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RESEARCH ARTICLE

Formulation and *In-Vitro* Evaluation of Immediate Release Tablets of Losartan Potassium Using Different Superdisintegrants

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ABSTRACT

In the present study an attempt has been made to prepare the various trails (T1 to T7) of immediate release tablets of losartan potassium by using a suitable diluent (Microcrystalline cellulose PH 101), a binder (Pregelatinised starch 1500) with different superdisintegrants (Crospovidone, Croscarmellose sodium and Sodium Starch Glycollate). The formulation development work was initiated with wet granulation. The prepared granules and tablets were evaluated for various pre and post compression parameters such as loss on drying, bulk density, tapped density, compressibility index, Hausner's ratio, particle size distribution, Weight variation, Tablet hardness, Thickness, Friability, Disintegration time, Drug content and *in-vitro* dissolution study. It was concluded that the immediate release tablets with proper hardness, disintegration time and with an increase rate of dissolution can be made using Crospovidone (T6). The optimized formulation (T6) is further selected and compared with the *in-vitro release* profile of the innovator product with various dissolution media such pH 1.2, pH 4.5 and pH 6.8. The results were found to be satisfactory.

KEYWORDS: Losartan potassium, immediate release tablet, superdisintegrants, crospovidone.

INTRODUCTION:

Immediate release tablets have started gaining popularity in recent days and acceptance as a drug delivery system, mainly because they are easy to administer, has quick onset of action, economical and lead to better patient compliance. They are also a tool for expanding markets, extending product life cycles and generating opportunities. (1, 2)

Losartan potassium, chemically, 2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-ylphenyl) benzyl] imidazole-5-methanol monopotassium salt, (3, 4, 5) is an orally active non peptide angiotensin-II receptor antagonist used in the treatment of hypertension due to mainly blockade of AT1 receptors.(6) The structure of losartan potassium is given in the fig 1.

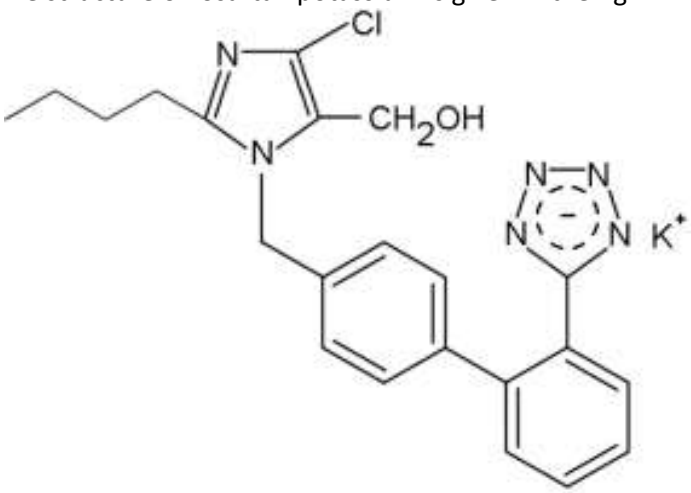

Figure 1: Structure of Losartan potassium

In the present study, we made an attempt to develop a stable formulation of oral immediate release losartan potassium tablets with optimum properties. To achieve this goal, various formulation trails of losartan potassium tablets were prepared and evaluated with respect to the various quality parameters both in process parameters for granules (loss on drying, bulk density, tapped density, compressibility index, Hausner's ratio) and parameters for finished products (average weight, weight variation, tablet thickness, friability, hardness, disintegration time, drug content, dissolution studies). On the basis of these parameters the formula was optimized and compared with the innovator product. Then, the *in-vitro* dissolution profile of optimized losartan potassium tablets was compared with the innovator product in various dissolution media.

EXPERIMENTAL:

MATERIALS:

Losartan potassium was procured as a gift sample from Cadila health care Ltd., Vadodara. Excipients like Lactose monohydrate, Microcrystalline Cellulose (Avicel PH101), Pregelatinised maize starch (Starch 1500), Crospovidone (Polyplasdone XL10), Croscarmellose sodium (Ac-Di-Sol), Sodium starch glycollate (Primogel) Croscarmellose sodium were procured from Signet chemical company, Mumbai. Opadry White was procured

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from Colorcon Asia Pvt. Ltd., Goa. All other ingredients were of laboratory grade.

METHODS:

Various trials of immediate release losartan potassium tablets were prepared with different superdisintegrants specified in Table 1 as per the following procedure.

Table 1: Composition of formulation trials of Losartan potassium tablets 100mg

Sr. No.	Ingredients	Formulation Trail Code [Quantity per tablet (mg)]						
		T1	T2	T3	T4	T5	T6	T7
Dry mix								
1	Losartan potassium	100	100	100	100	100	100	100
2	Microcrystalline cellulose (Avicel PH101)	115	115	115	115	115	115	115
3	Lactose monohydrate	40	40	40	40	40	40	40
4	Sodium starch glycollate (Primogel)	12	-	-	-	-	-	-
5	Croscarmellose sodium (Ac-Di-Sol)	-	12	-	-	-	-	-
6	Crospovidone (Polyplasdone XL)	-	-	12	-	-	-	-
7	Crospovidone (Polyplasdone XL 10)	-	-	-	12	9	6	3
8	Pregelatinised starch (Starch 1500)	30	30	30	30	30	30	30
Wet granulation								
9	Purified water	Quantity sufficient						
Lubrication								
10	Crospovidone (Polyplasdone XL 10)	-	-	-	-	3	6	9
11	Magnesium stearate	3	3	3	3	3	3	3
	Core weight	300	300	300	300	300	300	300
Film coating								
11	Opadry White	6	6	6	6	6	6	6
12	Purified Water	Quantity sufficient						
	Coated Tablet weight	**306**	**306**	**306**	**306**	**306**	**306**	**306**

Losartan potassium, Microcrystalline cellulose, Lactose monohydrate, Pregelatinised starch and disintegrant were sifted through 30# mesh using a vibratory sifter. The sifted raw materials were loaded into Rapid mixer granulator and mixed for 15 mts with impeller at slow speed and chopper off. Purified water was added slowly to the dry mix over a period of 5 mts with impeller at slow speed and chopper off. The granules were kneaded for 5 mts with impeller at fast speed and chopper off. The granules were dried in a fluid bed dryer with inlet temperature between 55 ^{o}C to 65^{o}C till the loss on drying was between 2.5 to 3.5%. The dried granules were then sifted through 30# mesh using a vibratory sifter. The retentions were milled using multi mill fitted with 1.5 mm screen in the knife forward direction at medium speed. The granules were then loaded into octagonal blender. Magnesium stearate was sifted through 30# mesh and added to the sized granules and mixed for 5 mts at slow speed. The lubricated granules were then compressed using 14x7mm oval shaped plain punches on Rimek 10 station single rotary "B" tooling machine. Finally, the compressed tablets were coated in Neocota fitted with 8" perforated pan by using the coating suspension containing Opadry white in purified water and then it was strained through 100# mesh.

EVALUATION OF IN- PROCESS PARAMETERS OF GRANULES: (T1 to T7)

The lubricated granules (T1 to T7) were evaluated for loss on drying, bulk density, tapped density, compressibility index, Hausner's ratio and particle size distribution as per standard procedure.

EVALUATION OF FINISHED FORMULATIONS OF TABLETS: (T1 to T7)

The finished tablets (T1 to T7) were tested for Weigh variation, Thickness, Hardness, Friability, Disintegration time, Drug content and *in-vitro* dissolution study as per following standard procedure.

WEIGHT VARIATION:

Twenty tablets were selected at random and their average weight was determined using an electronic

balance (Shimadzu Aux200, Japan). The tablets were weighed individually and compared with average weight.

THICKNESS:

Thickness of ten tablets was measured by dial caliper (Mitutoya, Japan) and average was calculated.

HARDNESS:

The hardness was determined for 10 tablets of each batch by using an Erweka tablet hardness tester. The average was determined.

FRIABILITY:

Twenty tablets were weighed and placed in the Electrolab friabilator and the apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were deducted and weighed again. The percentage friability was measured using the formula,

% F = {1-(Wt/W)} ×100

Where, % F = friability in percentage

W = Initial weight of the tablet

Wt = weight of tablets after revolution.

DISINTEGRATION TIME:

Disintegration is evaluated to ensure that the drug substance is fully available for dissolution and absorption from the gastrointestinal tract. (7) The disintegration test was done on 6 units using the apparatus described in United States pharmacopoeia method.

DRUG CONTENT:

The assay of Losartan potassium in tablets was estimated by chromatographic method.

Mode: LC ($C_{22}H_{22}ClKN_6O$); **Detector:** UV 250 nm; **Column:** 3.9-mm x15-cm; 5-µm packing L7. ; **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:** acetonitrile.

PROCEDURE:

***Sample stock solution*:** Ten tablets were transferred to a 500-ml volumetric flask. Solution A was added to fill the flask to about 50% of the final volume then it was sonicated by shaking for 15 mts. Finally, it was diluted with Solution A to volume and mixed well.

Sample solution: 0.25 mg/ml of losartan potassium in Solution A was taken from the Sample stock solution and mixed well. An aliquot of the solution was passed through a PTFE filter of 0.45-mm pore size and the filtrate was analysed by chromatographically.

***IN-VITRO* DISSOLUTION STUDIES:**

In Vitro dissolution study was carried out by spectrophotometrically.

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.

PROCEDURE:

The amount of losartan potassium ($C_{22}H_{22}ClKN_6O$) dissolved was determined 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. The appropriate dilution of the solutions was made with medium to be within the linear range of the spectrophotometer.

Calculate the percentage of losartan potassium ($C_{22}H_{22}ClKN_6O$) dissolved by using the formula, (A_U/A_S) x (C_S/L) x V x 100

Where, 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

Finally, the *in- vitro* dissolution profiles of various trials of losartan potassium tablets were compared with innovator product, Cozaar 100mg in water. The optimized formulation trial (T6) was selected on the basis of their In-vitro dissolution profile and it was further compared with innovator product, Cozaar 100mg in three different dissolution media such as pH 1.2 buffer, pH 4.5 acetate buffer and pH 6.8 phosphate buffer.

RESULTS AND DISCUSSION:

The lubricated granules obtained from T1 to T7 were evaluated for in process parameters like loss on drying, bulk density, tapped density, compressibility index and Hausner's ratio. These results were presented in the Table 2. It was found to be satisfactory.

Table 2: Evaluation of in process parameters of various trials granules

Parameters	Formulation Trail Code						
	T1	T2	T3	T4	T5	T6	T7
Loss on drying (%w/w) Mean±S.D	3.2±0.01	2.8±0.02	2.9±0.04	3.4±0.02	3.1±0.01	2.7±0.01	2.9±0.02
Bulk density (g/cc) Mean±S.D	0.556±0.03	0.532±0.02	0.581±0.05	0.543±0.04	0.521±0.04	0.510±0.06	0.500±0.05
Tapped density (g/cc) Mean±S.D	0.658±0.02	0.625±0.03	0.694±0.05	0.641±0.04	0.610±0.06	0.595±0.05	0.581±0.02
Compressibility index Mean±S.D	15.55±0.02	14.89±0.02	16.27±0.01	15.22±0.03	14.58±0.04	14.29±0.05	14.00±0.02
Hausner's ratio Mean±S.D	1.18±0.05	1.17±0.06	1.19±0.05	1.18±0.05	1.17±0.02	1.17±0.02	1.16±0.02
Particle size distribution	Cumulative % retained						
20#	10.36	8.52	12.65	10.68	7.54	9.52	10.22
30#	15.94	14.83	15.97	14.89	15.61	17.32	16.47
40#	38.62	40.58	45.62	40.36	38.42	34.86	40.98
60#	53.68	51.62	52.48	51.28	54.32	49.58	57.64
80#	68.92	63.52	62.80	64.35	68.27	65.76	66.48
100#	75.21	70.46	75.24	76.58	75.84	72.84	76.32

The coated compressed tablets were evaluated for time and assay. The results were found to be satisfactory parameters like weight variation, thickness, disintegration and were presented in Table 3.

Table 3: Evaluation of various trials of coated tablets of Losartan potassium

Parameters	T1	T2	T3	T4	T5	T6	T7
Weight variation (mg) Mean±S.D	306.23± 0.02	305.25± 0.05	306.29± 0.08	304.52± 0.52	305.48± 0.28	306.46± 0.25	307.55± 0.29
Disintegration time(sec) Mean±S.D	42± 0.02	56± 0.06	50± 0.29	64± 0.32	37± 0.42	11± 0.34	52± 0.18
Thickness(mm) Mean±S.D	4.55± 0.29	4.52± 0.28	4.58± 0.52	4.61± 0.08	4.58± 0.25	4.51± 0.05	4.58± 0.02
Assay (%) Mean±S.D	99.2± 0.02	99.8± 0.83	100.6± 0.25	100.4± 0.22	100.9± 0.25	100.1± 0.16	100.7± 0.18

The *in- vitro* dissolution profiles of various trials of losartan potassium tablets were compared with innovator product, Cozaar 100mg in water. The results were presented in Table 4 and also in the fig. 2. It was found to be satisfactory.

Table 4: *In-vitro* dissolution profiles of various trials of losartan potassium tablets compared with innovator, Cozaar 100mg in water

Time (Minutes)	% Drug release in water						
	Innovator Product (Cozaar 100mg)	T1	T2	T3	T4	T5	T6	T7
5	35.4	20.5	22.8	24.7	30.4	35.7	37.2	40.6
10	48.9	35.1	34.8	36.8	41.4	47.5	49.7	52.8
15	62.4	46.8	43.9	48.2	55.7	60.4	63.8	66.7
20	68.7	50.8	52.7	59.7	62.8	66.9	70.5	74.5
30	80.5	68.2	67.4	75.4	76.4	77.5	78.9	81.5
45	89.7	80.4	78.4	84.8	83.9	84.5	88.7	91.8
60	99.6	91.5	93.4	96.2	96.8	96.9	99.4	100.2

Figure 2: Comparative *In-vitro* dissolution profiles of various trials of losartan potassium tablets compared with innovator, Cozaar in water

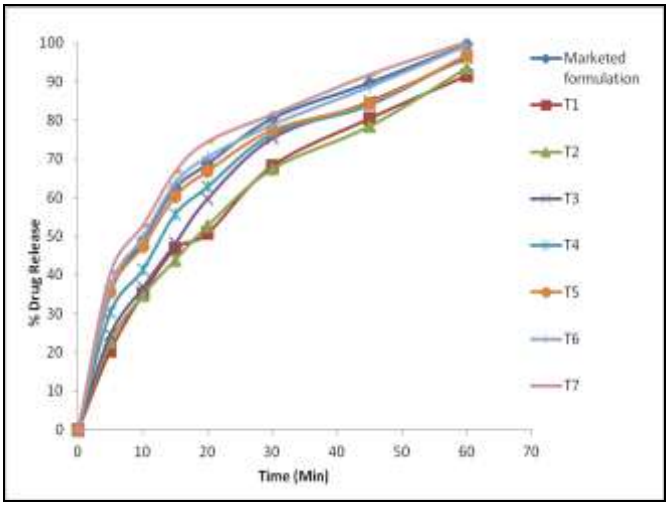
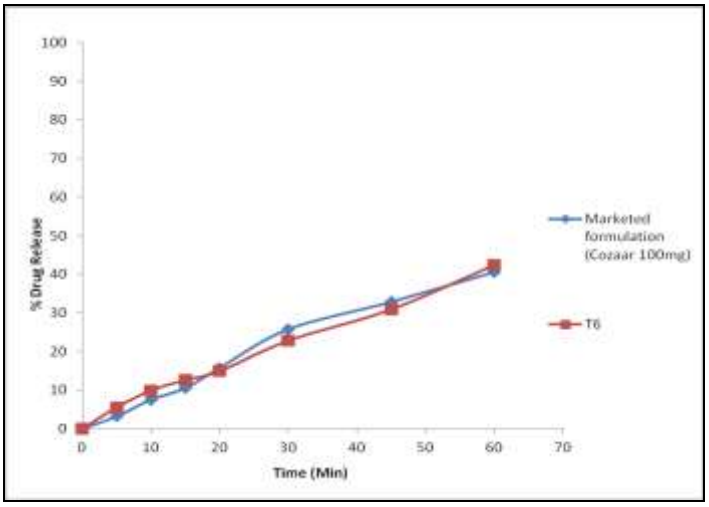


Figure 3: Comparative dissolution profiles of formulation trial T6 with innovator product, Cozaar in pH 1.2 buffer



The optimized formulation trial (T6) was selected on the basis of their In-vitro dissolution profile and it was finally compared with innovator product, Cozaar 100mg in three different dissolution media such as pH 1.2 buffer, pH 4.5 acetate buffer and pH 6.8 phosphate buffer. The results were presented in the Table 5, 6 and 7 respectively and the comparative dissolution profile of optimized formulation trial (T6) with the innovator product in the same media were shown in fig. 3, 4 and 5 respectively. The results were found to be satisfactory.

Table 5: Comparative dissolution profiles of formulation trial T6 with innovator, Cozaar 100mg in pH 1.2 buffer

Time (Minutes)	% Drug release in pH 1.2 buffer	
	Innovator Product (Cozaar 100mg)	T6
5	3.2	5.5
10	7.5	9.9
15	10.5	12.6
20	15.7	14.9
30	25.7	22.8
45	32.8	30.9
60	40.5	42.4

Table 6: Comparative dissolution profiles of formulation trial T6 with innovator product, Cozaar in pH 4.5 acetate buffer

Time (Minutes)	% Drug release in pH 4.5 acetate buffer	
	Innovator Product (Cozaar 100mg)	T6
5	9.4	7.2
10	15.3	13.4
15	20.7	18.8
20	24.8	27.1
30	32.9	34.4
45	42.5	39.2
60	48.2	45.5

Figure 4: Comparative dissolution profiles of formulation trial T6 with innovator product, Cozaar in pH 4.5 acetate buffer

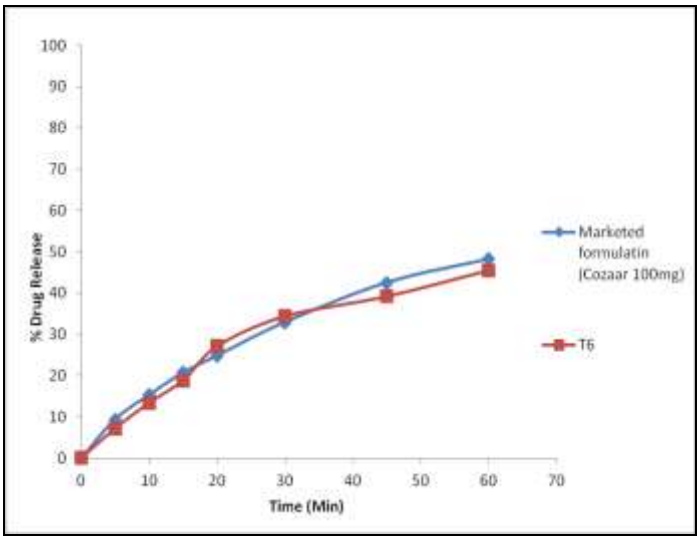
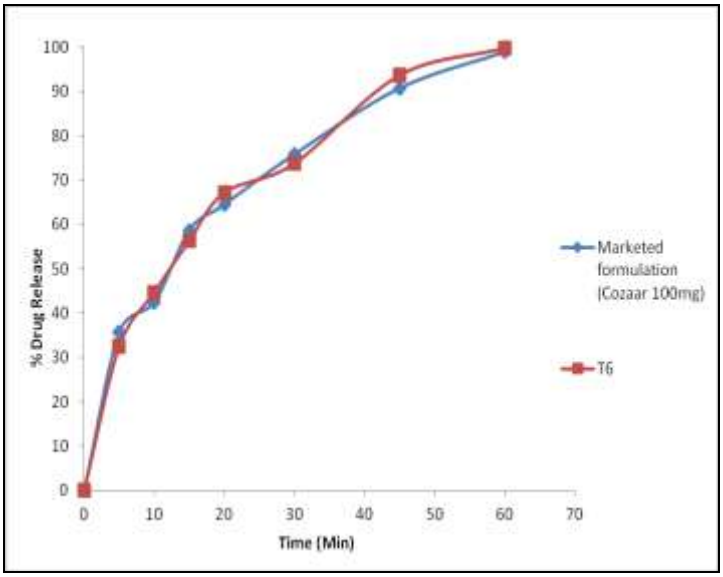


Table 7: Comparative dissolution profiles of formulation trial T6 with innovator product, Cozaar in pH 6.8 phosphate buffer

Time (Minutes)	% Drug release in pH 6.8 phosphate buffer	
	Innovator Product (Cozaar 100mg)	T6
5	35.7	32.5
10	42.4	44.7
15	58.7	56.4
20	64.5	67.2
30	75.8	73.8
45	90.7	93.7
60	98.9	99.8

Figure 5: Comparative dissolution profiles of formulation trial T6 with innovator product, Cozaar in pH 6.8 phosphate buffer



CONCLUSION:

The study was undertaken with an aim to develop an optimized formulation of immediate release tablets of Losartan potassium by oral drug delivery. The tablets were prepared by the wet granulation method by using various superdisintegrants. During development of the formula, various in process tests such as bulk density, tapped density, Hausner's ratio and compressibility index were evaluated for granules. Weight variation, hardness, thickness, disintegration time and assay were evaluated for the finished products. The developed trials were also tested for *in vitro* dissolution study and then compared with that of the innovator product. Based upon the dissolution performance, T6 was selected from the various trails of developed formulations and then it was further compared with the innovator product with three different dissolution media such as pH 1.2 buffer, pH 4.5 acetate buffer and pH 6.8 phosphate buffer. Therefore, it was finally concluded that the T6 trial was the satisfactory formulation that could perform therapeutically, with improved efficacy and better patient compliance like that of the innovator product.

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