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RESEARCH ARTICLE

Prospective Process Validation of Losartan Potassium Tablets 50mg

Vinod J*[1]

[1]*Department of Pharmaceutical Chemistry, Arulmigu Kalasalingam College of Pharmacy, Srivilliputtur, Tamilnadu, India.*

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ABSTRACT

The present research work focused on prospective process validation for Losartan potassium tablets 50mg. The tablets were manufactured by wet granulation method. Since the dose is 50mg, uniform distribution of the drug in the tablet is critical which can influence the content uniformity, assay and dissolution of the tablets. The critical parameters selected for process validation were dry mixing, blending, lubrication and compression. Uniformity of dry mixing was found to be excellent after 20 minutes because %RSD was less than 2.0%. The content uniformity after 15 minutes of blending was satisfactory since the % RSD was less than 1.5%. Physical parameters and assay at compression stage, i.e different turret speeds (20, 25 and 30 rpm), different hopper levels (Full hopper, half hopper and quarter hopper) and different time intervals (Initial, Middle and End) were within limits. Based on results at each critical stage for the specified parameters, it is concluded that the wet granulation method can ensure uniform distribution of Losartan potassium and the tablets can be effectively manufactured with the desired specifications& reproducible quality standards.

KEYWORDS

Prospective Process Validation**,** Losartan potassium tablets, Wet granulation

INTRODUCTION

The foremost priority of regulatory agencies is to ensure the safety of general public. The bioavailability of drugs is influenced by the dosage form characteristics and it is imperative to ensure the consistent performance of product from batch to batch. The central role of quality control tests is limited to end product testing. Hence quality has to be built in to the manufacturing process. The facilities and processes involved in pharmaceutical production have a significant impact on the quality of products. Each step of the manufacturing process must be controlled to maximize the probability that the finished Product meets all quality and design specifications, and hence be validated. Validation is an integral part of quality assurance.[1] Validation involves controlling the critical steps of a system which results in output of repeatable attributes of product consistently from batch to batch. Validation begins with process development. It requires that process developers understand the necessity to design a process that will be capable of ultimately meeting predetermined specifications without being subject to deviations within a defined range of preset operating parameters.[2]

***Address for Correspondence:**
Vinod J
Department of Pharmaceutical Chemistry,
Arulmigu Kalasalingam College of Pharmacy,
Srivilliputtur taluk-626126, Tamilnadu, India.
E-Mail Id: vinoddivien2001@yahoo.com

Advantages of Validation

In addition to being a regulatory requirement, process validation offers several advantages to the manufacturer such as:

1) Reduction in risk of non compliance with the regulatory agencies.
2) Significant time reduction in commercialization of new products.
3) Reduction in failure of new products.
4) Reduction in overall cost.
5) Reduction is in process controls and end product testing.
6) Better understanding and execution of manufacturing process.

Applications of Process Validation[3]

Process validation should be considered in the following cases:

1) If the manufacturing process is totally new.
2) If new manufacturing equipment is introduced in manufacturing facility.
3) If end product testing cannot guarantee product quality.

Types of Process Validation[4]

There are three basic types of process validation:

Prospective Validation

This is also called as premarket validation. Here the process is validated prior to the manufacture of commercial batches.

Concurrent Validation

Here the manufacturing process is validated during the manufacture of commercial batches. This type of validation is done if prospective validation is not feasible.

Retrospective Validation

This type of validation is done for processes that have been in use for some time without any significant changes.

MATERIALS AND METHOD

The raw materials used in the manufacture of Losartan potassium tablets 50mg complied as per USP specifications. The product profile of Losartan potassium tablets 50mg is given in Table 1.

Table1: Product Profile of Losartan Potassium Tablets 50 Mg

Product Name	Losartan potassium tablets 50 mg
Dosage form	Tablet
Label claim	Each film coated tablet contains Losartan potassium 50 mg
Batch size	1,00,000 Tablets
Shelf life	36 months

Table 2: List of equipment used in manufacturing process

Processing Stage	Name of equipment	Capacity	Make
Weighing	Weighing balance	100 kg	Electolab
Sifting	Vibratory sifter	16 inch	Gansons Ltd
Mixing and Granulation	Rapid Mixer Granulator	100 L	Gansons Ltd
Drying	Fluid Bed dryer	100 L	Gansons Ltd
Sizing	Multimill	---	Gansons Ltd
Blending & Lubrication	Octagonal blender	100 L	Gansons Ltd
Compression	Compression machine	37 station double rotary	Cadmach
Coating	Coating pan (Neocota)	24 inch	Gansons Ltd

The manufacturing formula for batch size of 1, 00, 000 tablets is given below:

Table 3: Composition of Losartan Potassium Tablets 50mg

S.No	Ingredients	Mg/tablet	Kg/Batch
Core			
Dry Mixing			
1.	Losartan Potassium	50.000	5.000
2.	Microcrystalline Cellulose (Avicel PH101)	67.500	6.750
3.	Lactose monohydrate	100.000	10.000
4.	Pregelatinised Maize Starch (Starch 1500)	15.000	1.500
5.	Crospovidone (Polyplasdone XL-10)	5.000	0.500
Wet Graulation			
5.	Purified water	---	5.000*
Lubrication			
6.	Crospovidone (Polyplasdone XL-10)	10.000	1.000
Blending			
7.	Magnesium stearate	2.500	0.250
	Core weight	**250.000**	**25.000**
Film Coating**			
8.	Opadry white	5.000	0.600
9.	Purified water*	---	5.400*
	Coated tablet weight	**255.000**	**25.500**

* Evaporated during drying process

** Includes 20% overages to compensate process loss

The rationale for selection of critical process steps for validation is given below:

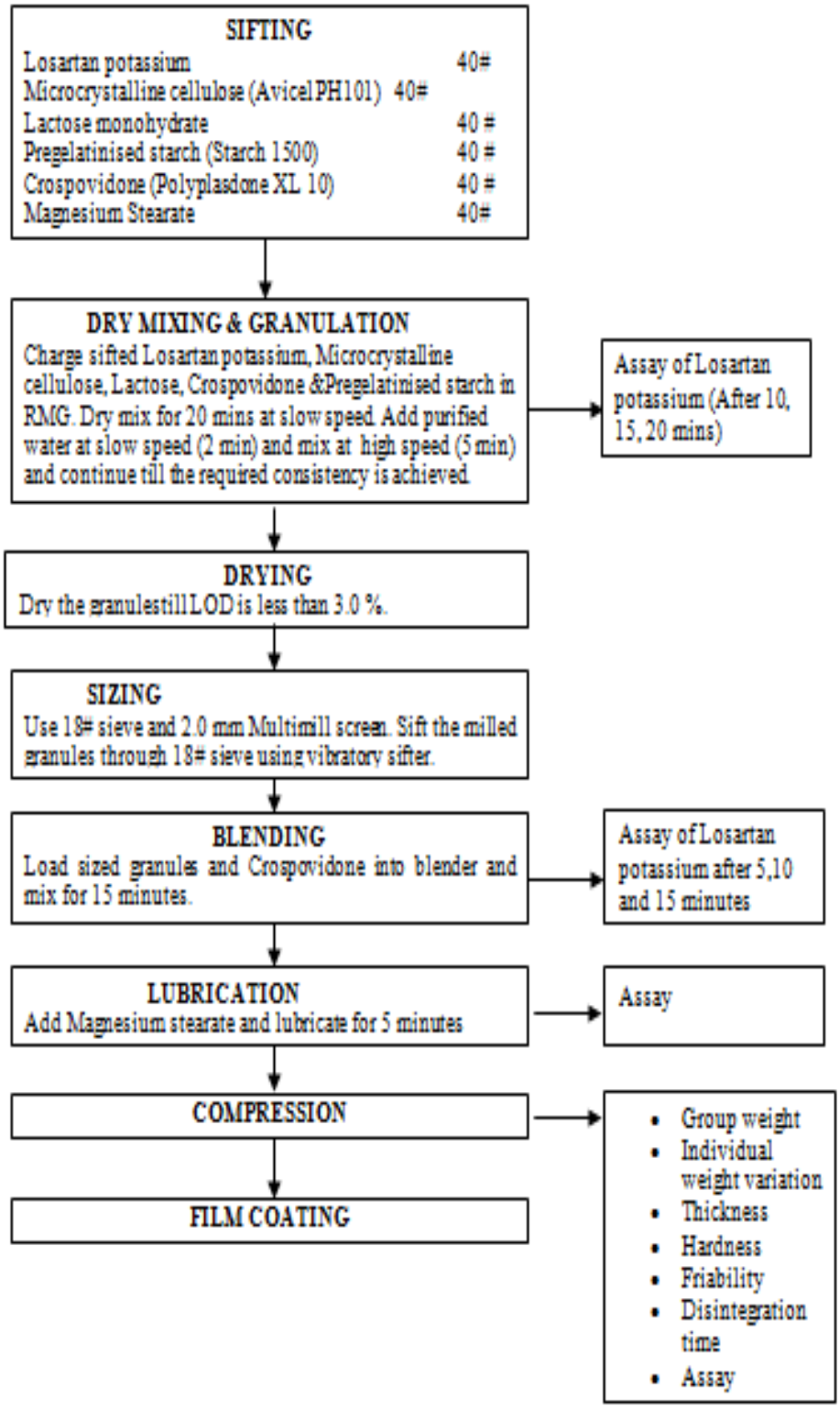
Dry Mixing

This step involves mixing of Losartan potassium with other excipients. Mixing speed and time are critical variables in this process. Since speed of the RMG is constant, proper mixing time shall be determined. Mixing is a critical step as less mixing time will result in non-uniform distribution of drug whereas more mixing time will result in de-mixing, leading to non-uniform distribution of drug and increase in disintegration time.[5] Proper mixing shall be established by checking content uniformity of drug at all the time intervals mentioned in protocol.

Blending

Blending involves mixing of granules with other extra granular ingredients.[6] The purpose is to get a uniform distribution of Losartan potassium with other ingredients. Blending speed and time are critical variables in this process. Since speed of the blender is constant, proper blending time shall be determined. Blending is critical as less blending will result in non-uniform distribution of drug whereas more blending will result in de-mixing, leading to non-uniform distribution of drug and increase in disintegration time. Proper blending shall be established by checking content uniformity of drug at all the time intervals mentioned in protocol.

FLOWCHART FOR THE MANUFACTURING PROCESS



Lubrication

This step involves mixing of blended granules with lubricant to achieve good flow and anti adherent properties to aid satisfactory compression parameters.[7] Lubrication time and speed are critical variables in this process. Since speed of the blender is constant, proper lubrication time shall be determined. Proper lubrication shall be established by checking content uniformity of drug and physical parameters of lubricated granules.

Compression

This step involves conversion of lubricated granules into tablets as per specifications. Speed of machine and hopper levels are the major variables. So, following parameters are to be checked to establish the above-mentioned variables at regular intervals:

- Weight variation (group and individual)
- Hardness
- Thickness
- Friability
- Disintegration time
- Assay

Film Coating

The coating step involves the covering of tablet surface with a polymer film. The pan rpm, inlet and exhaust temperatures, spray rate, gun distance and air pressure are critical process variables. These parameters affect the coating and final appearance of the tablets.

Pan RPM

If the speed of the pan is not controlled, uneven distribution of the coating solution on tablet surface may happen.

Inlet / Exhaust Temperature

If the inlet and exhaust temperature are not controlled, drying will be insufficient which may result in twining andsticking of tablets or rough surface andcracking of the film?

Spray Rate

If the spray rate is not controlled, then the coating will not be uniform.

Gun to Bed Distance

If gun to bed distance is not adequate, rough surface or over wetting during coating may happen.

Air Pressure

If the compressed air pressure (Atomization) is not adequate, peeling of rough surface of tablets may occur.

Table 4: Process Control Steps for Validation

Sl. No.	Process Step	Control Variable	Measured Response
1.	Dry mixing	a) Mixing time (10, 15, 20 min) b) Mixing speed	a)Assay of Losartan potassium
2.	Blending	a) Blending time (5,10, 15 min) b) Speed	a)Assay of Losartan potassium
3.	Lubrication	a) Lubrication time b) Speed	a) Assay
4.	Compression	a) Machine speed (20, 25, 30 rpm) b) Initial, middle, end of compression c) Full hopper, half hopper, quarter hopper levels	a)Appearance b)Group weight c)Individual weight d)Thickness e)Hardness f)Friability g)Disintegration time h)Assay

Table 5: Sampling and Testing Plan

Stage	Sample Location	Sample size	Test
Dry Mixing	5 positions from Rapid Mixer Granulator after 10, 15 and 20 minutes of Dry mixing.	Approximately one to three unit dose withdrawn in triplicate	Assay
Blending	10 positions from paddle mixer after 5, 10 and 15minutes of blending	Approximately one to three unit dose withdrawn in triplicate	Assay
Lubrication	Composite sample from center of the top, middle & bottom level of paddle mixer	Approx. 150 g	Assay
Compression	After each interval (From RHS and LHS) 30, 60,90&120 minutes RPM: 20. 25. 30 Full hopper, Half Hopper, Quarter hopper	100 tablets	1.Group weight 2. Individual weight 3. Thickness 4. Hardness. 5. Assay 6.Disintegration time 7.Friability

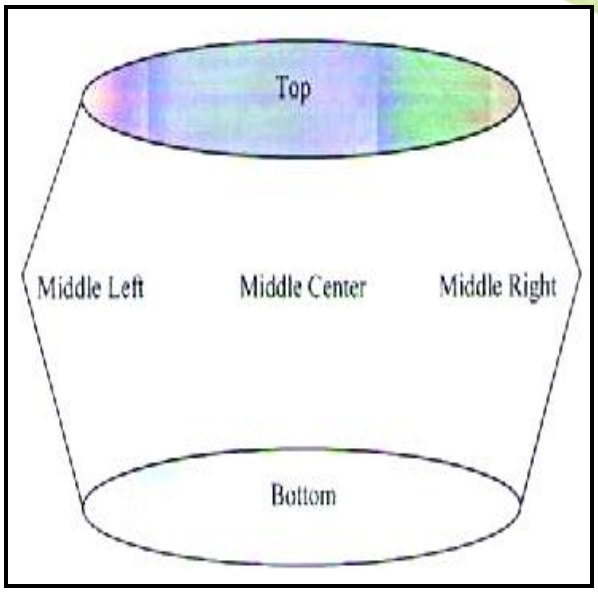


Figure 1: Sampling position of Rapid Mixer Granulator

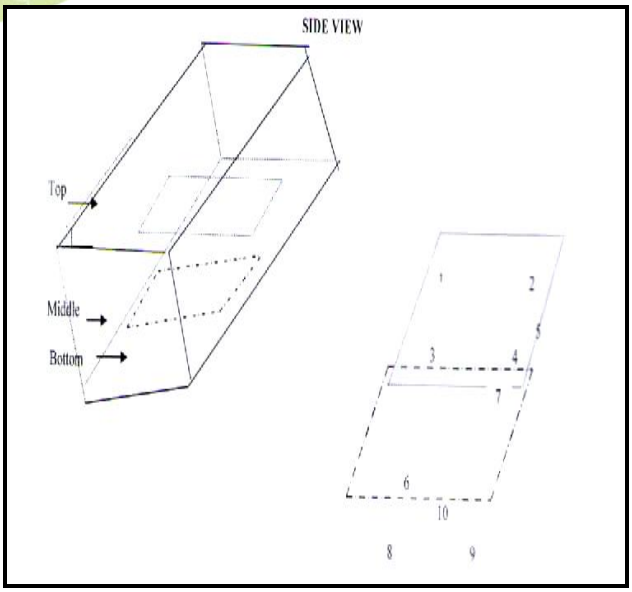


Figure 2: Sampling position of Paddle mixer

Method of Analysis

Weight Variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if none of the individual tablet weight deviates from the average weight by more than the 5 % of the average weight.

Hardness

The crushing strength in Kg/cm^2 of tablets was determined for 10 tablets of each batch by using Monsanto tablet hardness tester. The average hardness and standard deviation was determined.

Friability

Ten tablets were weighed and placed in the Electrolab friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were deducted and weighed the percentage friability was measured using the formula: **% F = {1-(Wt/W)} ×100**

Where,

% F = friability in percentage

W = Initial weight of tablets

Wt = weight of tablets after revolution

Disintegration

6 tablets were placed in beaker containing water in electrolab disintegration tester with disc and the time to disintegrate was recorded.

Assay

Losartan potassium was estimated as per the United States pharmacopoeia method.[8]

Chromatographic System

Mode: LC ($C_{22}H_{22}ClKN_6O$)

Detector: UV 250 nm

Column: 3.9-mm x 15-cm; 5-mm packing

Procedure:

Buffer: 1.25 mg/mL of monobasic potassium phosphate and 1.5 mg/mL of dibasic sodium phosphate in water.

Solution A: Acetonitrile and Buffer (15:85)

Solution B: Use acetonitrile.

Sample Stock Solution: Transfer the drymix powder to a 500-mL volumetric flask, add Solution A to fill the flask to about50% of the final volume, and sonicate with shaking for 15 min. Sonicate for an additional 10 min. Dilute with Solution A to volume, and mix well.

Sample Solution: 0.25 mg/mL of losartan potassium in Solution A from the Sample stock solution. Mix well. Passan aliquot of the solution through a PTFE filter of 0.45-mm pore size, and use the filtrate.

Dissolution

In Vitro dissolution study was carried out as per United States pharmacopoeia method.

Number of units: 6

Medium: Water; 900 mL, deaerated

Apparatus 2:50 rpm.

Time: 30 min

Standard solution: (L/1000) mg/mL of USP Losartan Potassium RS in Medium, where L is the Tablet label claim, in mg

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-mm pore size.

Analysis: Determine the amount of losartan potassium ($C_{22}H_{22}ClKN_6O$) dissolved by using UV absorption at the wavelength of maximum absorbance at about 256 nm on portions of the Sample solution in comparison with the Standard solution, using Medium as blank. Make the appropriate dilution of the solutions with Medium to be within the linearity range of the spectrophotometer.

Calculate the percentage of losartan potassium ($C_{22}H_{22}ClKN_6O$) dissolved:

Result = $(A_U/A_S) \times (C_S/L) \times V \times 100$

A_U = absorbance of the Sample solution

A_S = absorbance of the Standard solution

C_S = concentration of USP Losartan Potassium RS in the Standard solution (mg/mL)

L = label claim (mg/Tablet)

V = volume of Medium, 900 mL

Tolerances: NLT 75% (Q) of the labeled amount of losartan potassium ($C_{22}H_{22}ClKN_6O$) is dissolved.

Uniformity of Dosage Units

The uniformity of dosage units was determined as per United States pharmacopoeia method. 30 tablets were selected. 10 tablets were assayed individually.

Procedure:

Buffer: Dissolve 1.36 mg/mL of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 2.5.

Diluent: Dissolve 17.42 g of dibasic potassium phosphate in 900 mL of water. Adjust with phosphoric acid to a pH of 8.0. Dilute with water to a volume of 1000 mL, and mix well. Further dilute with water (1 in 10), and mix well.

Mobile phase: Acetonitrile and Buffer (60:40)

Standard solution: 0.05 mg/mL of USP Losartan Potassium RS in Diluent

Sample stock solution: Transfer 1 Tablet to a 100-mL volumetric flask, add about 65 mL of Diluent, and shake mechanically for 30 min. Dilute with Diluent to volume, and mix well.

Sample solution: 0.05 mg/mL of losartan potassium in Diluent from the Sample stock solution. Filter an aliquot of the solution, and use the filtrate.

Chromatographic system

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm x 25-cm; 10-mm packing L7

Calculate the percentage of the labeled amount of losartan potassium ($C_{22}H_{22}ClKN_6O$) in the portion of the Tablet taken:

Result = $(r_U/r_S) \times (C_S/C_U) \times 100$

r_U = peak response of losartan from the Sample solution

r_S = peak response of losartan from the Standard solution

C_S = concentration of USP Losartan Potassium RS in the Standard solution (mg / mL)

C_U = nominal concentration of losartan potassium in the Sample solution (mg / mL)

Acceptance criteria: 90 to 110% of labeled claim

Impurities

Solution A, Solution B, Mobile phase, System suitability solution, Sample solution, and Chromatographic system: Prepare as directed in the Assay.

Calculate the percentage of each impurity in the portion of Tablets taken:

Result = $(r_U/r_S) \times (C_S/C_U) \times 100$

r_U = peak response of each individual impurity from the Sample solution

r_S = peak response of losartan from the Standard solution

C_S = concentration of USP Losartan Potassium RS in the Standard solution (mg/mL)

C_U = nominal concentration of losartan potassium in the Sample solution (mg/mL)

Acceptance criteria:

Name	Acceptance Criteria (NMT%)
1H-Dimer	0.5
2H-Dimer	0.5
Total impurities	NMT 1.0

RESULTS

Since the amount of the drug in the tablet is around 20%, the critical process steps that can affect the distribution of drug in the tablet were evaluated. Non uniform drug distribution can affect the weight, dissolution and assay. The results are presented below.

Dry Mixing

The dry mixing of three batches was performed and the samples at the designated locations were drawn after 10, 15, 20 minutes of blending for determining the content uniformity and %RSD values of Losartan potassium. The %RSD values after 20 minutes of mixing were most satisfactory. The assay of Losartan potassium in dry mix stage is presented in table 6.

Table 6: Assay of Losartan potassium in dry mix

Time Interval	Sample Location	Batch number		
		LPV-101	LPV-102	LPV-103
10 min	Top	120.61	101.5	115.31
	Middle left	81.53	94.31	112.56
	Middle	103.52	89.26	88.57
	Middle right	106.51	90.57	76.34
	Bottom	119.21	115.32	124.32
	Mean	**106.27**	**98.19**	**103.42**
	%RSD	**15.75**	**10.69**	**20.10**
15 min	Top	109.25	106.82	104.51
	Middle left	93.45	97.62	103.54
	Middle	102.42	91.56	92.56
	Middle right	105.57	93.45	96.52
	Bottom	108.52	105.86	109.54
	Mean	**103.84**	**99.06**	**101.33**
	%RSD	**6.41**	**7.00**	**6.75**
20 min	Top	103.57	101.67	100.52
	Middle left	98.64	99.84	103.54
	Middle	102.59	97.64	99.78
	Middle right	102.87	99.47	99.64
	Bottom	101.69	102.51	100.57
	Mean	**101.87**	**100.23**	**100.81**
	%RSD	**1.93**	**1.92**	**1.58**
Limit	**95.0 to 105.0% w/w**			

Blending

Table 7: Assay of Losartan potassium in blending stage

Time Interval	Sample Location	Batch number		
		LPV-101	**LPV-102**	**LPV-103**
5 min	S1	91.52	95.84	98.51
	S2	96.82	106.54	106.54
	S3	99.54	99.41	93.57
	S4	105.64	99.83	99.54
	S5	107.85	101.51	102.2
	S6	89.52	103.64	106.54
	S7	100.54	102.54	105.41
	S8	99.64	100.84	100.54
	S9	94.32	107.54	100.67
	S10	108.21	89.54	98.64
	Mean	**99.36**	**100.72**	**101.22**
	%RSD	**6.51**	**5.21**	**4.10**
10 min	S1	98.53	97.54	98.85
	S2	99.24	104.51	102.41
	S3	99.54	99.54	97.54
	S4	99.53	99.43	98.42
	S5	102.54	100.54	101.69
	S6	96.54	102.68	102.65
	S7	100.32	101.57	103.47
	S8	99.08	103.41	101.37
	S9	98.54	100.54	103.54
	S10	104.21	102.21	102.64
	Mean	**99.81**	**101.20**	**101.26**
	%RSD	**2.16**	**2.09**	**2.19**
15 min	S1	101.52	99.87	98.57
	S2	99.51	100.64	100.97
	S3	100.54	99.46	99.46
	S4	102.41	99.24	99.42
	S5	102.34	100.34	100.25
	S6	99.68	100.47	102.64
	S7	100.24	102.34	103.41
	S8	99.99	100.54	100.67
	S9	99.54	102.39	100.46
	S10	102.18	99.64	99.67
	Mean	**100.80**	**100.49**	**100.55**
	%RSD	**1.20**	**1.10**	**1.49**
Limit	**95.0 to 105.0% w/w**			

The blending of three batches was performed and the samples at the designated locations were drawn after 5, 10, 15 minutes of blending for determining the assay and %RSD values of Losartan potassium. The values meet the acceptance criteria after 15 minutes of blending. Hence the blending time of 15 minutes was validated.

Lubrication

This step involves mixing of blended granules with lubricant to achieve good flow and anti-adherent properties to aid satisfactory compression parameters. Proper lubrication was established by checking content uniformity of drug and physical parameters of lubricated granules.

The physical parameters and assay of lubricated granules is presented in Table 8.

Compression

The compression for all the three batches has been validated for different turret speeds (20, 25 and 30 rpm), different hopper levels (full, half and quarter hopper levels) and different time intervals (initial, middle and end) of compression. The physical parameters and assay of the tablets were well within the acceptable limits. The results were comparable among all the three batches. Hence the compression step was validated. The results of different turret speeds at compression stage are presented in table 9.

Table 8: Physical parameters of lubricated granules

TEST	Acceptance criteria	Batch Number		
		LPV-101	LPV-102	LPV-103
Appearance	White colored granules	White colored granules	White colored granules	White colored granules
Assay	95.0 to 105.0%w/w	99.64 %	99.45 %	98.12 %
LOD	NMT 3.0 w/w	2.64%	2.82%	2.74%
Bulk density	For information only	0.598 g/cc	0.567 g/cc	0.587 g/cc
Tapped density	For information only	0.656 g/cc	0.684 g/cc	0.674 g/cc
Particle size distribution	For information only	Cumulative % retained		
20#		17.8%	19.4%	15.5%
30#		29.3%	28.2%	25.3%
40#		36.4%	38.2%	33.2%
60#		47.5%	47.1%	46.1%
80#		67.3%	68.5%	64.8%
100#		76.6%	82.5%	79.9%

Table 9: Physical parameters at different turret speeds

Turret Rpm	Test	Acceptance Criteria	Batch Number		
			LPV-101	LPV-102	LPV-103
20 rpm	Appearance	A white coloured circular slightly biconvex uncoated tablet plain on both sides.	Complies	Complies	Complies
	Av. Weight	250 mg ± 2%	248.3 mg	252.5 mg	251.1 mg
	Uniformity of weight	± 5 % of average weight	243.2 to 253.2 mg	245.6 to 255.5 mg	248.8 to 253.1 mg
	Thickness	3.5 ± 0.3 mm	3.62 mm	3.51 mm	3.45 mm
	Friability	Not more than 1.0 %	0.23%	0.35%	0.34%
	Hardness	Not less than 5 Kg/cm^2	5.7 Kg/cm^2	6.8 Kg/cm^2	6.6 Kg/cm^2
	Disintegration Time	Not more than 15 minutes	7 min 25 sec	7 min 30 sec	7 min 45 sec
	Assay	95.0 to 105.0 %w/w	99.5%	99.8%	100.2%
25 rpm	Appearance	A white coloured circular slightly biconvex uncoated tablet plain on both sides.	Complies	Complies	Complies
	Av. Weight	250 mg ± 2%	247.7 mg	248.6 mg	251.2 mg
	Uniformity of weight	± 5 % of average weight	245.2 to 253.2 mg	245.6 to 253.5 mg	248.8 to 254.1 mg
	Thickness	3.5 ± 0.3 mm	3.71 mm	3.65 mm	3.69 mm
	Friability	Not more than 1.0 %	0.30%	0.35%	0.23%
	Hardness	Not less than 5 Kg/cm^2	5.8Kg/cm^2	6.6Kg/cm^2	6.7Kg/cm^2
	Disintegration Time	Not more than 15 minutes	7 min 25 sec	7 min 40 sec	7 min 55 sec
	Assay	95.0 to 105.0 %w/w	99.1%	99.5%	99.2%
30 rpm	Appearance	A white coloured circular slightly biconvex uncoated tablet plain on both sides.	Complies	Complies	Complies
	Av.Weight	250 mg ± 2%	247.3 mg	248.5 mg	248.1 mg
	Uniformity of weight	± 5 % of average weight	243.2 to 255.2 mg	245.6 to 253.5 mg	246.8 to 254.1 mg
	Thickness	3.5 ± 0.3 mm	3.67 mm	3.60 mm	3.51 mm
	Friability	Not more than 1.0 %	0.33%	0.55%	0.36%
	Hardness	Not less than 5 Kg/cm^2	6.9Kg/cm^2	6.7Kg/cm^2	6.5Kg/cm^2
	Disintegration Time	Not more than 15 minutes	7 min 25 sec	7 min 30 sec	7 min 40 sec
	Assay	95.0 to 105.0 %w/w	99.9%	99.7%	100.2%

The results of different hopper levels at compression stage are presented in table 10.

Table 10: Physical parameters at different hopper levels

Hopper Levels	Test	Acceptance Criteria	Batch Number		
			LPV-101	LPV-102	LPV-103
Full hopper	Appearance	A white coloured circular slightly biconvex uncoated tablet plain on both sides.	Complies	Complies	Complies
	Av. Weight	250 mg ± 2%	246.2 mg	253.8 mg	250.8 mg
	Uniformity of weight	± 5 % of average weight	244.3 to 252.2 mg	244.6 to 252.2 mg	247.4 to 252.8 mg
	Thickness	3.5 ± 0.3 mm	3.69 mm	3.58 mm	3.57 mm
	Friability	Not more than 1.0 %	0.28%	0.37%	0.37%
	Hardness	Not less than 5 Kg/cm^2	5.9 Kg/cm^2	6.5 Kg/cm^2	6.9 Kg/cm^2
	Disintegration Time	Not more than 15 minutes	7 min 12 sec	7 min 18 sec	7 min 27 sec
	Assay	95.0 to 105.0 %w/w	99.4%	99.2%	100.8%
Half hopper	Appearance	A white coloured circular slightly biconvex uncoated tablet plain on both sides.	Complies	Complies	Complies
	Av. Weight	250 mg ± 2%	247.7 mg	248.6 mg	251.2 mg
	Uniformity of weight	± 5 % of average weight	245.2 to 253.2 mg	245.6 to 253.5 mg	248.8 to 254.1 mg
	Thickness	3.5 ± 0.3 mm	3.71 mm	3.65 mm	3.69 mm
	Friability	Not more than 1.0 %	0.30%	0.35%	0.23%
	Hardness	Not less than 5 Kg/cm^2	5.8Kg/cm^2	6.6Kg/cm^2	6.7Kg/cm^2
	Disintegration Time	Not more than 15 minutes	7 min 25 sec	7 min 40 sec	7 min 55 sec
	Assay	95.0 to 105.0 %w/w	99.1%	99.5%	99.2%
Quarter hopper	Appearance	A white coloured circular slightly biconvex uncoated tablet plain on both sides.	Complies	Complies	Complies
	Av.Weight	250 mg ± 2%	247.3 mg	248.5 mg	248.1 mg
	Uniformity of weight	± 5 % of average weight	243.2 to 255.2 mg	245.6 to 253.5 mg	246.8 to 254.1 mg
	Thickness	3.5 ± 0.3 mm	3.67 mm	3.60 mm	3.51 mm
	Friability	Not more than 1.0 %	0.33%	0.55%	0.36%
	Hardness	Not less than 5 Kg/cm^2	6.9Kg/cm^2	6.7Kg/cm^2	6.5Kg/cm^2
	Disintegration Time	Not more than 15 minutes	7 min 25 sec	7 min 30 sec	7 min 40 sec
	Assay	95.0 to 105.0 %w/w	99.9%	99.7%	100.2%

The results of different time intervals at compression stage are presented in table 11.

Table 11: Physical parameters at different time intervals

Time	Test	Acceptance Criteria	Batch Number		
			LPV-101	LPV-102	LPV-103
Initial	Appearance	A white coloured circular slightly biconvex uncoated tablet plain on both sides.	Complies	Complies	Complies
	Av. Weight	250 mg ± 2%	249.6 mg	251.3 mg	252.9 mg
	Uniformity of weight	± 5 % of average weight	245.8 to 253.9 mg	244.8 to 253.7 mg	243.8 to 252.2 mg
	Thickness	3.5 ± 0.3 mm	3.47 mm	3.41 mm	3.52 mm
	Friability	Not more than 1.0 %	0.35 %	0.27 %	0.36 %
	Hardness	Not less than 5 Kg/cm^2	6.5 kg/cm^2	6.8 kg/cm^2	7.2 kg/cm^2
	Disintegration Time	Not more than 15 minutes	7min31sec	7min26sec	7min15sec
	Assay	95.0 to 105.0 %w/w	99.4 %	99.2 %	98.4 %
Middle	Appearance	A white coloured circular slightly biconvex uncoated tablet plain on both sides.	Complies	Complies	Complies
	Av. Weight	250 mg ± 2%	247.8 mg	251.9 mg	252.9 mg
	Uniformity of weight	± 5 % of average weight	246.8 to 256.8 mg	245.9 to 254.7 mg	243.7 to 256.8 mg
	Thickness	3.5 ± 0.3 mm	3.58 mm	3.63 mm	2.85 mm
	Friability	Not more than 1.0 %	0.29%	0.31%	0.39%
	Hardness	Not less than 5 Kg/cm^2	6.4 Kg/cm^2	6.9 Kg/cm^2	7.2 Kg/cm^2
	Disintegration Time	Not more than 15 minutes	6 min 55 sec	7 min 14 sec	7 min 05 sec
	Assay	95.0 to 105.0 %w/w	100.3%	100.6%	99.8%
End	Appearance	A white coloured circular slightly biconvex uncoated tablet plain on both sides.	Complies	Complies	Complies
	Average Weight	250 mg ± 2%	251.6 mg	252.6 mg	98.1 mg
	Uniformity of weight	± 5 % of average weight	248.5 to 254.9 mg	245.1 to 255.5 mg	94.8 to 102.1 mg
	Thickness	3.5 ± 0.3 mm	3.48 mm	3.43 mm	3.55 mm
	Friability	Not more than 1.0 %	0.33%	0.25%	0.31%
	Hardness	Not less than 5 Kg/cm^2	6.7 Kg/cm^2	7.1 Kg/cm^2	7.5 Kg/cm^2
	Disintegration Time	Not more than 15 minutes	6 min 45 sec	7 min 15 sec	7 min 23 sec
	Assay	95.0 to 105.0 %w/w	99.1%	99.5%	100.2%

The individual weight variation during compression is presented in table 12.

Table 12: Individual weight variation during compression (mg)

S.No	B.No.LPV-101			B.No.LPV-102			B.No.LPV-103		
	Initial	Middle	End	Initial	Middle	End	Initial	Middle	End
1.	248.8	249.8	256.8	255.4	261.3	251.8	255.6	258.6	248.6
2.	248.9	246.5	249.5	246.8	245.6	248.6	249.7	246.5	245.6
3.	254.9	247.5	245.9	253.6	255.7	254.9	258.7	257.4	249.8
4.	260.5	248.6	246.8	256.9	251.4	253.8	251.8	255.6	250.6
5.	248.7	248.5	256.9	251.2	250.3	249.8	255.6	249.8	251.6
6.	246.9	253.6	255.3	255.6	255.7	255.9	249.8	248.6	255.6
7.	254.8	255.8	257.8	255.7	256.5	256.8	254.8	248.9	248.9
8.	256.3	257.9	261.8	254.6	248.3	245.8	245.9	260.5	255.8
9.	255.4	258.4	252.5	259.1	246.8	254.8	255.8	250.7	255.7
10.	251.7	248.6	254.9	244.6	245.9	249.8	260.8	251.8	245.6
11.	256.8	245.8	253.8	242.3	254.6	247.6	259.4	260.8	255.3
12.	259.7	246.9	253.7	256.8	254.3	247.9	249.1	255.7	246.5
13.	245.6	255.6	245.3	253.6	255.8	251.8	249.5	256.7	248.9
14.	256.7	257.8	253.6	251.3	256.7	248.2	249.8	249.8	256.8
15.	248.9	255.4	253.1	255.3	251.8	245.6	246.8	250.8	260.7
16.	248.7	253.8	250.8	256.8	250.9	259.8	249.5	251.8	245.6
17.	248.6	256.7	250.5	255.4	256.9	251.9	248.7	252.6	248.9
18.	258.7	263.5	255.9	255.8	257.5	251.9	248.6	253.7	256.3
19.	245.9	254.8	255.4	255.4	242.9	252.8	257.6	250.8	246.3
20.	258.8	256.7	245.8	253.6	259.8	260.8	258.3	258.9	248.5
Mean	**252.8**	**253.1**	**252.8**	**253.5**	**252.9**	**252.0**	**252.8**	**253.5**	**251.1**
Maximum	**245.6**	**245.8**	**245.3**	**242.3**	**242.9**	**245.6**	**245.9**	**246.5**	**245.6**
Minimum	**260.5**	**263.5**	**261.8**	**259.1**	**261.3**	**260.8**	**260.8**	**260.8**	**260.7**
%RSD	**5.0**	**5.0**	**4.5**	**4.3**	**5.1**	**4.3**	**4.6**	**4.2**	**4.6**

The results of hardness at compression stage are presented in table 13.

Table 13: results of hardness during compression (kg/cm^2)

S.No	B.No.LPV-101			B.No.LPV-102			B.No.LPV-103		
	Initial	Middle	End	Initial	Middle	End	Initial	Middle	End
1.	6.1	6.2	6.5	6.2	5.9	6.2	6.5	6.2	6.2
2.	6.5	5.9	6.6	6.1	5.8	6.3	6.1	5.9	6.5
3.	5.9	6.3	6.1	6.5	5.7	6.1	6.5	5.1	6.1
4.	5.7	6.9	6.2	5.9	5.9	5.8	6.1	5.6	6.4
5.	7.1	7.1	5.8	5.7	5.6	5.6	5.9	5.6	5.9
6.	5.6	5.9	5.5	5.9	5.9	5.4	5.5	5.7	5.7
7.	5.9	5.8	5.9	5.6	5.1	5.6	5.6	5.9	5.5
8.	6.4	6.5	5.6	5.6	6.5	5.9	6.1	5.6	6.1
9.	6.5	6.1	5.6	5.9	6.5	6.1	6.3	5.7	5.8
10.	6.4	6.5	5.9	5.7	6.4	6.3	5.6	6.2	5.1
Mean	**6.1**	**6.3**	**6.2**	**5.1**	**5.9**	**5.9**	**6.0**	**5.8**	**5.9**
%RSD	**0.5**	**0.4**	**0.4**	**0.3**	**0.4**	**0.3**	**0.4**	**0.3**	**0.4**

Table 14: Dissolution of tablets

Tablet	% Drug dissolved		
	B.No.LPV-101	B.No.LPV-102	B.No.LPV-103
Tablet 1	99.5	95.6	96.7
Tablet 2	95.8	95.8	98.7
Tablet 3	102.5	96.7	99.4
Tablet 4	103.5	100.5	100.2
Tablet 5	100.8	102.5	102.5
Tablet 6	101.8	103.5	101.6
Mean	**100.7**	**99.1**	**99.9**
%RSD	**2.7**	**3.5**	**2.1**

Table 15: Results of Finished Product (Film coated tablets)

Parameters	**Specification**	**B.No. LPV-101**	**B.No. LPV-102**	**B.No. LPV-103**
Appearance	White to Offwhite oval shaped film coated tablets, plain on both sides	Complies	Complies	Complies
Average weight	255.0mg ±2% (249.9 to 261.1 mg)	256.6	255.2	257.8
Uniformity of weight	±5.0% of average weight	249.2 to 257.6	250.3 to 258.4	251.2 to 257.8
Thickness	3.80±0.30 mm (3.50 to 4.10 mm)	3.65 to 3.85	3.68 to 3.90	3.69 to 3.94
Disintegration Time	NMT 30 minutes	8 min 40sec	7 min 50 sec	7 min 30 sec
Uniformity of dosage units	90 to 110% of labeled claim	96.5 to 99.3	95.6 to 103.2	97.2 to 102.8
Assay (%w/w)	95 to 105% w/w of labeled claim (47.5 to 52.5 mg)	99.2	99.8	100.4
Dissolution	NLT 75% of labeled claim dissolved in 45 minutes	93.8 to 98.7	94.2 to 99.2	92.3 to 100.3
Impurities 1*H*-Dimer *2H*-Dimer Total impurities	 NMT 0.5% NMT 0.5% NMT 1.0%	 0.01 0.01 0.03	 0.02 0.01 0.04	 0.01 0.02 0.03

Table 16: Comparative dissolution profiles of Losartan potassium tablets 50mg (validation batches) vs marketed formulation (Cozaar 50mg)

Time (Minutes)	**% Drug release of validation batches and Innovator**			
	Innovator (Cozaar 50mg)	**B.No. LPV-101**	**B.No. LPV-102**	**B.No. LPV-103**
5	30.5	29.3	32.3	30.8
10	45.2	45.8	48.2	46.5
15	60.8	58.2	61.5	59.3
20	75.3	76.9	74.5	76.2
30	90.5	88.3	87.5	89.8
45	95.8	94.2	96.2	97.3
60	99.3	98.5	100.5	100.9
F1		**1.20**	**0.70**	**0.70**
F2		**85.69**	**83.85**	**90.28**

Comparative Dissolution Profiles

The dissolution profile of finished product of all three validation batches were compared with that of marketed formulation, Cozaar 50mg as per USP method and was found to be similar.

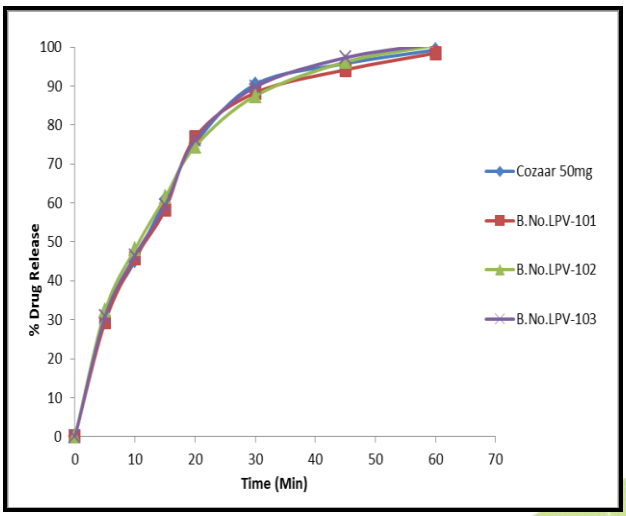


Figure 3: Comparative dissolution profiles of Losartan potassium tablets 50mg (validation batches) vs marketed formulation (Cozaar 50mg)

CONCLUSION

The manufacturing process should be controlled in order that the finished product meets all quality specifications. In this study prospective process validation was carried out for Losartan potassium tablets 50mg with three batches of same batch size of 100,000 tablets with same manufacturing process and formula. The entire manufacturing and sampling procedure was done with the approved validation protocol and sampling plan. The critical process steps like drymixing, blending, lubrication and compression were validated. Based on the review of critical process parameters and analytical results for critical process parameters as detailed in results section, it can be concluded that the manufacturing process for Losartan potassium tablets 50mg, described in batch manufacturing record for batch size of 100,000 tablets is validated and can consistently produce the finished product, meeting all pre-determined specification and quality attributes. Further research work may be envisaged on direct compression process.

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AUTHOR'S STATEMENT

The author declares no conflict of interest.

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