except the operating firm will sell the product during the qualification runs, to the public at its market price. This validation involves in process monitoring of critical processing steps and product testing.

Revalidation:

Almost all GMP texts recommend that whenever there are significant changes in the facility, process , equipment or revalidation should be carried out. The FDA process validation guidelines state that the quality assurance system in place that requires revalidation whenever there are changes in packaging (assumed to be the primary container-closure system), formulation, equipment or processes (meaning not clear) which could impact on product effectiveness or product characteristics and whenever there are changes in product characteristics. When revalidation is to be performed is given below as follews:

- Any Change in a critical component (usually refers to raw materials).
- Any Change or replacement in a critical piece of modular (capital) equipment.
- Any Change in a facility and/or plant (usually location or site).
- If there is increase or decrease in batch size
- Consecutive batches that fail to meet product and process specifications.

Advantages of Process Validation [6]

- Increase in output
- Decrease in refusals and reworks
- Decrease in utility costs
- Prevention of capital expenditures
- Rarer complaints about process related failures
- Reduced analysis in process and finished goods
- More quick and accurate investigations into process nonconformities
- More quick and reliable start-up of new equipment
- Easier scale-up from development work
- Easier conservation of the equipment
- Improved employee awareness of processes
- More fast automation

Reason for Process Validation [7]

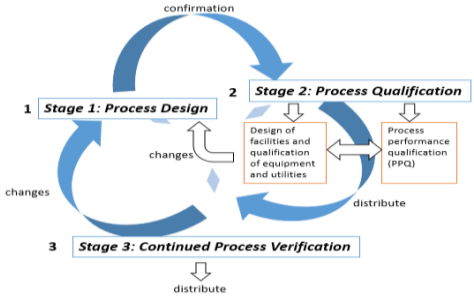
The possible reason of performing process validation may include:

- Existing products or New product as per SUPAC changes.
- Change in location of manufacturing.
- Change in lot size.
- Change in equipment.
- Change in process existing products.
- Change in composition or components.
- Change in the critical control parameters.
- Change in vendor of API or critical excipient.
- Change in specification on input material.

- Abnormal trends in quality parameters of product through review during Annual Product Review (APR).
- Trend of Out of Specification (OOS) or Out of Trend (OOT) in consecutive batches.

Stages of Process Validation:

Stage 1 — Process Design
Stage 2 — Process Qualification
Stage 3 — Continued Process Verification



Manufacturing process in brief:

1. Raw Material sifting:

Mix and sift required Quantities of corn starch and sunset yellow FCF global no. 5085 Al Lake E110 C113283 IHT through 100#. Sift propranolol HCl, lactose monohydrate and sodium starch glycolate through 40# using vibratory sifter.

2. Binder preparation:

The binder is prepared in rapid mixer granulator. Take required quantity of purified water and start the mixer at slow speed and add half a quantity of binder manually by opening the lid of binder addition port of RMG for about 2 min. with chopper off. Start mixer with adding the additional quantity of binder at slow speed impeller for about 2 min. with chopper off and continue mixing with fast speed impeller. Add additional purified water (1-5 L) and impeller and fast speed chopper. Mix the mass for about 1 min. at fast speed impeller and fast speed chopper to reach the end point.

3. Dry Mixing:

Load the sifted raw materials into RMG and Mix for 10 min. at slow speed (50±2 RPM) with chopper off.

4. Wet mixing:

Add binder solution into RMG and mix for 10 min. impeller at slow speed and chopper off. Stop the mixing and shake materials and mix for 1-2minutes impeller at fast speed with chopper at slow speed. Continue mixing till granulation end point is reached. If required purified water can be added to achieve granulation end point.

Determination of end point:

1. **Banana breaking test:**

Precaution: Use hand gloves for this test.

Procedure: Take one handful of wet mass in the palm and press to form a lump. Open the palm and break the lump by pressing the thumb at the center of the lump.

Observation: The lump shall break into small pieces.

2. At the end point of granulation,

a. Impeller: 27 Ampere
b. Chopper: 9 Ampere

5. Drying:

Dry the wet granules at 55-65^{o}C inlet air temperature till the loss on drying (LOD) of the granules is achieved between 1.5-4.0 % (w/w) at 105^{o}C in Fluid bed dryer.

6. Milling

Dried granules are milled in oscillating granulator using 1 mm screen.

7. Premixing

Milled granules are premixed for 5 min. using the bin blender.

8. Lubricants sifting:

Sift lubricants through 40# using vibratory sifter, sift sodium starch glycolate and magnesium stearate separately and collect in a separate polybag.

9. Lubrication:

Mixing of sodium starch glycolate with premixed granules for 10 min. and mixing with magnesium stearate for 2 min in bin blender.

10. Compression:

Compress the tablets using tablet compression machine. Compress the tablets at the average weight 105 mg ± 3.0 % double rotary compression machine.

Machineries

Vibratory Sifter (30 inch) (Wintech Pharmachem), Rapid Mixer Granulator (Sainath Boiler), Binder preparation vessel (Wintech Pharmachem), Fluid bed dryer (Allience), Oscillating granulator (Kanath Eng.), Bin blender (R. P. Product), Tablet Compression Machine (Cadmach), Tablet Deduster (Omega Pharma), Tablet Deduster (Omega Pharma), Metal Detector (Technofore), Metal Detector (Technofore).

Utilities

HVAC System (ABB), HVAC System (ABB), Compressed air System (Ingersollrand), Purified water System (Christnisotec).

Instruments used for analysis

HPLC (Waters), Weighing Balance (Mettler), Disintegration Apparatus (Electro Lab), Disintegration

Apparatus (Electro Lab), UV Spectrophotometer (Perkin Elmer), Sieve Shaker (Elactron Pharma), Tap Density Tester (Electrolab), Weighing Balance (Mettler Toledo), Friability Apparatus (Electrolab), Hardness Test Apparatus (Pharmatron).

Table 1. List of Raw Materials and their Functions

Sr. No.	Raw Material	Function
Granulation Ingredients:		
1.	Propranolol Hydrochloride	Active pharmaceutical ingredient
2.	Lactose Monohydrate	Diluent
3.	Corn Starch	Glidant and binder
4.	Sodium Starch Glycollate	Disintegrant
5	Sunset Yellow FCF Global No.:5058A1 lake E11O C113283	Colourant
6	D & C Yellow no. 1	Colorant
7	Povidone CPVPK30	Disintegrant
8	Purified Water*	Solvent
Lubricants:		
9	Sodium starch- Glycolate (primojel)	Disintegrant
10.	Magnesium stearate (vegetable grade)	Lubricant

Process stages, control variables and measuring response / justifications

Following process parameters will be monitored during the manufacturing process

Table 2. Critical Control Parameter

Stage	Step	Control Variables	Measuring Response/Justifications
Granulation	**Dry mixing**	Time	Uniform distribution of active ingredients with excipients
	Wet mixing	Mixer speed	Proper mixer speed is required so that mixing and binding is completed in optimal mixing time
		Mixing time	Over mixing / under-mixing will greatly affect the granular composition of mix and characteristic of the granules. Ampere reading at end point consistency of wet mass.
	Drying	Inlet and outlet temperature	Control of inlet air temperature is essential for drying of the granules.
		Drying time	Over or under drying of the granules may lead to problems during compression.
			LOD of dried granules.
	Sizing	Speed of the blade	More or less time lead to compression problem & flow property of the granules.
	Lubrication	Mixing time	Control over mixing time and speed of blender determines the distribution of lubricants in overall mix, which is very essential to achieve blend uniformity and trouble free compression.
		Sequence of the addition of the lubricants	Yield of lubricated granules.

Sampling Plan:

During the manufacturing process of propranolol hydrochloride 10 mg tablets various samples were collected to perform various tests.

Table 3. Sampling plan

Process step	Equipment	Sampling plan	Monitoring/ evaluation parameter
Dry mixing	RMG	Collect approximately 1 to 3 time of unit dose sample quantity required for analysis from 10 1ocations of the RMG using sampling device on completion of dry mixing process.	Content of active ingredients in dry mix
Wet mixing	RMG	-	Appearance of wet mass

			Ampere reading at the end of granulation end point
Wet milling	Multi mill		Size of screen used
Drying	FBD	Collect 5 sample of different locations of FBD as mentioned in the sampling plan	Loss of drying
			Inlet and outlet temperature
			Total drying time
Sifting & sizing	Vibratory sifter & multi mill		Size of sieve used
			Total sizing time
Lubrication	Octagonal blender	Collect approximately 1 to 3 times of unit dose sample quantity required for analysis from 1010 cations of octagonal blender using sampling devise on completion of lubrication process.	Content of active ingredients in lubricated granules.
		Composite sample of approximately 20g from all the 10 sampling points.	LOD/sieve analysis, bulk density, granules flow properties.
Compression	Compression machine	Collect tablets at initial, middle and end stage of compression	-
		30 tablets each at initial, middle and end stage of compression	Assay and dissolution rate in QC
		10 tablets each at initial, middle and end stage of compression	Thickness
Compression	Compression machine	*10 tablets each at initial, middle and end stage of compression	Friability
		10 tablets each at initial, middle and end stage of compression	Hardness
		20 tablets each at initial, middle and end stage of compression	Average weight
		#80 tablets each at initial, middle and end stage of compression	Uniformity of weight
		6 tablets each at initial, middle and end stage of compression	Disintegration test
		$ approximately 100 tablets (composite sample)	Complete analysis in QC

RESULTS AND DISCUSSION

Table 4. Observations and Acceptance Criteria for Hardness Challenge Study

Batch No. A				
Test	Acceptance criteria	Observation		
		Min speed	Optimum speed	Max speed
Machine speed	Feeder speed	12 RPM	18 RPM	18 RPM
	Turrent speed	12 RPM	30 RPM	50 RPM
Compression force	Pre compression force	-	-	-
	Main compression force	4.83 kN	6.23 kN	5.51 Kn
Appearance	Orange coloured, round biconvex tablets, embossed with “P” and “10” on either side of the breaking on one side and plain on the other side.	Complies	Complies	Complies
Average weight	105 mg ± 5 %	104.08 mg	105.36 mg	104.78 mg
Uniformity of weight	Within ± 5 % of average weight	Min:102.34 mg Max:107.34 mg	Min: 102.3 mg Max:107.3 mg	Min:102.3 mg Max:107.6 mg
Diameter	6.5 ± 0.2 mm	Max:6.23 mm Min: 6.96 mm	Max:6.26 mm Min: 6.94 mm	Max: 6.34 mm Min: 6.89 mm

Thickness	3.0 ± 0.3 mm	Max: 2.93 mm Min: 3.00 mm	Max: 2.97 mm Min: 3.01 mm	Max: 2.95 mm Min: 3.04 mm
Hardness	NLT 30 N	69 – 100 N	96 – 125 N	68 – 105 N
Friability	NMT 1.0 % w/w	0.02 % w/w	Nil	Nil
Disintegration time	NMT 15 minutes	2min 23 sec.	2min 56 sec.	2min 43 sec.

Batch No. A			
Test	Acceptance criteria	Observation	
Appearance	Orange coloured, round biconvex tablets, embossed with "P" and "10" on either side of the breaking on one side and plain on the other side.	Complies	Complies
Average weight	105 mg ± 5 %	104.71 mg	105.34 mg
Uniformity of weight	Within ± 5 % of average weight	Min: 103.9 mg Max: 106.9 mg	Min: 104.4 mg Max: 107.7 mg
Dimension	6.5 ± 0.2 mm	Min: 6.29 mm Max: 6.92 mm	Min: 6.24 mm Max: 6.96 mm
Thickness	3.0 ± 0.3 mm	2.89-2.98 mm	2.96-2.98 mm
Hardness	NLT 30 N	24-29 N	23-28 N
Friability	NMT 1.0 % w/w	0.02 % w/w	0.02 % w/w
Disintegration time	NMT 15 minutes	2min 39 sec.	2min 45 sec.
Compression force	Pre compression force	-	-
	Main compression force	3.01 kN	12.19 kN

Table 5. Batch yield of compressed tablets

Batch No.	**A**	**B**	**C**
Yield	96.56 %	97.75 %	97.54 %

Table 6. Results of Dry Mixing (Blend uniformity)

Sr. no	**Sampling point**	**Batch 1**		**Batch 2**		**Batch 3**	
		LOT A	**LOT B**	**LOT A**	**LOT B**	**LOT A**	**LOT B**
1.	Top (Left)	99.8 %	101.5 %	97.6 %	98.8 %	101.0 %	97.9 %
2.	Top (Rear)	99.1 %	100.1 %	99.6 %	97.8 %	100.3 %	97.9 %
3.	Top (Front)	99.9 %	98.2 %	96.0 %	99.4 %	99.0 %	98.6 %
4.	Top (Right)	102.4 %	99.3 %	97.5 %	98.6 %	98.7 %	101.4 %
5.	Middle (Left)	97.8 %	100.3 %	99.5 %	101.4 %	99.6 %	98.8 %
6.	Middle (Right)	98.3 %	98.8 %	97.5 %	100.5 %	99.0 %	100.7 %
7.	Bottom (Left)	99.4 %	99.8 %	96.7 %	99.7 %	100.3 %	100.2%
8.	Bottom (Rear)	98.2 %	97.5 %	98.2 %	98.8 %	98.8 %	99.7 %
9.	Bottom (Front)	97.7 %	98.5 %	99.1 %	98.2 %	101.9 %	98.8 %
10.	Bottom (Right)	99.5 %	100.2 %	96.0 %	96.5 %	99.7 %	99.9 %
	Average	99.21	99.42	97.77	98.97	99.83	99.39
	SD	1.38439718	1.18958	1.32837	1.38327	1.0478	1.17988
	% RSD	1.39542101	1.19652	1.35866	1.39767	1.04959	1.18712

Limit: (% LC) (by HPLC) 90.0 % - 110.0 % of label amount, RSD: NMT 5.0 %.

Mean of individual test result: 95.0 % - 105.0 %. Hence 15 min dry mixing time at slow speed (50±2 RPM) with chopper off shall remain validated.

Drying:

Table 7. Results of LOD for Drying

Sr. no.	**Sampling location**	**Batch 1**		**Batch 2**		**Batch 3**	
		LOT A	LOT B	LOT A	LOT B	LOT A	LOT B
1.	Left	2.89 %	3.12 %	2.90 %	2.49 %	2.81 %	3.05 %
2.	Right	2.88 %	3.42 %	2.67 %	2.98 %	2.91 %	3.24 %

3.	Centre	2.79 %	3.22 %	2.79 %	2.99 %	2.76 %	2.34 %
4.	Front	2.82 %	3.17 %	2.80 %	3.03 %	2.39 %	3.28 %
5.	Back	2.88 %	3.61 %	2.62 %	3.06 %	2.57 %	2.95 %
6.	Composite	2.89 %	3.26 %	2.79 %	2.96 %	2.93 %	2.89 %

Limit: 1.5-4 % w/w at 105°C for 60 min.

The drying time observed in the range of 104-182 min (limit: 20-60 min) for each lot manufactured.

Hence drying parameter within the inlet temperature 55-65^{o}C remain validated. Outlet temperature of 45-55^{o}C shall be change to 45-60^{o}C. Drying time to be finalized as 75-200 (since we are targeting LOD time limit has no impact at the particular inlet temperature.

Table 8. Batch yield of lubricated granules:

Batch No.	A	B	C
Yield	98.61 %	98.71 %	98.58 %

Pre-Lubrication:

Table 9. Results of Blend Uniformity for Pre-Lubrication

Sr. No.	Sampling location	Batch 1	Batch 2	Batch 3
1.	Top (Left)	101.4 %	99.7 %	96.9 %
2.	Middle (Left)	100.1 %	102.5 %	97.5 %
3.	Bottom (Left)	99.2 %	98.8 %	99.5%
4.	Top (Rear)	98.0 %	101.0 %	98.1 %
5.	Bottom (Rear)	103.8 %	100.6 %	97.5 %
6.	Top (Front)	101.7 %	99.8 %	101.0 %
7.	Bottom (Front)	98.9 %	98.8 %	98.4 %
8.	Top (Right)	99.7 %	100.4 %	100.1 %
9.	Middle (Right)	100.3 %	97.9 %	99.1 %
10.	Bottom (Right)	101.9 %	98.3 %	99.3 %
	AVERAGE	100.5	99.78	98.74
	SD	1.71399	1.39825	1.28944
	% RSD (NMT 5.0 %)	1.70547	1.40134	1.3059

Limit: (% LC) (by HPLC) 90.0 % - 110.0 % of label amount, RSD: NMT 5.0 %

Mean of individual test result: 95.0 % - 105.0 %

Hence 10 min pre-lubrication time shall be remained validated.

Lubrication:

Table 10. Results of Blend Uniformity of Lubrication Stage

Sr. No	Sampling location	Batch 1	Batch 2	Batch 3
1.	Top (Left)	99.3 %	99.7 %	98.9 %
2.	Middle (Left)	100.1 %	98.1 %	97.9 %
3.	Bottom (Left)	97.7 %	100.2 %	98.3 %
4.	Top (Rear)	98.4 %	99.9 %	98.5 %
5.	Bottom (Rear)	100.5 %	98.5 %	99.8 %
6.	Top (Front)	98.2 %	99.7 %	101.5 %
7.	Bottom (Front)	98.7 %	101.7 %	99.1 %
8.	Top (Right)	100.2 %	98.4 %	99.2 %
9.	Middle (Right)	98.4 %	100.8 %	100.8 %
10.	Bottom (Right)	98.8 %	99.9 %	98.2 %
	AVERAGE	99.03	99.69	99.22
	SD	0.95225	1.11699	1.16886
	% RSD (NMT 5.0 %)	0.96158	1.12046	1.17804

Limit: (%LC) (by HPLC) 90.0%-110.0 % of label amount, RSD: NMT 5.0 %

Mean of individual test result: 95.0 %-105.0 %.

Table 11. Sieve Analysis on Composite Sample

Sieve Analysis	% Passed through		
	Batch 1	Batch 2	Batch 3
Mesh 40 (425 µ)	78.34 %	77.87 %	78.98 %
Mesh 60 (250 µ)	72.19 %	74.78 %	73.86 %
Mesh 80 (180 µ)	68.71 %	67.93 %	69.85 %
Mesh 100 (150 µ)	64.74 %	65.64 %	64.94 %
Sieve Analysis	**% Retained**		
	Batch 1	Batch 2	Batch 3
Mesh 60 (250 µ)	27.81 %	27.96 %	28.81 %
Mesh 100 (150 µ)	36.56 %	35.67 %	34.26 %

Table 12. Bulk density and LOD

Batch No.	A	B	C
P – bulk density g/ml (untapped)	0.68	0.69	0.67
Pt – bulk density g/ml (tapped)	0.84	0.83	0.83
LOD (1.5-4.0 % w/ w)	3.20 %	3.31 %	3.44 %

Table 13. Hausner's ratio

Batch No.	A	B	C
Hausner's ratio (Pt / P)	1.23	1.20	1.23

Table 14. % Compressibility

Batch No.	A	B	C
% Compressibility $=\frac{(pt-p)}{pt} * 100$	19.04	16.86	19.27

Table 15. Observations and Acceptance Criteria for in process test (QC)

Test	Observation			Acceptance criteria
Batch	**A**	**B**	**C**	
Assay	98.3 %	100.8 %	99.9 %	90.0-110.0 % of the labelled amount
Dissolution	Min: 99.2 % Max: 102.8 %	Min: 99.8 % Max: 100.8 %	Min: 98.2 % Max: 100.6 %	NLT 75% (Qty. of the labeled amount of Propranolol HCl is dissolved in 30 min as per USP)

Table 16. Observations and Acceptance Criteria for in process test (QC) for tablet

Specification: ABC				
Test	**Observation**			**Acceptance Criteria**
Batch	**A**	**B**	**C**	
Appearance	Conforms	Conforms	Conforms	Orange coloured, round biconvex tablets, embossed with "P" and "10" on either side of the breaking on one side and plain on the other side.
Average weight	104.708	105.336	104.7	105 ± 5%
Uniformity of weight	Min:102.34 mg Max:107.34 mg	Min: 102.3 mg Max:107.3 mg	Min:102.3 mg Max:107.6 mg	Within ± 5 % of average weight
Diameter	Max:6.23 mm Min: 6.96 mm	Max:6.26 mm Min: 6.94 mm	Max: 6.34 mm Min: 6.89 mm	6.5 ± 0.2 mm
Thickness	Max: 2.93 mm Min: 3.00 mm	Max: 2.97 mm Min: 3.01 mm	Max: 2.95 mm Min: 3.04 mm	3.0 ± 0.3 mm
Hardness	69 – 100 N	96 – 125 N	68 – 105 N	NLT 30 N
Friability	0.02 % w/w	Nil	Nil	NMT 1.0 % w/w
Disintegration time	2min 23 sec.	2min 56 sec.	2min 43 sec.	NMT 15 min
Assay	98.3 %	100.8 %	99.9 %	90.0-110.0 % of the labelled amount
Dissolution	Min: 99.2 % Max: 102.8 %	Min: 99.8 % Max: 100.8 %	Min: 98.2 % Max: 100.6 %	NLT 75% (Qty. of the labeled amount of Propranolol HCl is dissolved in 30 min as per USP)

CONCLUSION

On the basis of data generated from the three batches (Batch-1, Batch-2, Batch-3), it is concluded that the manufacturing process of Propranolol HCl USP 10 mg tablet is capable of producing a product meeting its quality attributes and predetermined specification. The results of all stages were found within the standard specification and acceptance criteria mentioned in the process validation protocol and finished product specification. Hence manufacturing process of Propranolol HCl USP 10 mg tablet is considered validated and approved for routine production.

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CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

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