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Preparation and Characterization of Losartan Potassium Tablets

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ABSTRACT: ***The objective of the present study was to Preparation and characterization of losartan potassium drug. The active ingredient of losartan potassium is an angiotensin receptor blocker which works by preventing of high blood pressure (hypertension). The development of three strengths (25 mg, 50mg and 100 mg), trials were taken only for higher strength (100 mg) and optimized to get an inter convertible formula to perform the in-vitro drug release pattern from tablet and compared with the innovator sample of Cozaar tablets. Blend was evaluated for tests such as bulk density, compressibility index, LOD, tapped density, hardness ratio and sieve analysis before being punched as tablets. Tablets were tested for weight variation, thickness, hardness, friability and disintegration. the batches of LP-1 to LP-7 were taken for trails and subjected for tests. In vitro dissolution tests were performed and F1 and F2 values were calculated. Dissolution profile of LP 4 formulation was matched with innovator and F2 value was satisfactory. The formulation LP-04 has been selected as the final formula for Losartan potassium tablets (100mg), accordingly, it can be concluded that the final formulation is a robust one and the performance is less likely to be affected by the various factors studied. An excellent in vitro and in vivo correlation is expected as evident from degree of similarity found in gradient dissolution in different media and release kinetics with respect to reference listed drug product Cozaar.***

Keywords: Losartan potassium, angiotensin receptor blocker, cozaartablets , in-vitro drug release.

I.INTRODUCTION:

The objective of the present study is to develop a pharmaceutically equivalent, stable and robust formulation of losartan potassium comparable with the innovator. The active ingredient losartan potassium, which is an angiotensin II antagonist. It works by preventing the action of a hormone in the body called angiotensin-II. To achieve this goal various prototype trials we are taken and evaluated with respect to the various quality parameters such as dissolution and impurity. The formula was finalized by comparing the in-vitro dissolution profile with that of the Innovator in various pH Medias.To study the ***in vitro*** drug release pattern from tablets and compare with the innovator samples of ***COZAAR TABLETS.***

To study the effect of manufacturing process and to developing process design parameters by accelerating it to worst cases.

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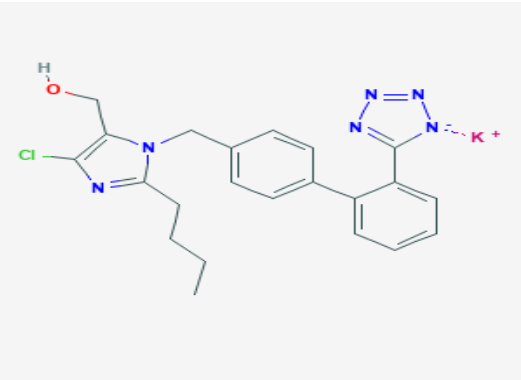
The best new therapeutic entity in the world is of little value without an appropriate delivery system. Tablet delivery systems can range from simple immediate release formulations to complex extended or modified release dosage forms. The most important role of drug delivery system is to get the drug delivered to the site of action in sufficient amount and at the appropriate rate; however it must also meet a no. of other essential criteria. These include physical and chemical stability, ability to be economically mass-produced in a manner that assures the proper amount of drug in each and every dosage form and in each batch produced and as far as possible patient acceptability the drug and the delivery systems cannot be separated.

II. DRUG SPECIFIC REVIEW

DRUG PROFILE OF *LOSARTAN POTASSIUM*

1. **Chemical Name***:* [2-butyl-5-chloro-3-[[4-[2-(1,2,3-triaza-4 azanidacyclopenta-2,5-dien-5-yl)phenyl]phenyl]methyl]-3H-imidazol-4-yl]methanol
2. **Chemical Formula**:$C_{22}H_{22}ClKN_6O$
3. **Molecular Weight**: 461.01 g/mol
4. **Official status**: API- USP
5. **Organoleptic properties**: white to off-white free flowing crystalline powder.
6. **Chemical Structure**:

III. LOSARTAN POTASSIUM



[2-butyl-5-chloro-3-[[4-[2-(1,2,3-triaza-4azanidacyclopenta-2,5-dien-5-yl)phenyl]phenyl]methyl]-3H-imidazol-4-yl]methanol

IV.MATERIAL AND METHODS:

The present work was done at Twilight Litaka Pharma Ltd (F R&D) aimed towards developing Losartan potassium film coated tablet on dierect compression method. The following ingredients was used in the losartan potassium formulation.

Losartan potassium, maize starch (Dried), purified talc, colloidal silicon-di-oxide(Aerosil 200), sodium starch glycolate, magnesium sterate, D&C yellow no.Aluminiumlake, FD&C blue no.aluminium lake, hypromellose (HPMC-15cps), lactose monohydrate, PEG 6000, titanium-di-oxide, opadry 11 green, opadry 11 white .

TABLE NO.01:IN-*VITRO* DRUG RELEASE PROFILE OF INNOVATOR (COZAAR) TABLETS

Product Name				**Cozaar**					
Label claim				100mg					
Batch No.				F2665					
Condition				Innovator					
AR No.				RDF963/06					
Dissolution medium				Water (900) ml					
Apparatus				Paddle (50 rpm)					
Time in min.	**Tab -1**	**Tab-2**	**Tab-3**	**Tab-4**	**Tab-5**	**Tab-6**	**Mean**	**SD**	**% RSD**
10	44.1	42.1	44.8	40.7	45.4	43.1	43.4	1.76	4.06
20	86	73.5	79	71.8	72.9	73.4	76.1	5.47	7.19
30	130.1	85.5	97.6	85.6	83.9	85.8	90.3	8.05	8.91
45	104.6	93.7	102.8	93.7	89.7	92.2	96.1	6.07	6.32

PREPARATION OF LOSARTAN POTASSIUM TABLET:

V.DISSOLUTION CONDITION:

Dissolution medium: Water
Pharmacopoeia: USP
Apparatus: Type II
RPM: 50
Volume of media: 900 ml
Temperature: 37 ± 0.5°

TABLE NO.02: FORMULATION LOSARTAN POTASSIUM BATCHES

s.no	ingredients	Quantity in mg			
		F1	F2	F3	F4
01.	Losartan potassium	100	100	100	100
02.	Maizestarch (dried)	20.0	20.0	20.0	20.0
03.	Avicel pH 200	159.2	159.2	159.2	159.2
04.	Talc	3.2	3.2	3.2	3.2
05.	Aerosil	4.8	5.6	5.6	5.6
06.	SSG	8.0	9.0	9.0	9.0
07.	Magnesium stearate	4.8	3.0	3.0	3.0
	coating solution				
08.	Opadry green	22.5 mg			
09.	Purified water	150ml			

Procedure:

Dispense all the ingredients as per the batch size. Sift Losartan potassium, maize starch (dried) Avicel pH 200, purified talc, Aerosil 200 through mesh size (#) 40 separately. and Mix API with the SSG, than mix half of the avicel with the blend, than mix maize starch with the blend, than mix another half of the avicel with the blend and than mix purified talc and Aerosil to the blend(Table 01). For each step mix the blend at least 5 minutes.Mix the above blend for 25 minutes in a cone blender.Sift the magnesium Stearate through # 40 and mix with the above blend for further 3 minutes.Compress the above blend using the teardrop shaped punches.Dimension: 11.65x7.1 mm tear drop.

Table no: 03In-*vitro*Drug releaseprofile of Losartan Potassium Formulation

Time in minutes	Tab -1	Tab-2	Tab-3	Tab-4	Tab-5	Tab-6	Mean	SD	% RSD
10	46.8	50.9	53.9	46.8	54.2	39.9	48.8	5.42	11.11
20	75.8	91.0	84.9	83.1	91.8	92.9	86.6	6.60	7.62
30	103.5	100.9	101.9	101.4	100.1	103.8	101.9	1.44	1.41
45	105.4	104.4	103.5	101.7	102.6	104.0	103.6	1.33	1.28
60	106.1	104.5	104.3	101.8	104.2	104.2	104.2	1.40	1.34

Table no:04In-vitroDissolution studies for Losartan Potassium Formulation

Time in minutes	Tab -1	Tab-2	Tab-3	Tab-4	Tab-5	Tab-6	Mean	SD	% RSD
10	39.9	26.6	34.2	34.4	30	46.9	35.3	7.23	20.48
20	85.9	59.7	82.2	88.2	74.0	77.6	77.9	10.34	13.27
30	102.4	83.4	100.8	106.3	96.6	92	96.9	8.25	8.51
45	103.6	88.1	102.1	107.3	98.8	97.8	99.6	6.61	6.64
60	104.0	90.4	102.7	108.1	100.4	101.7	101.2	5.91	5.84

Table no: 05In-vitroDissolution studies for Losartan Potassium Formulation

Time in minutes	Tab -1	Tab-2	Tab-3	Tab-4	Tab-5	Tab-6	Mean	SD	% RSD
10	39.9	26.6	34.2	34.4	30.0	46.9	35.3	7.23	20.48
20	85.9	59.7	82.2	88.2	74.0	77.6	77.9	10.34	13.27
30	102.4	83.4	100.8	106.3	96.6	92.0	96.9	8.25	8.51
45	103.6	88.1	102.1	107.3	98.8	97.8	99.6	6.61	6.64
60	104.0	90.4	102.7	108.1	100.4	101.7	101.2	5.91	5.84

Table no:06In-vitroDissolution studies for Losartan Potassium Formulation

Time in minutes	Tab -1	Tab-2	Tab-3	Tab-4	Tab-5	Tab-6	Mean	SD	% RSD
10	40.2	39.5	40.2	37.8	42.4	38.2	39.4	2.98	7.72
20	82.0	61.0	79.4	70.0	72.8	79.5	74.1	7.86	10.61
30	101.2	75.8	97.1	94.7	94.5	81.8	90.8	9.83	10.83
45	102.4	81.5	99.4	98.0	96.6	101.1	96.5	7.64	7.92
60	104.7	84.8	100.7	100.3	99.6	101.9	98.6	7.03	7.13

Table no: 07Calculations of F1 and F2 for Losartan Potassium Formulation

Time (min)	Rt	Tt	Rt-Tt	(Rt-Tt)^2
0	0	0	0	0
10	43.4	48.8	5.4	29.16
20	76.1	86.6	10.5	110.25
30	90.3	101.9	11.6	134.56
45	96.1	103.6	7.5	56.25
60	99.1	104.2	5.1	26.01
∑	**405**	**445.1**	**40.1**	**356.23**
Number of points		**6**		
F1	**9.9**			
F2	**55.48**			

Observation:F2value crosses the 50 mark.

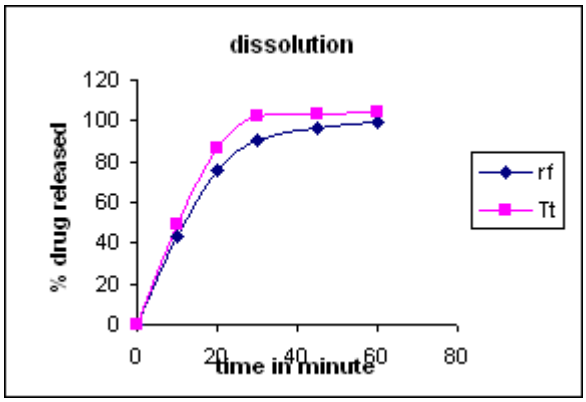


Fig no.01 :In-*vitro*Drug release profile

Plan of Action: To increase the F2 value another trial batch was taken by increasing the aerosil for fast release of the drug.

Table no: 08Calculations of F1 and F2 for Losartan Potassium Formulation

Time (min)	Rt	Tt	Rt-Tt	(Rt-Tt)^2
0	0	0	0	0
10	43.4	38.7	4.7	22.09
20	76.1	75.9	0.2	0.04
30	90.3	90.8	0.5	0.25
45	96.1	93.6	2.5	6.25
60	99.1	95	4.1	16.81
∑	**405**	**394**	**12**	**45.44**
Number of points		**6**		
F1	**2.96**			
F2	**76.67**			

Observation: Capping of the tablets was occurred**.**

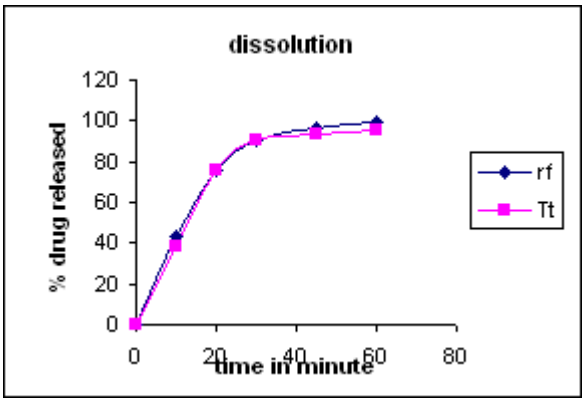


Fig no.02 :In-vitro Drug release profile

Plan of Action: Another trial batch was taken with decreasing the pressure to 85-95N. Tablets were to be coated to obtain a weight gain of 2.5% w/w.

Table no: 09Calculations of F1 and F2 for Losartan Potassium Formulation

Time (min)	Rt	Tt	Rt-Tt	(Rt-Tt)^2
0	0	0	0	0
10	43.4	38.7	4.7	22.09
20	76.1	75.9	0.2	0.04
30	90.3	90.8	0.5	0.25
45	96.1	93.6	2.5	6.25
60	99.1	95	4.1	16.81
∑	**405**	**394**	**12**	**45.44**
Number of points		**6**		
F1	**2.96**			
F2	**76.67**			

Observation: Coated tablet shown more F2 value.

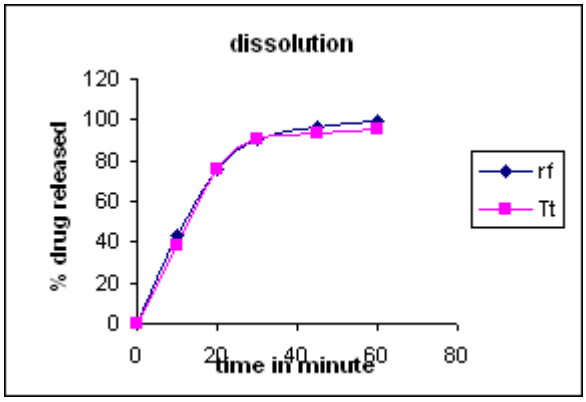


Fig no.03: In-*vitro*Drug release profile

Plan of Action: Another trial batch was taken to coat the tablet by 3% w/w.

Table no: 10Calculations of F1 and F2 for Losartan Potassium Formulation

Time (min)	Rt	Tt	Rt-Tt	(Rt-Tt)^2
0	0	0	0	0
10	43.4	39.9	3.5	12.25
20	76.1	74.1	2	4
30	90.3	90.8	0.5	0.25
45	96.1	96.5	0.4	0.16
60	99.1	98.6	0.5	0.25
∑	**405**	**399.9**	**6.9**	**16.91**
Number of points		**6**		
F1	**1.7**			
F2	**85.45**			

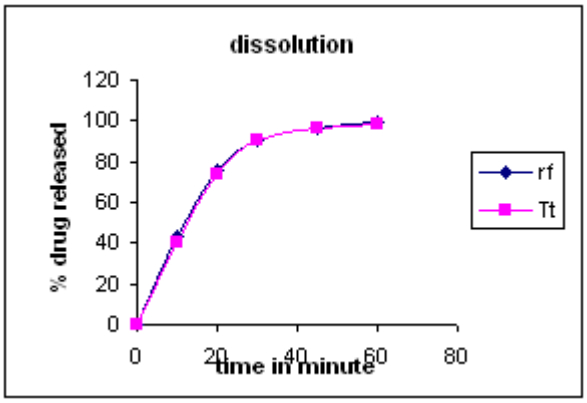


Fig no.04: In-*vitro* Drug release profile

Observation: The F2value matches with the innovator.

Plan of Action: Another three batches were taken with same formula and same parameter and coated with 3% weight gain for the stability batches.

Table No.11: Drug Release Profile inDifferent Medium (DPDM)

Product Name				**Cozaar**					
Label claim				100mg					
Batch No.				F2665					
Condition				Innovator					
AR No.				RDF1290/06					
Dissolution medium				pH 6.8 Buffer					
Apparatus				Paddle (50 rpm)					
Time in mts	**Tab -1**	**Tab-2**	**Tab-3**	**Tab-4**	**Tab-5**	**Tab-6**	**Mean**	**SD**	**% RSD**
10	35.6	40.3	42.9	42.3	26.6	37.9	37.6	6.04	16.06
20	77.0	78.6	82.5	77.8	59.6	69.8	74.2	8.25	11.12
30	97.4	95.5	98.2	90.4	78.0	87.0	91.1	7.73	8.49
45	98.8	91.6	99.4	98.1	88.2	97.7	95.6	4.61	4.82
60	99.9	98.3	99.9	98.9	91.7	99.7	98.0	3.18	3.24

Table No.12:Drug Release Profile in Different Medium (DPDM)

Product Name					**Cozaar**				
Label claim					100mg				
Batch No.					F2665				
Condition					Innovator				
AR No.					RDF1290/06				
Dissolution medium					0.1N-HCl				
Apparatus					Paddle (50 rpm)				
Time in minutes	**Tab -1**	**Tab-2**	**Tab-3**	**Tab-4**	**Tab-5**	**Tab-6**	**Mean**	**SD**	**% RSD**
10	2.1	1.5	2.2	2.4	2.3	2.3	2.1	0.33	15.71
20	5.0	3.9	5.4	5.5	5.9	5.9	5.3	0.75	14.15
30	8.5	6.6	9.0	8.9	10.3	10.0	8.9	1.33	14.94
45	12.4	9.3	13.3	12.7	16.0	14.5	13.0	2.25	17.31
60	23.4	16.2	22.4	21.4	42.2	25.6	25.2	8.84	35.08

Table No.13:Drug Release Profile inDifferent Medium (DPDM)

Product Name				**Losartan Potassium**					
Label claim				100mg					
Batch No.				LP-04					
Condition				Initial					
AR No.				NIL					
Dissolution medium				pH 4.5 Buffer					
Apparatus				Paddle (50 rpm)					
Time in minutes	Tab - 1	Tab-2	Tab-3	Tab-4	Tab-5	Tab-6	Mean	SD	% RSD
10	4.2	3.4	3.1	4.2	3.8	3.4	3.7	0.46	12.43
20	12.2	24.1	20.3	11.8	24.5	24.2	19.5	6.07	31.13
30	37.8	41	31.4	27.9	36.2	36.8	35.2	4.74	13.47
45	40.9	42.8	37.6	41.2	38.9	40.7	40.3	1.82	4.52
60	41.8	44	38.5	43.4	39.7	41.5	41.5	2.11	5.08

Table No.14: Drug Release profile in Different Medium (DPDM)

Product Name	**Cozaar**
Label claim	100mg
Batch No.	F2665
Condition	Innovator

AR No.				RDF1290/06					
Dissolution medium				pH 4.5 Buffer					
Apparatus				Paddle (50 rpm)					
Time in minutes	Tab -1	Tab-2	Tab-3	Tab-4	Tab-5	Tab-6	Mean	SD	% RSD
10	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0	0
20	0.3	2.4	0.3	1	0.2	0.3	0.8	0.86	107.5
30	3.9	3.1	0.5	1.2	0.4	0.5	1.6	1.53	95.63
45	4.8	4	0.8	1.5	1.3	1	2.2	1.71	77.73
60	5.5	4.7	1.6	1.8	2.2	2.4	3	1.63	54.33

Table No.15: Drug Release Profile inDifferent Medium (DPDM)

Product Name				**Losartan Potassium**					
Label claim				100mg					
Batch No.				LP-04					
Condition				Initial					
AR No.				NIL					
Dissolution medium				0.1N HCl (900ml)					
Apparatus				Paddle (50 rpm)					
Time in minutes	**Tab - 1**	**Tab-2**	**Tab-3**	**Tab-4**	**Tab-5**	**Tab-6**	**Mean**	**SD**	**% RSD**
10	2	2.9	2.8	2.7	3.1	2.8	2.7	0.38	14.07
20	4.7	8.4	8.5	6.9	7.6	8.4	7.4	1.47	19.86
30	8.9	13.3	14.6	14.6	13	14.9	13.2	2.27	17.2
\45	14.2	17.8	20.1	26.9	20.3	21.3	20.1	4.19	20.85
60	29.6	26.2	34.1	47.9	34.6	33.3	34.3	7.39	21.55

VI.RESULTS:

Table No.16: Present Data of Various Formulations: 100 mg/Unit Dose

Name of ingredient	**LP-01**	**LP-02**	**LP03**	**LP-04**	**LP05**	**LP-06**	**LP-07**
Losartan Potassium	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Maize Starch (dried)	20.0	20.0	20.0	20.0	20.0	20.0	20.0
Avicel pH 200	159.2	159.2	159.2	159.2	159.2	159.2	159.2
Talc	3.2	3.2	3.2	3.2	3.2	3.2	3.2
Aerosil	4.8	5.6	5.6	5.6	5.6	5.6	5.6
SSG	8.0	9.0	9.0	9.0	9.0	9.0	9.0
Magnesium stearate	4.8	3.0	3.0	3.0	3.0	3.0	3.0

VII.EVALUATION OF BLEND:

Table.17:Pre-compressional parameter study data

Sl.no	**Parameters**	**LP-01**	**LP-02**	**LP-03**	**LP-04**	**LP-05**	**LP-06**	**LP-07**
1	**Loss on drying or water content % w/w**	4.37	4.19	4.23	4.35	4.28	4.39	4.35
2	**Bulk density gm/ml**	0.563	0.437	0.437	0.437	0.437	0.435	0.437
3	**Tapped density gm/ml**	0.667	0.537	0.537	0.537	0.537	0.539	0.539
4	**Compressibility Index %**	20.93	23.75	23.75	23.75	23.75	23.69	23.69
5	**Hausner' s Ratio**	1.2	1.31	1.31	1.31	1.31	1.31	1.31

Table.18:Pre-compression parameter sieve analysis study

Sl..No	SIEVE NO.	% Blend retained						
		LP-01	LP-02	LP-03	LP-04	LP-05	LP-06	LP-07
1	Sieve No.20	0	0	0	0	0	0	0
2	Sieve No.40	2.5	0	0	0	0	0	0
3	Sieve No.60	32.5	27	27	27	29	29	29
4	Sieve No.80	47	44	48	48	52	52	52
5	Sieve No.100	59	56	59	63	67	67	67
6	Receiver	100	100	100	100	100	100	100

Table.19:Results Precompression parameter study finished product evaluation

LP-NO	Hardness(N)	Thickness (mm)	Friability (% w/w)	Disintegration time (min)	
				Core tablets	Coated tablets
1	80-90	4.35-4.39	0.34	12.0	NA
2	95-115	4.62-4.69	0.542	13.0	NA
3	85-95	4.46-4.5 4.58-4.67	0.442	10.2	12.3
4	85-95	4.58-4.64 4.73-4.83	0.548	9.4	13.4
5	85-95	4.53-4.65	0.568	9.6	13.8
6	85-95	4.55-4.67	0.532	9.5	13.6
7	85-95	4.53-4.65	0.593	9.4	13.5

TABLE No .20: Comparative table of F1 and F2

FORMULATION NO.	1	2	3	4	5	6	7
F1	9.9	2.96	2.96	1.7	1.6	1.6	1.7
F2	55.48	76.67	76.67	85.45	83.49	83.15	84.13

TABLE No .21: DISSOLUTION DATA

MEAN OF % DISSOLVED	FORMULATION CODE						
	F 1	F 2	F3	F4	F5	F6	F7
	LP1	LP2	LP3	LP4	LP5	LP6	LP7
	104.2	101.2	101.2	98.6	99.1	98.2	99.2

VIII.SUMMARY & CONCLUSION:

The present work was done at Twilight Litaka Pharma Ltd (F R&D) aimed towards developing Losartan potassium film coated tablet. The literature review showed that the drug was an antihypertensive, mainly used in the treatment of high blood pressure due to vasoconstriction by angiotensin II.Before going to pre-formulation a detail literature review were carried out to know about the innovator (Types of dosage form available in market, its dimensions, shapes, sizes, all other physical parameters and excipients used.) and the patent status of the drug.Pre-formulation study and drug excipients compatibility study was done initially and results directed the further course of formulation (Table 02). With the data's from literature review, Pre-formulation and drug excipients compatibility study (Table 11&12), prototype formulations trials were started. As the development was for three strengths (100 mg, 50mg and 25 mg), trials were taken only for higher strength (100 mg) and was optimized to get an inter convertible formula. Wet granulation was not possible because the active ingredient i.e. Losartan potassium was moisture sensitive. So the direct compression method was followed. Blend was evaluated for tests such as LOD, Bulk density. Tapped density, Compressibility index, and Hausner ratio and sieve analysis before being punched as tablets. Tablets were tested for weight variation, thickness, hardness, friability and disintegration. In vitro dissolution tests were performed and F1 and F2 values were calculated. Dissolution profile of LP 8 formulation was matched with innovator and F2 value was satisfactory.The main objective of this study was to develop the process design parameters by accelerating in all worst conditions. Batches LP-1 to LP-4 were taken for trails and subjected for tests, by this study we monitored some parameters during the process are as follows:

1. Mix Sodium starch glycolate with API first which leads to the proper release of the drug. Follow the mixing according to the procedure mentioned in the formulation in the LP-05.Increase the blending time to 25 minutes.
2. Drying should be done at 105ºC and LOD should be between 4 and 5 % w/w.
3. Dry maize starch to lower LOD the moisture content of the maize starch.
4. Since the Losartan potassium is both light and moisture sensitive, do all the process under the dehumidified condition and sodium lamp.
5. Increase in hardness results in capping problem and decrease in hardness does not match the drug release profile of the innovator.

The formulation LP-04 has been found to posses' ideal characteristics required for Losartan potassium tablets, so it was concluded as the final formula for Losartan potassium tablets 100mg (Table 19).The release profile of Losartan potassium tablets compared with the innovator sample with finished product specification (Table 20). So the optimized formula for Losartan potassium tablets with film coating of 3% w/w weight gain was follows:

FINAL FORMULA FOR LOSARTAN POTASSIUM:

Table no.22: Prediction of Losartan Potassium Final Formula

S.No	Ingredients	mg/tab
1	Losartan Potassium	100.0
2	Maize Starch (dried)	20.0
3	Avicel pH 200	159.2
4	Talc	3.2
5	Aerosil	5.6
6	SSG	9.0
7	Magnesium stearate	3.0
	Coating solution	
9	Opadry green	22.5 gm
10	Purified water	150 ml

FINISHED PRODUCT SPECIFICATION:

Table no.23: Prediction of Losartan potassium final formula specification

SNo.	Test Parameters	Specifications (100mg)
1.	Description	Light green, tear drop shaped film coated tablets
2.	Dimension	11.65±0.2mm x 7.1±2mm tear drop
3.	Thickness	4.5±0.2mm – 4.65±0.2mm
4.	Average Weight	309±2% mg
5.	Hardness	85–95N
6.	Friability	NMT – 1%
7.	Disintegration Time	NMT – 30 min.
8.	Content Uniformity	Labelled claim ± 15%

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