Innovations in Pharmaceuticals and Pharmacotherapy

www.innpharmacotherapy.com

eISSN: 2321–323X

Original Article

Formulation and evaluation of bilayered tablets of losartan potassium

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Abstract

Bi-layer tablet is suitable for sequential release of two drugs in combination and also for single drug as immediate dose and maintenance dose. Losartan Potassium is an anti hypertensive drug acts by antagonizing Angiotensine II receptors. The aim of present study is to prepare bilayer tablets of Losartan Potassium with an immediate release and a sustained release layer. The immediate release layer was prepared using super disintegrant sodium starch glycolate and sustained release layer is formulated with different polymers such as xanthum gum, gum karaya and hydroxy propyl methyl cellulose K4M, individually in different concentrations and in combinations. The preformulation studies of formulations showed good flow properties and feasibility for direct compression. The compressed bilayered tablets were evaluated for hardness, friability, weight variation, drug content uniformity and in vitro drug release. Formulation contained combination of xanthum gum and gum karaya was optimized which showed prolonged release of Losartan Potassium for about 24 hrs. No significant change either in physical appearance, drug content or in dissolution pattern was observed after storing at 40°C/75% relative humidity (RH) for 1 month in respect of the optimized formulation. FTIR studies revealed no chemical interaction between drug and adjuvant as well as adjuvant and adjuvant which indicates the stability of drug in tablets.

Keywords: Losartan Potassium, Bilayered tablets, Immediate and Sustained release.

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1. Introduction

The concept of Bilayer tablet technology is utilized to develop sustain release and immediate formulation for a single drug or combination of drugs. Bilayer tablets are preferred in some cases because they maintain uniform drug levels, reduce dose, side effects, increase the safety margin for high-potency drugs and thus offer better patient compliance. Losartan potassium is an anti hypertensive drug which acts by controlling antagonizing effect on the angiotensine II receptors. The aim of this investigation is to formulate and evaluate the sustain

release bilayer tablets of Losartan Potassium using different synthetic and natural polymers Losartan potassium possess short biological half life (1.5- 2 hrs),which demands frequent administration usually thrice a day leading to patient noncompliance exposing him to risk of side effects. In order to overcome this, Losartan potassium sustained release dosage forms are formulated as bilayered tablet which comprises of two layers among which the first layer is immediate release layer and the second layer is sustained release layer. The immediate release portion ensures quicker onset of action by eliciting MEC in less time while the sustained release fractions maintain the same levels offering once a day convenient dosing. The current research is to formulate and evaluate an ideal bilayer matrix tablet of sustained release profile by using suitable methods by using different polymers.

2. Materials and Methods

Losartan potassium was obtained from Vijashree chemicals. Pvt Ltd. Hyderabad, the exepients such as micro crystalline cellulose, Sodium starch glycolate, xanthum gum, gum karaya, HPMC K4M, magnesium stearate, Talc of analytical grade were obtained from S.D fine chemicals. India.

1. Preformulation Studies:
It gives information needed to define the nature of the drug substance and provide frame work for the drug combination with pharmaceutical exepients in the dosage form.
1.1. Bulk density:
It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume.

Bulk density BD = (M/V) g/cc

1.2. Tapped density
It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume.

Tapped density Td = Mass/Tapped volume

1.3. Hausner's ratio
Hausner's ratio is an index of ease of powder flow; it is calculated by following formula.

Hausner's ratio = Tapped density/Bulk density

1.4. Carr's Index
Tapped and bulk density measurements can be used to estimate the Carr's index of a material. Carr's index was determined by,
C.I (%) = Tapped density – bulk density /Tapped density*100

1.5. Angle of repose
It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.

$\theta = \tan^{-1}(h/r)$

2. Formulation of bilayered tablets:
Bilayered tablets were prepared by direct compression technique. All the ingredients of immediate and controlled release layer

are passed through standard sieve 40#. Controlled release layer containing xanthum gum, gum karaya and HPMC K4M in different concentrations and combinations was compressed into tablets using 11mm flat round punch set. On this tablet the immediate release layer is compressed. [Table-1]

3. Evaluation of bilayered tablets:

3.1 Weight Variation:
20 tablets were selected randomly from the lot and weighted individually to check for weight variation. The individual weighed is then compared with average weight for the weight variations. [Table-3]

3.2 Hardness:
The strength of tablet is expressed as tensile strength (kg/cm2). The tablet crushing load, which is the force required to break a tablet into pieces by compression. It was measured using a tablet hardness tester (Monsanto hardness tester). Three tablets from each formulation batch were tested randomly and the average readings were noted [table 3].

3.3 Friability:
Friability of the tablets was determined using Roche Friabilator. This device consists of a plastic chamber that is set to revolve around 25 rpm for 4 min dropping the tablets at a distance of 6 inches with each revolution. Pre weighed sample of 20 tablets was placed in the friabilator and were subjected to 100 revolutions and reweighed. The friability (F %) is given by the following formula

$$F (\%) = (1 - W0 / W) \times 100$$

Where, W0 is weight of the tablets before the test
W is the weight of the tablets after test.

3.4. Swelling studies:
One tablet from each formulation was weighed and kept in Petri dish containing 20 ml of phosphate buffer of pH 6.8. At the end of specified time intervals tablets were withdrawn from Petri dish and excess buffer blotted with tissue paper and weighed. The % weight gain by the tablet was calculated by following formula.

$$R = wa - wb/ wb \times 100$$
Where, wa = weight of tablet after absorption
wb = weight of tablet before absorption

3.7. In vitro dissolution studies:
The dissolution studies were carried out in pH 1.2 for 2 hrs & in pH 6.8 for next 22 hrs at 37 ± 0.50C at 100 rpm using basket type tablet dissolution apparatus USP type-I. At regular time interval, 5 ml of sample was withdrawn from the dissolution medium and replaced with equal volume of fresh medium. The samples were analyzed at 205 nm for Losartan potassium against blank using UV-Visible Spectrophotometer

3. Results and Discussion

In the present study, 13 formulations of bilayered tablets of Losartan Potassium were prepared, in them ingredients of the immediate layer were kept constant and the controlled release layer ingredients like xanthum gum, gum karaya, HPMC K4M were used in different concentrations and in combinations.

S.no.	Formulation code	L1	L2	L3	L4	L5	L6	L7	L8	L9	L10	L11	L12	L13
Ingredients for IR layer														
1	Drug	10	10	10	10	10	10	10	10	10	10	10	10	10
2	SSG	3	3	3	3	3	3	3	3	3	3	3	3	3
3	MCC	36.5	36.5	36.5	36.5	36.5	36.5	36.5	36.5	36.5	36.5	36.5	36.5	36.5
4	Mg stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Ingredients for CR layer														
5	XG	160	180	-	-	-	-	80	90	80	90	-	-	60
6	GK	-	-	160	180	-	-	80	90	-	-	80	90	60
7	HPMC K4M	-	-	-	-	160	180	-	-	80	90	80	90	60
8	MCC	142	122	142	122	142	122	142	122	142	122	142	122	122
9	PVP	20	20	20	20	20	20	20	20	20	20	20	20	20
10	Talc	4	4	4	4	4	4	4	4	4	4	4	4	4
11	Mg stearate	4	4	4	4	4	4	4	4	4	4	4	4	4
	Total	450	450	450	450	450	450	450	450	450	450	450	450	450

Table 1: Composition of bilayer matrix tablets of losartan potassium

Formulation code	Angle of repose (θ)	Carr's index (%)	Hausner's ratio
L1	41.22 ± 0.16	31.19 ± 0.14	1.45 ± 0.07
L2	17.66 ± 0.32	18.25 ± 0.09	1.22 ± 0.02
L3	18.41 ± 0.15	19.37 ± 0.02	1.24 ± 0.01
L4	19.33 ± 0.87	18.05 ± 0.14	1.22 ± 0.02
L5	21.32 ± 0.41	17.90 ± 0.11	1.21 ± 0.03
L6	23.31 ± 1.27	19.12 ± 0.30	1.23 ± 0.01
L7	24.56 ± 3.01	17.46 ± 0.21	1.21 ± 0.03
L8	26.10 ± 0.94	19.72 ± 0.18	1.24 ± 0.01
L9	30.12 ± 2.19	18.14 ± 0.22	1.25 ± 0.03
L10	29.31 ± 2.41	19.09 ± 0.13	1.23 ± 0.01
L11	28.46 ± 1.34	19.58 ± 0.14	1.22 ± 0.03
L12	26.04 ± 0.95	19.57 ± 0.19	1.24 ± 0.03
L13	27.12 ± 1.41	19.58 ± 0.13	1.24 ± 0.01

Table 2: Preformulation parameters pre compressional blend.

Formulation code	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	Drug content (%)	Weight variation
L1	5.46	0.31	4.47	98.21	2.33
L2	5.48	0.28	4.52	98.01	1.72
L3	5.71	0.22	4.47	98.45	1.38
L4	5.64	0.34	4.44	98.32	1.22
L5	5.71	0.32	4.55	98.41	1.71
L6	5.63	0.29	4.48	98.11	2.37
L7	6.06	0.35	4.53	99.32	1.62
L8	7.2	0.21	4.52	99.91	1.53
L9	6.56	0.29	4.50	98.43	1.73
L10	7.3	0.20	4.51	99.81	2.32
L11	6.3	0.27	4.49	98.44	1.83
L12	6.0	0.25	4.51	99.82	1.37
L13	6.8	0.22	4.25	99.56	1.56

Table 3: Post compressional parameters of bilayered tablets. All values are expressed as mean of 3 readings

	% Swelling Index												
Time (hrs)	L1	L2	L3	L4	L5	L6	L7	L8	L9	L10	L11	L12	L13
0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	97.59	120.6	29.33	82.66	5.32	6.19	0.43	96.78	1.03	76.78	8.39	12.44	96.78
2	167.5	189.3	93.22	105.2	15.32	16.83	1.59	163.8	3.1	143.8	22.45	33.72	153.8
3	226.1	249.9	152.4	162.8	29.03	36.82	7.05	221.4	10.3	181.4	54.67	88.32	201.4
4	251.3	287.9	172.5	198.3	40.22	54.31	13.3	243.3	18.6	203.3	83.67	101.2	233.3
5	283.8	318.5	193.8	212.5	62.22	83.23	18.9	273.3	25.8	233.3	103.9	143.3	263.3
6	312.4	351.2	231.4	256.5	89.93	106.3	27.8	308.7	37.9	258.7	146.1	157.9	288.7
7	347.9	381.8	258.9	285.4	113.6	143.7	37	342.2	54.4	272.2	154.7	173.3	322.2
8	386.8	421.8	283.1	308.3	146.8	163.2	44.3	379	83.3	309	178	207.2	349
9	419.3	458.2	317	358.1	173.5	189.4	59.9	411	109	321	212.2	238.9	381
10	449.8	489.1	348.3	375.2	193.3	221.1	103	438.9	129	388.9	243.8	252.2	418.9
11	483.5	542.3	384.3	405.7	234.8	237.7	121	478.5	162	458.5	257.7	283.3	448.5
12	539	599.8	427.6	435.3	241.9	259.8	143	528.9	203	508.9	285.9	321.4	518.9
15	587.8	662.9	472.4	446.9	267.3	286.7	183	578.9	219	558.9	327.9	342.3	558.9
18	652.7	693.6	519.1	483.2	258.9	281.7	173	637.9	209	617.9	373.2	406.1	627.9
21	687.8	750.5	561.3	540.4	247.9	263.3	164	683.7	194	653.7	413.7	448.4	663.7
24	749.4	810.3	610.2	610.9	239.6	247.5	152	720.5	179	670.5	452.4	493.3	675.5

Table 4: Swelling Index of L1 to L13

	% drug release											
Time (hrs)	**L1**	**L2**	**L4**	**L5**	**L6**	**L7**	**L8**	**L9**	**L10**	**L11**	**L12**	**L13**
0	0	0	0	0	0	0	0	0	0	0	0	0
1	15.99	14.65	16.18	17.7	15.61	16.49	13.5	20.74	16.18	22.48	21.69	13.12
2	21.3	18.43	24.36	21.9	20.36	31.64	15.36	29.34	24.36	27.68	27.84	14.79
3	35.98	30.25	37.91	31.63	24.36	41.58	23.59	34.49	37.91	40.64	33.37	22.61
4	44.42	34.12	47.3	36.63	29.13	47.86	26.48	41.36	47.3	46.6	41.76	26.26
5	55.38	38.2	55.98	41.84	34.31	58.35	30.92	51.88	55.98	52.03	50.96	34.39
6	66.21	42.87	64.51	48.03	38	72.77	35.75	57.9	64.51	59	55.27	38.87
7	74.25	48.89	76.13	54.06	43.23	77.65	38.9	64.52	76.13	65.83	60.36	41.66
8	83.66	54.57	85.35	62.03	46.96	84.21	41.88	72.5	85.35	73.45	65.86	45.23
9	92.75	61.8	93.47	67.57	51.29	86.06	44.88	79.96	93.47	80.35	71.58	49.58
10	98.27	66.41	97.84	72.57	55.83	93.77	48.65	85.75	97.84	86.15	77.33	53.19
11	-	72.18	-	78.17	61.15	98.84	53.01	92.7	-	92.74	85.58	57.19
12	-	79.88	-	84.75	67.27	-	56.83	99.32	-	99.17	90.07	68.07
15	-	99.79	-	96.3	81.39	-	69.02	-	-	-	-	78.62
18	-	-	-	-	93.87	-	79.38	-	-	-	-	88.65
21	-	-	-	-	-	-	90.56	-	-	-	-	98.17
24	-	-	-	-	-	-	99.14	-	--	-	-	-

Table 5: *In-vitro* release of losartan potassium bilayer matrix tablets from controlled release

Time (hrs)	Log Time	√T	Cumulative % drug release*	Log cumulative % drug release	% drug remained	Log % drug remained
0	0	0	0	0	100	2
0.5	0.301	0.707	12.289	1.089	87.710	1.943
1	0.000	1.000	13.497	1.130	86.502	1.937
1.5	0.176	1.224	14.521	1.162	85.478	1.931
2	0.301	1.414	15.361	1.186	84.638	1.927
2.5	0.397	1.581	22.786	1.357	77.213	1.887
3	0.477	1.732	23.587	1.372	76.412	1.883
4	0.602	2.000	26.483	1.422	73.516	1.866
5	0.698	2.236	30.915	1.490	69.084	1.839
6	0.778	2.449	35.751	1.553	64.248	1.807
7	0.845	2.645	38.904	1.589	61.095	1.786
8	0.903	2.828	41.883	1.622	58.116	1.764
9	0.954	3.000	44.878	1.652	55.121	1.741
10	1.000	3.162	48.649	1.687	51.350	1.710
11	1.041	3.316	53.010	1.724	46.989	1.671
12	1.079	3.464	56.825	1.754	43.174	1.635
15	1.176	3.872	69.021	1.838	30.978	1.491
18	1.255	4.242	79.383	1.899	20.616	1.314
21	1.322	4.582	90.561	1.956	9.438	0.974
24	1.380	4.898	99.139	1.996	0.861	0.065

Table 6: Kinetic release of losartan potassium from bilayer matrix tablets (L8).

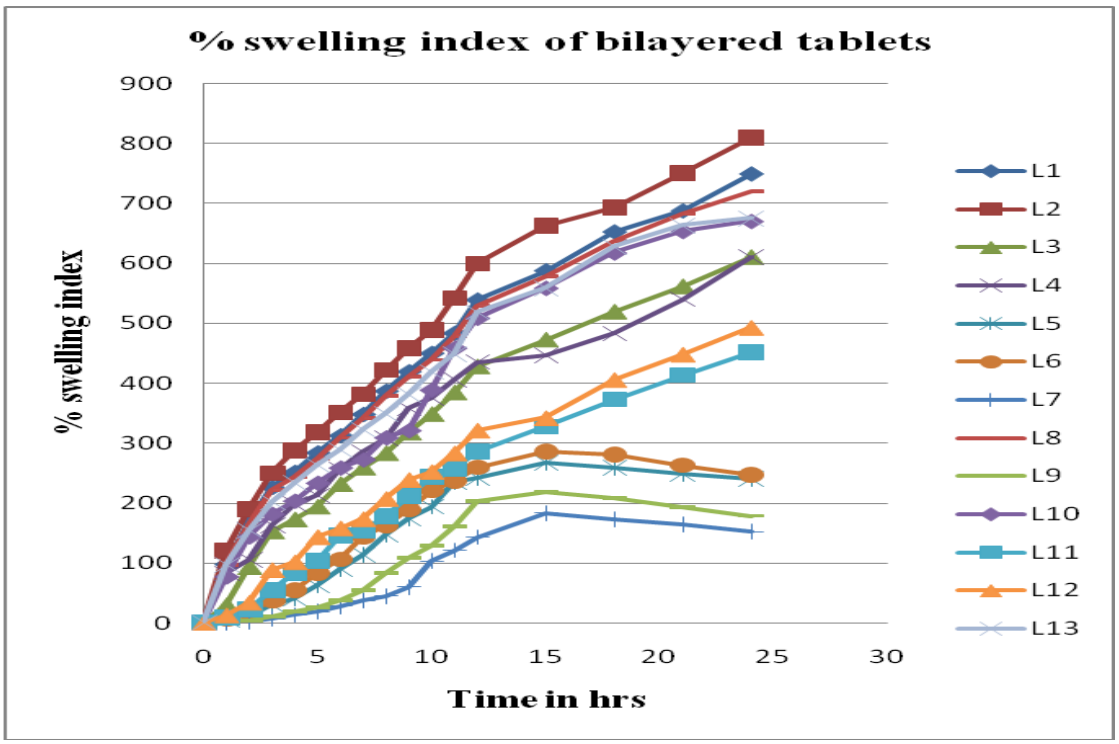

Fig 1: swelling studies of bilayered tablets

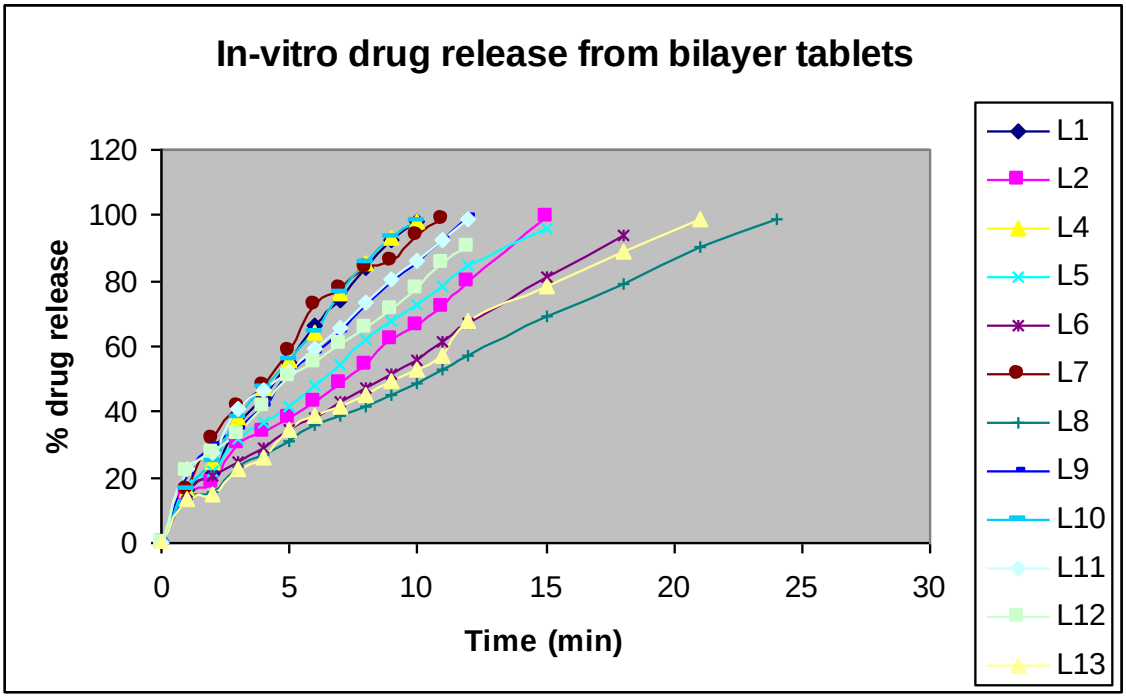

Fig 2: *In vitro* drug release from bilayer tablets of Losartan potassium

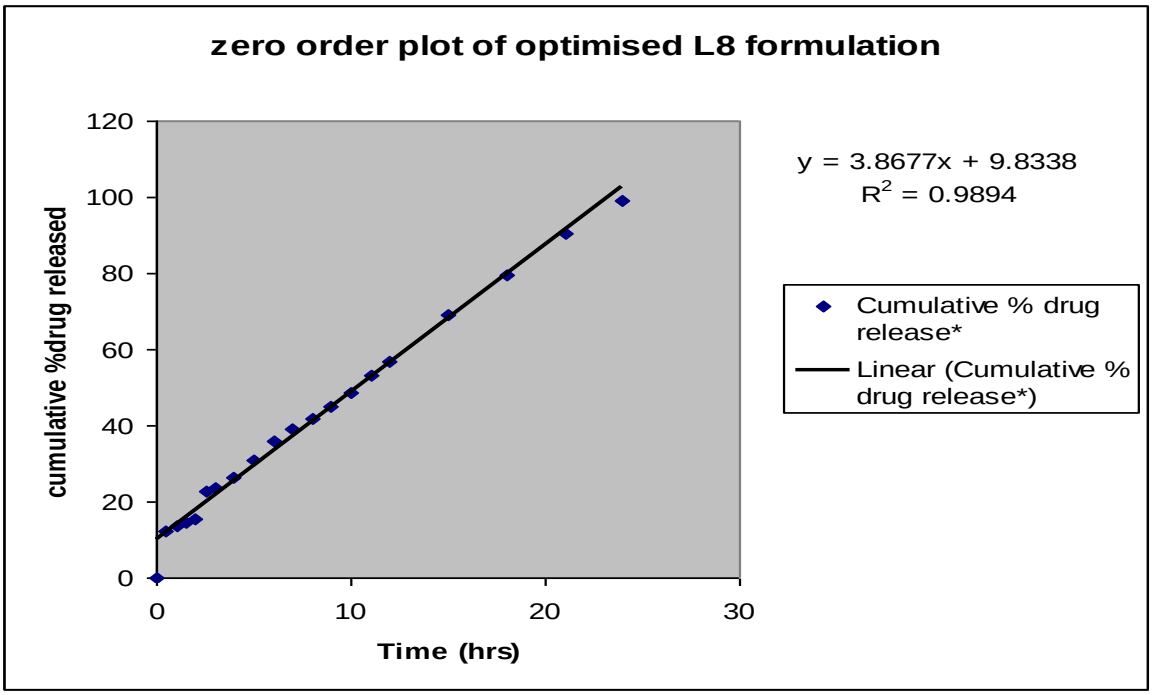

Fig 3: Zero order plots of selected bilayer matrix tablets (L8).

The values of pre-compression parameters evaluated were within prescribed limits [angle of repose17.66 - 30.12o, Carr's index 14.73 - 20.17% and Hausner's ratio of 1.19 - 1.29 (table no.2)] indicated good flow property. IR spectroscopy indicated no drug exepients interaction. Post-compression parameters such as hardness were found to be 5.46 to 7.31 kg/cm2 (table no.3) sufficient enough to withstand the mechanical stress conditions while handling. In all the formulations the friability value is less than 1% and meets the Indian Pharmacopoeial limits. The percentage drug content of all the tablets was found to be almost or nearer to 100% swelling index of matrix tablets were directly proportional to the concentration of the polymer. (Table no.4) Formulation (L8) containing combination of xanthum gum and gum karaya showed better swelling index than that of formulation (L13) containing xanthum gum, gum karaya and HPMC K4M. In vitro drug release from the controlled release layer increased with an increase in the polymer concentration because of increase in the thickness of the gel layer, which retarded drug diffusion out of tablet. Formulation (L8) containing combination of xanthum gum and gum karaya in equal proportions showed the drug release up to 24 hrs (table no.5). Kinetic release studies of optimized formulation L8 showed Zero order release (Table no. 6).

Conclusion

From the observed parameters it was concluded that the formulation (L8) satisfied all the official requirements. The tablets had acceptable hardness of average 5.46 to 7.31 kg/ cm2, 0.20 to 0.35 % friability, Swelling index of 720 and in-vitro drug release of 99.32% respectively. Hence it can be concluded that Xanthum

gum and Gum Karaya combination proved prolonged release of Losartan Potassium upto 24 hrs.

Conflict of Interest: None

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