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Process Validation of Labetalol Hydrochloride 200 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 labetalol hydrochloride 200 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.The process validation of labetalol hydrochloride tablet of dosage 200 mg completed for 3 back to back bunches of batch no. 1 , batch no. 2, batch no. 3which include the validation of critical steps of manufacturing constituting dispensing , sifting , dry mixing , drying blending, compression and coating. 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. The results obtained of the three batches were found within limits. Therefore the product with require specification can consistently obtained.***

Keywords: Labetalol hydrochloride, process validation, quality assurance, performance qualification, standard operating procedure

1. Introduction

Validation is the way toward building up narrative proof exhibiting that a system, process , or movement did in testing and afterward creation keeps up the coveted level of consistence at all stages.in pharmaceutical business , it is imperative that notwithstanding last testing and consistence of items, it is additionally guaranteed that the procedure will reliable deliver the normal outcomes.[1]

Validation mainly based on, FDA regulation describing current good manufacturing practice (CGMP) for finished pharmaceutical are provided in 21CFR parts 210 and 211.

The basic principles for validation may be stated as follows.

1) Establish that the process equipment has the capability of operating within required parameters.
2) Demonstrate that controlling, monitoring, and measuring equipment and instrumentation are capable of operating within the parameters prescribed for the process equipment.
3) Monitor the validated process during routine operation. As needed prequalify and recertify the equipment.

A wide verity of procedures, processes, and activities need to be validated, the field of validation is divided in to a number of subsections including the followings:[2]

- Equipment validation
- Facilities validation
- HVAC validation
- Analytical validation
- Cleaning validation
- Process validation
- Computer system validation
- Packaging validation

Similarly, the activity of qualifying system and equipment is divided in to a number of subsections including the following:

- Design qualification (DQ)
- Component qualification (CQ)
- Installation qualification (IQ)
- Operational qualification (OQ)
- Performance qualification (PQ)

Need of Process Validation

- **Assurance of the quality of product –** Assurance of the item can't be guaranteed for a procedure by routine quality control testing in light of restriction of the factual examining and constrained affectability of the completed item testing quality contrast among units inside a cluster or among various bunches are seldom distinguished by testing of complete item tests. Approved changes the agreeableness and dependability of a framework or procedure to meet preset criteria [3]
- **Optimization of process –**the advancement of the procedure is very extreme effectiveness, while keeping up quality principle, is result of approval. Exacting importance of word to enhance is to make as successful impeccable or helpful as could be expected under the circumstances. The improvement of the office, gear, framework, and procedures about an itemthat meets.
- **Quality requirement at the lowest cost-** the direct fiscal advantage of approval is a decrease in the cost related with process checking, examining and testing. Investigation of different examples would not be require so as to moderate homogeneity for an approved mixing process. The consistency and unwavering quality of an approved procedure to deliver a quality item.
- To reduce the mix ups and contaminations
- Minimal batch failure improved efficiently and productivity
- Reduction in rejection and reducing the cost and time of reprocessing
- Increase the output
- Avoidance of capital expenditure
- Fewer complaint about process related failures
- Reduce testing in process and product
- More rapid and reliable starts – up of new finished goods
- Easier maintains of equipment

- More rapid automation [4]

2. Phases of Process Validation

The validation studies may be classified into three

Phase 1: Pre-validation Qualification Phase - this is also known as process design phase focusing mainly on qualification efforts. This phase covers all activities relating to product RnD, formulation pilot batch studies , scale up studies technology transfer to commercial scale batches, established stability condition and storage , and handling of in- process and finished dosage forms , equipment qualification , installation qualification , master product document , operational qualification and process capacity.

Phase 2: process qualification- during this stage the process which is designed in process design phase is evaluated whether the process is capable of reproducible commercial manufacturing. It conform that all the establish limits of critical process parameters are valid and satisfactory products can be produced.
There are 2 aspect of process qualification;

1) **Design of facilities and qualification equipment and utilities-** activities perform to assure proper facility design and that the equipment and utility are suitable for their intended use and perform properly.
2) **Process performance qualification** – it involves defining performance criteria and deciding what to collect when, how much data, and appropriate analysis of data. Manufacturer must scientifically determine suitable criteria and justified it.

Phase 3: continued process verification- This is known as the Validation Maintenance Phase, it requires frequent review of all process related documents, including validation of audit reports, to assure that there have been no changes, deviations, failures an modification to the process and that all standard operating procedures (SOPs), including change control procedures, have been followed. At this stage, the validation team comprising of individuals representing all major departments also assures that there have been no changes/deviations that should have resulted in requalification and revalidation. [6, 7]

3. Material and Method

Dry mixing
3 sample by thief sampler at 5 different locations from RMG and 1 composite sample after 10 & 15 min. mixing interval. And assay of the collected sample were performed. Wet mixing at slow speed of agitator for 15 minutes chopper was started at slow speed for 5 min.

Drying
Drying was performed in FBD. The wet mass was loaded in FBD bowl in equal two lots. Wet mass was air dried at ambient temperature for 20 minute. Rack the mass of bowl then dried at 50 0c – 55 0c inlet temperatures and the material was dried for 40 minutes. After drying 2.0 gm. sample was collected by sampling thief at 5 different location from the FBD bowl and one composite as per given blow and LOD was checked , it should be 1.0% - 3.0% . The above steps were repeated for second lot.After drying the granules were shifted thorough # 14 sieves using vibratory sifter. The sifted and sized granules were collected in clean container.

Lubrication
5 gm. sample was collected by sampling thief from 5 different locations and one composite sample from octagonal blender shown below after 10, 20, 30 min. mixing interval. Samples to be analyzed for assay, loss on drying, bulk density, tapped density and sieve analysis

Compression
Sample was collected separately at high hardness (pressure) & low hardness (pressure) samples were collected. Machine was run within the different RPM (low and high) range of speed for about 16, 21, 26 RPM sample was collected separately.

Coating
This steps involved coating of Uncoated /Semi finish tablets in conventional coating pan at defined speed. Transfer the uncoated tablets to the coating area. Charge the uncoated tablets in the cleaned coating pan set the coating pan RPM, Spray distance Spray rate. Start spraying the coating solution over the tablet bed .After completion of spraying dry the coated tablets for 10-15 minutes. Allow the coated tablets to dry for 30 minutes. Then unload the tablets and collect in cleaned plastic drum lined with double polythene bag. Affix the proper identification label to each drum.

Table 1: List of raw material

Name of material	Function
Labetalol hydrochloride	Active
Lactose	Excipient
Starch	Excipient
Methyl Paraben (Methyl Hydroxy Benzoate) Start	Excipient
Propyl Paraben (Propyl Hydroxy Benzoate)	Excipient
Isopropyl Alcohol	Excipient
Hydroxy Propyl Methyl Cellulose (Hypromellose)	Excipient
Methylene Dichloride (Dichloromethane)	Excipient
Croscarmellose Sodium	Excipient
Purified Talc	Excipient
Magnesium Stearate	Excipient
Colloidal Anhydrous Silica	Excipient
Hydroxy Propyl Methyl Cellulose (Hypromellose	Excipient
Isopropyl Alcohol	Excipient
Methylene Dichloride (Dichloromethane)	Excipient
Colour : Sunset Yellow Lake	Excipient
Colour : Ponceau 4 R Lake	Excipient
Propylene Glycol	Excipient
P.E.G. -400	Excipient

Table 2: Control points

S.No	*Stage*	*Risk Point*	*Check Point*
1.	Dispensing	1) Avoid product cross contamination 2) Avoid balance variation	1) Completely previous product removed, proper cleaning & Deferential pressure monitoring. 2) Before use balance calibrated.
2.	Dry Mixing	1) Avoid product cross contamination 2) Blend uniformity of API	1) Completely previous product removed & proper cleaning 2) Proper mixing
3.	Granulation	1) Avoid Product cross contamination 2) Speed Control 3) Bulk density	1) Completely previous product removed & proper cleaning 2) Continues monitoring of speed 3) Proper mixing & flow characteristics of granules.
4.	Drying	1) Avoid Product cross contamination 2) Moisture content 3) Temperature Control	1) Completely previous product removed & proper cleaning 2) After drying check of moisture. 3) Continuous check of Inlet & outlet temp.
5.	Blending	1) Avoid Product cross contamination 2) Speed Control 3) Uniformity of the bulk	1) Completely previous product removed & proper cleaning 2) Continues monitoring of speed 3) Proper mixing.
6.	Compression	1) Avoid Product cross contamination 2) Speed Control 3) Pressure Control	1) Completely previous product removed & proper cleaning 2) Continues monitoring of speed at differential interval. 3) Continues monitoring of pressure.
7.	Coating	1) Avoid Product cross contamination 2) Speed Control 3) Spray Rate Control 4) Temperature Control	1) Completely previous product removed & proper cleaning 2) Continues monitoring of speed at differential interval.

4. Result and Discussion

Table 3: Result of dry mixing

LOCATION	Batch no 1			Batch no 2			Batch no 3		
	5 MIN.	10 MIN.	15 MIN.	5 MIN.	10 MIN.	15 MIN.	5 MIN.	10 MIN.	15 MIN.
TOP	96.89%	101.58%	101.37%	104.33%	101.44%	100.85%	96.35%	102.32%	100.46%
MIDDLE	103.67%	102.49%	100.41%	99.75%	100.78%	99.89%	102.56%	101.83%	101.39%
BOTTOM	100.45%	100.57%	101.51%	101.28%	101.25%	100.48%	98.74%	98.83%	101.59%
COMPOSITE	103.67%	101.51%	102.65%	100.45%	100.78%	100.85%	103.67%	100.47%	100.46%

Limit - %(LC) BY (HPLC) 90.0%to110% of label amount, RSD =NMT 5.0%, mean of individual result = 90.0% to 110.0%

Table 4: Result of LOD for drying process

LOCATION	Time			TIME			TIME		
	5MIN	10MIN	15MIN	5MIN	10MIN	15MIN	5MIN	10MIN	15MIN
S1	2.19	1.72	0.86	2.13	1.55	0.53	2.12	1.52	0.64
S2	2.22	1.52	0.65	2.14	1.57	0.57	2.16	1.55	0.64
S3	2.21	1.73	0.69	2.21	1.76	0.83	2.12	1.63	0.66
S4	2.15	1.67	0.28	2.18	1.77	0.65	2.19	1.54	0.62
S5	2.17	1.84	0.28	2.19	1.56	0.67	2.16	1.87	0.66
S6	2.16	1.58	0.08	2.24	1.82	0.65	2.17	1.73	0.63
S7	2.13	1.69	0.25	2.15	1.81	0.64	2.16	1.65	0.65
S8	2.19	1.84	0.09	2.12	1.57	0.63	2.14	1.76	0.55
S9	2.12	1.53	0.08	2.16	1.58	0.74	2.17	1.65	0.85
% RSD	1.58	1.47	0.84	1.82	1.58	0.72	1.09	1.79	0.54

Limit- Drying Time: 15-20 minutes. Drying Temperature= 40-45ºC for 15-20 minutes. Equipment = Fluid bed dryer (FBD). Time = 15-20 minutes Moisture Content: Between 0.6 to 1.4 % w/w

Table 5: Result of blending process

LOCATION	Batch no./Time			Batch no./time			Batch no./ time		
	5MIN.	10MIN	15MIN	5MIN	10MIN	15MIN	5MIN	10MIN	15MIN
S1	103.21	99.76	98.78	101.89	102.68	100.49	98.86	98.97	102.68
S2	100.23	99.89	99.38	102.05	101.89	100.89	99.68	100.87	100.54
S3	102.21	102.67	100.21	101.99	102.99	101.55	98.64	99.41	102.48
S4	101.58	100.22	100.87	98.97	102.68	101.65	98.86	99.89	102.12
S5	102.44	101.29	102.67	102.05	102.05	102.84	99.41	99.41	100.39
S6	102.51	99.56	102.53	102.99	102.56	102.43	98.04	100.87	96.87
S7	101.58	100.22	100.87	102.05	99.84	100.52	98.76	98.97	97.87
S8	102.34	101.28	101.9	102.56	98.97	102.78	98.81	102.98	99.85
S9	102.45	101.25	98.97	102.68	101.65	101.68	98.25	101.79	102.69
S10	101.64	101.39	99.78	101.89	103.63	102.86	98.68	100.65	101.76
S11	102.32	102.48	101.49	102.99	101.76	102.84	98.87	102.29	100.78

S12	101.45	100.78	100.43	102.05	102.56	102.43	98.86	102.15	102.49
S13	100.39	99.76	102.89	102.56	102.68	100.52	98.78	102.35	100.45
Composite	101.52	98.76	102.78	102.99	101.76	102.84	98.87	102.29	100.78
RSD	0.83	1.15	1.49	0.52	1.29	1.59	0.42	1.31	1.80

Limit - %(LC) BY (HPLC) 90.0% to 110.0% of label amount, Equipment = Octagonal Blender, Speed = 10 RPM Time = 5-7 minutes, RSD =NMT 5.0%, mean of individual result = 90.0% to 110.0%

Table 6: Result of blend uniformity after blending

Test	Observation Batch no. 1	Acceptance criteria
Description	White granular powder	For information purpose only
Assay of labetalol hydrochloride tablet	99.87%	
Tapped density	0.98 g/ml	
Compressibility index	26.19%	
Bulk density	0.61g/ml	
Hausner ratio	1.35	

Table 7: Observation and acceptance criteria of compression stage at slow speed

Test	Standard	Batch 1		batch 2		batch 3	
		LHS	RHS	LHS	RHS	LHS	RHS
Machine RPM	16RPM ±2RPM	14	14	14	14	14	14
Compression Force	6 Ton ± 1 Ton	6	6	6	6	6	6
Appearance	White, Oval Shaped, biconvex, uncoated tablets	Meets	Meets	meets	meets	meets	Meets
Average Weight	280 mg ± 5 % (Limit :266 mg to 294 mg)	282	284	285	283	282	284
Weight of 20 Tablets	5.600gm ± 2% (Limit: 5.488 gm. to 5.712 gm.)	5.640	5.680	5.700	5.660	5.640	5.680
Thickness	3.80mm ± 0.30 mm (Limit: 3.50mm to 4.10mm)	3.82	3.83	3.84	3.85	3.86	3.87
Hardness	NLT: 3.0kg/cm² (Limit: 4.0 kg/cm² to 6.0 kg/cm²)	4.20	4.30	4.50	5.10	4.40	4.60
Friability	NMT 1.0 %	0.99%	0.75%	0.69%	0.56%	0.57%	0.27%
Disintegration	NMT 15 Min.	2-3 Min	2-3 min	2-3 min	2-3 min	2-3 min	2-3 min

Table 8: Observation and acceptance criteria of compression stage at optimum speed

TEST	STANDARD	Batch 1		batch 2			batch 3
		LHS	RHS	LHS	RHS	LHS	RHS
Machine RPM	16RPM ±2RPM	15	15	15	15	15	15
Compression Force	6 Ton ± 1 Ton	7	7	7	7	7	7
Appearance	White, Oval Shaped, biconvex, uncoated tablets	Meets	Meets	meets	meets	meets	Meets
Average Weight	280 mg ± 5 % (Limit :266 mg to 294 mg)	281	280	282	283	282	284
Weight of 20 Tablets	5.600gm ± 2% (Limit: 5.488 gm. to 5.712 gm.)	5.602	5.600	5.700	5.664	5.640	5.725
Thickness	3.80mm ± 0.30 mm (Limit: 3.50mm to 4.10mm)	3.81	3.83	3.85	3.86	3.87	3.84
Hardness	NLT: 3.0kg/cm² (Limit: 4.0 kg/cm² to 6.0 kg/cm²)	4.20	4.40	4.540	5.10	4.41	4.62
Friability	NMT 1.0 %	0.50%	0.51%	0.48%	0.46%	0.55%	0.42%
Disintegration	NMT 15 Min.	4-5 Min	4-5 Min	4-5 min	4-5 min	4-5 min	4-5 Min

Table 9: Observation and acceptance criteria of compression stage at fast speed

Test	Standard	Batch 1		batch 2		batch 3	
		LHS	RHS	LHS	RHS	LHS	RHS
Machine RPM	16RPM ±2RPM	18	18	18	18	18	18
Compression Force	6 Ton ± 1 Ton	7	7	7	7	7	7
Appearance	White, Oval Shaped, biconvex, uncoated tablets	Meets	meets	meets	meets	meets	Meets
Average Weight	280 mg ± 5 % (Limit :266 mg to 294 mg)	282	284	282	281	282	283
Weight of 20 Tablets	5.600gm ± 2% (Limit: 5.488 gm. to 5.712 gm.)	5.640	5.642	5.740	5.620	5.700	5.660
Thickness	3.80mm ± 0.30 mm (Limit: 3.50mm to 4.10mm)	3.82	3.84	3.86	3.86	3.87	3.88
Hardness	NLT: 3.0kg/cm² (Limit: 4.0 kg/cm² to 6.0 kg/cm²)	5.20	5.10	4.80	4.70	5.10	5.50
Friability	NMT 1.0 %	0.45%	0.25%	0.20%	0.46%	0.89%	0.77%
Disintegration	NMT 15 Min.	6-7 Min	6-7 Min	6-7 Min	6-7 Min	6-7 Min	6-7 Min

Table 10: Observation and acceptance criteria of coating process

Process Parameter		Observation
Test	Standard	
Appearance	Red coloured, Oval Shaped, biconvex, Film coated tablets.	Complies
Coating Pan RPM	4 – 6 RPM	5
Spray Rate	150-200 ml / min.	178
Spray Distance	30-35 cm.	Ok

Inlet Temperature	50C – 60 0C	55
Bed Temperature	40C – 50 0C	42
Spray Gun Nozzle Suitability	Red colored, Oval Shaped, biconvex, Film coated tablets.	Ok
Coating Process Time	Approx. 6 hours	6 hr. 05 min
Average Weight	286 mg ± 5 % (Limit : 271.7 mg to 300.3 mg)	287
Weight of 20 Tablets	5.720 gm. ± 2 % (Limit: 5.605 gm. to 5.834gm)	5.740
Thickness	3.85 mm ± 0.3 mm (Limit: 3.55mm to 4.15mm)	3.86
Disintegration	NMT 30 minutes	7-8 min

Table 11: Observation and acceptance criteria of finished product analysis

Result		Batch		
Tests	Standards	1	2	3
Appearance	Red coloured, Oval Shaped, biconvex, Film coated tablets	Meet	Meet	Meet
Average Weight	286 mg ± 5 % (Limit : 271.7 mg to 300.3 mg)	283	287	286
Weight of 20 Tablets	5.720 gm ± 2 % ((Limit : 5.605 gm to 5.834gm)	5.739	5.740	5.720
Thickness	3.85 mm ± 0.3 mm (Limit: 3.55mm to 4.15mm)	3.90	3.86	3.82
Disintegration	NMT 30 minutes	06 – 07	06 – 07	06 – 07
Assay	Not less than 90% to not more than 110% of the label amount	1O1.63%	101.60%	101.72%

5. 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 labetalol HCl USP 200 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 labetalolHCl 200 mg

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