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Research Article

Formulation and evaluation of gastro-retentive drug delivery system of losartan potassium by using raft-forming approach

Sarkar Rao K*, Gnana Prakash K, Kumar B, Prasad K, Madhavi C, Gobinath M

Ratnam institute of Pharmacy, Pidthapolur, SPSR Nellore District, Andhra Pradesh, India

ABSTRACT

Losartan potassium is angiotensin type-II receptor antagonist, used for the treatment anti hypertension. The purpose of this investigation is to improve bioavailability, gastro residence time and to reduce frequency of administration by preparing a gastro-retentive drug delivery system by using raft-forming technique. Losartan potassium was prepared by direct compression method by using various polymers such as HPMC K4M, xanthan gum and carbopol 971p at various concentrations. Sodium bicarbonate and sodium alginate were incorporated as gas generating agents and foaming agents. Lubricating agent like talc and magnesium stearate, lactose as sweetening agent, and microcrystalline cellulose as binding agent, FTIR spectroscopy study reveals that no interaction between drug and polymers. F1-F12 formulations were developed, and evaluated for thickness, weight variation, friability, drug content, floating time, lag time and in-vitro drug release. The *in-vitro* cumulative % drug release of all formulation ranged from 94.28% to 98.88% at 12hr. the floating time and lag time for the optimized formulation F9 was found to be 20min and 12hrs respectively. *In-vitro* drug released was found to be 98.88% for F9 at the end of 12hrs and which was considered as best formulation**.**

Keywords: Gastro-retentive; losartan potassium; In-vitro drug release; tablet; raft-forming.

INTRODUCTION

Losartan potassium is angiotensin type-II receptor antagonist, used for the treatment anti hypertension. Side effects include hyperkalemia, angioedema and dry cough. Losartan potassium is well absorbed after administration of tablet, with peak plasma concentration occurring within 1.5 hours to 2 hours, the steady state volume of distribution of losartan potassium is 34L or 99.7%, losartan potassium metabolized by cytochrome P450 isoenzymes CYP2C9 and CYP3A4. E-3174 is an active metabolite with 10- to 40-fold higher potency than its parent compound, losartan. Approximately 14% of losartan is converted to E-3174, losartan potassium elimination of urine and about 60% in the feces.

Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastro retentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. That is less soluble in a high pH environment. Also prolonged gastric retention time (GRT) in the stomach could be advantageous for local action in the upper part of the small intestine. Site specific drug delivery to stomach can be achieved increases gastric residence time, better therapeutic effect, increases patient compliance by reducing dosing frequency.

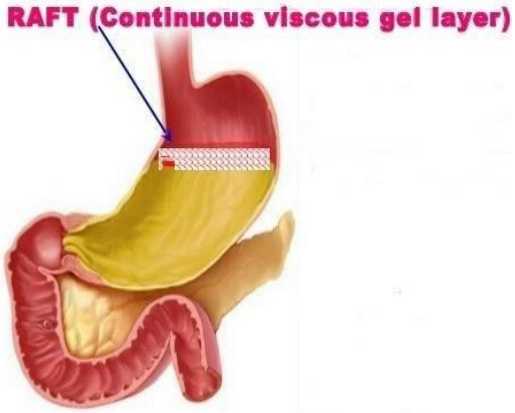

Figure 1: Raft-forming system

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, where in each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of low bulk density created by the formation of CO_2. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO_2 to make the system

* Corresponding Author
Email: sankarkomari312@gmail.com
Contact: +91-8985275719
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less dense and float on the gastric fluids an antacid Raft forming floating system. The system contains gel forming agent (e.g. alginic bicarbonate) sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft) when in contact with gastric fluids. The raft formed floats on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the esophagus by acting as a barrier between the stomach and esophagus figure 1.

MATERIALS AND METHODS

Materials: losartan potassium, HPMC K4M, carbopol 971p, xanthan gum, sodium bicarbonate, sodium aliginate, lactose, MCC, magnesium stearate was gifted by Tini Pharma, Tirupathi, India.

Method

Drug and polymer compatibility studies: The compatibility of the drug in the formulation was confirmed by FTIR spectral analysis. FTIR spectra of losartan potassium and xanthan gum, carbopol 971p, HPMC K4M were determined by using the shimadzu FT-IR 8300 spectrophotometer in the frequency range of 400- 4000 cm-1 with the resolution of 4 cm-1 using potassium bromide dispersion method. By using above mixture of sample there is no incompatibility in the mixtures.

Preparation of losartan potassium tablets

The gastro-retentive drug delivery system of raft-forming approach of losartan potassium tablets were prepared by direct compression method using different polymers. Tablet using tablet compression machine cad Mach machinery, at the weight of each tablet 350mg.

Parameters for evaluation

Pre compression parameter

1. Angle of repose: The angle of repose of powder was determined by the funnel method. The accurately weight powder were taken in funnel, and height (h) of the funnel fixed in tip and above a flat horizontal surface on the paper was placed. Powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of the funnel.

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

Where**, '**θ' is the angle of repose, 'h' is the height of pile; 'r' is radius of the base of the pile

2. Bulk density (Db): It is the ratio of mass of the powder taken to its bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured into graduated measuring cylinder through large funnel and volume was measured (Bourne DW, 2002) which is called initial bulk volume. Bulk density is expressed in gm/cc and is given by,

$$Db = M / Vo$$

Where, 'M' is the Mass of powder, 'Vo' is the Bulk volume of powder

3. Tapped density (DT): Ten grams of powder was introduced into a clean, dry 100ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and tapped volume was read. It is expressed in gm/cc and is given by,

$$DT = M / V_t$$

Where, "M" is the Mass of powder, "V_t" is the Tapped volume of powder.

4. Carr's index (compressibility index): An indirect method of measuring powder flow from bulk densities was developed by Carr. The percentage compressibility of powder was a direct measurement of the potential powder arch or the bridge strength and stability Carr's index of each formulation was calculated according to equation given below:

$$\mathbf{I} = (Dt - Do/Do \times 100$$

Where, 'Dt' is the tapped density, 'Do' is the bulk density

5. Hausner's ratio (H): Hausner's ratio is an index of ease of powder flow; it is calculated by the following formula.

$$\text{Harsner's ratio} = tapped\ density / bulk\ density$$

Post compression evaluation parameter

1. Thickness: Twenty tablets from the representative sample were randomly taken and individual tablet thickness was measured by using digital Vernier caliper. Average thickness was calculated. (Deppika k et al., 2014)

2. Hardness: Tablet hardness was measured by using Monsanto hardness tester. Measured the pressure required to break diametrically placed tablet, by a coiled spring. (Deppika k et al., 2014)

3. Weight variation: Twenty tablets were selected randomly form each formulation ,weight individually using a digital balance and determined averages weight .the individual weight compared to averages weight for the weight variation. (Deppika k et al., 2014)

4. Friability: Form each formulation, the friability of tablet using 20tablets were measured using a Roche friabilator. Apparatus was operated for 100 rotations at 25rpm .the tablets take out, degusted and re-weighted. The % friability was calculated by,

%F= (W initial) – (W final) / (W initial) ×100

5. Drug content: Form each formulation, ten tablets were weighed and crushed powder are equivalent weight of tablet dosage form taken dissolved in 100ml volumetric flask containing 0.1N HCL solution by using

Table 1: Development of various tablet formulation

INGREDIENT	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Losartan potassium	50	50	50	50	50	50	50	50	50	50	50	50
HPMC K4M	50	100	150	100	_	_	_	_	_	_	_	-
Carbopal971p	_	_	_	_	50	100	150	100	_	_	_	_
Xanthan gum	_	_	_	_	_	_	_	_	50	100	150	100
Sodium bicarbonate	40	40	40	50	40	40	40	50	40	40	40	50
Sodium alginate	60	60	60	80	60	60	60	80	60	60	60	80
MCC	73.5	48.5	23.5	33.5	73.5	48.5	23.5	33.5	73.5	48.5	23.5	33.5
Lactose	73	48	23	37	73	48	23	37	73	48	23	37
Magnesium stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Total weight	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**

Table 2: pre-compression parameter of losartan potassium

Formula Code	Bulk density(g/cc)	Tapped density(g/cc)	Hausner's ratio	Compressibility index (%)	Angle of repose (θ)
F1	0.41±0.02	0.44±0.02	1.06±0.03	16.06±0.02	33.69±0.05
F2	0.43±0.03	0.50±0.01	1.14±0.02	12.50±0.02	34.21±0.04
F3	0.45±0.01	0.56±0.02	1.24±0.01	19.35±0.01	34.00±0.02
F4	0.46±0.02	0.53±0.03	1.15±0.03	13.33±0.03	36.60±0.02
F5	0.48±0.03	0.58±0.04	1.21±0.02	17.85±0.02	34.01±0.04
F6	0.45±0.02	0.56±0.03	1.25±0.04	20.00±0.01	32.61±0.03
F7	0.45±0.04	0.55±0.01	1.24±0.04	19.35±0.04	35.83±0.03
F8	0.46±0.02	0.55±0.02	1.20±0.02	16.66±0.03	36.60±0.02
F9	0.44±0.03	0.52±0.02	1.19±0.03	16.12±0.02	33.42±0.02
F10	0.45±0.01	0.54±0.03	1.18±0.02	15.78±0.04	34.99±0.04
F11	0.45±0.02	0.52±0.01	1.15±0.02	13.15±0.01	35.09±0.01
F12	0.41±0.04	0.48±0.04	1.16±0.04	14.28±0.02	35.53±0.02

Table 3: Post–compression parameter of losartan potassium

Formula code	Hardness (kg/cm2)	Thickness (mm)	Weight variation(mg)	Friability (%)	Drug content (%)
F1	3.3±0.15	6.21±0.15	351.3±0.40	0.69±0.15	98.89±1.12
F2	3.3±0.11	6.40±0.12	351.4±0.39	0.66±0.12	99.12±1.18
F3	3.4±0.13	6.25±0.12	351.5±0.48	0.64±0.11	97.99±1.16
F4	3.3±0.15	6.25±0.14	351.4±0.50	0.61±0.11	101.21±1.15
F5	3.4±0.12	6.35±0.12	351.6±0.34	0.61±0.13	98.54±1.16
F6	3.4±0.12	6.23±0.13	351.9±0.56	0.52±0.14	98.69±1.19
F7	3.5±0.11	6.21±0.11	351.4±0.28	0.52±0.12	97.87±1.11
F8	3.6±0.13	6.26±0.12	352.0±0.38	0.56±0.13	99.58±1.12
F9	3.3±0.15	6.26±0.14	350.6±0.38	0.52±0.12	101.58±1.15
F10	3.4±0.11	6.29±0.11	352.8±0.33	0.47±0.11	96.74±1.19
F11	3.4±0.13	6.25±0.13	351.5±0.24	0.58±0.13	98.23±1.15
F12	3.3±0.12	6.22±0.13	351.4±0.53	0.47±0.11	97.51±1.16

Table 4: Losartan potassium tablets floating and lag time

Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Floating Time(hr)	9	9	10	10	11	9	9	11	12	11	12	11
Lag Time(min)	10	13	13	14	8	4	6	5	20	18	20	21

Fast-clean ultrasonic cleaner (15min) after sample was filtered what man filter paper no.40. Solution was 1ml pipetted out and added up to 10ml 0.1N HCL. The losartan potassium content was estimated at 280nm using a UV spectrophotometer, using 0.1N hydrochloride as blank.

6. In vitro dissolution study: In vitro drug release rate of losartan potassium was determined using type II Apparatus (paddle type) dissolution test. The dissolution test carried out using 900ml of 0.1N hydrochloride at 37±0.5 ˚C at 50rpm for 14hr. A 5ml of sample was withdrawn from the dissolution apparatus at specified

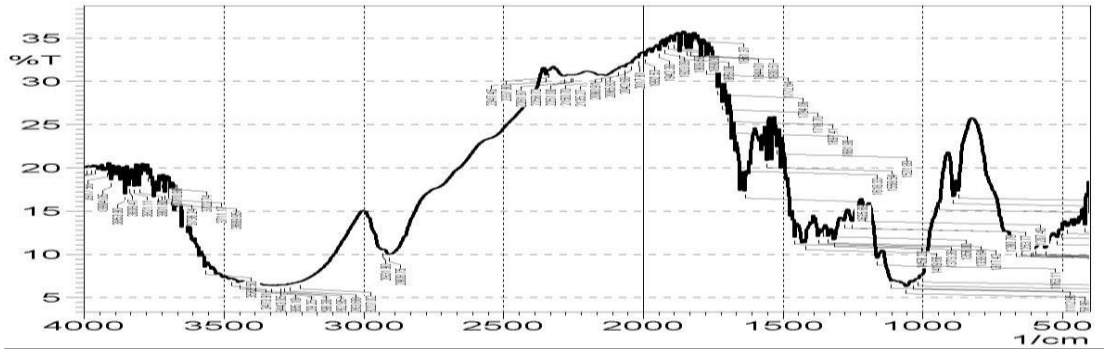

Figure 1: FTIR spectrum of losartan potassium

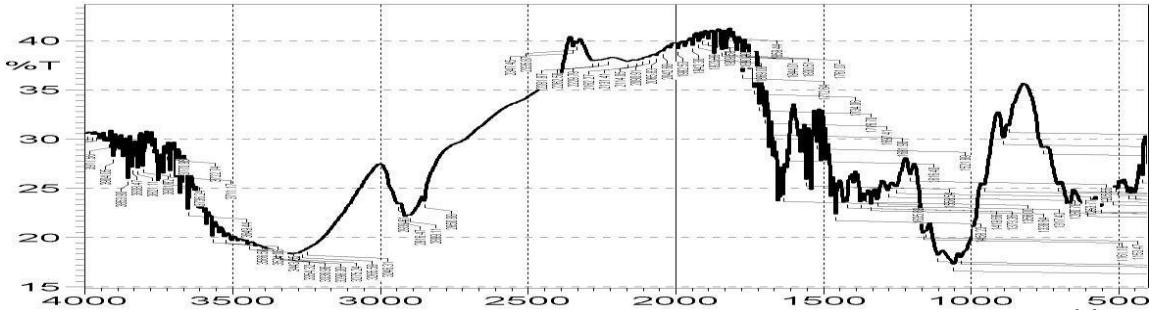

Figure 2: FTIR spectrum of xanthan gum

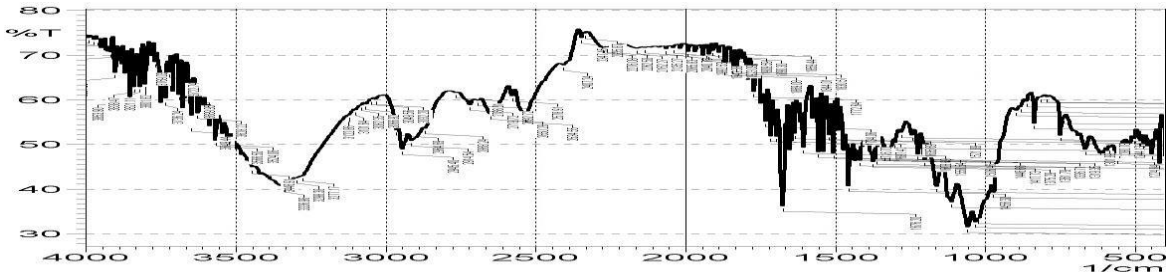

Figure 3: FTIR spectrum of Carbopol 971 p

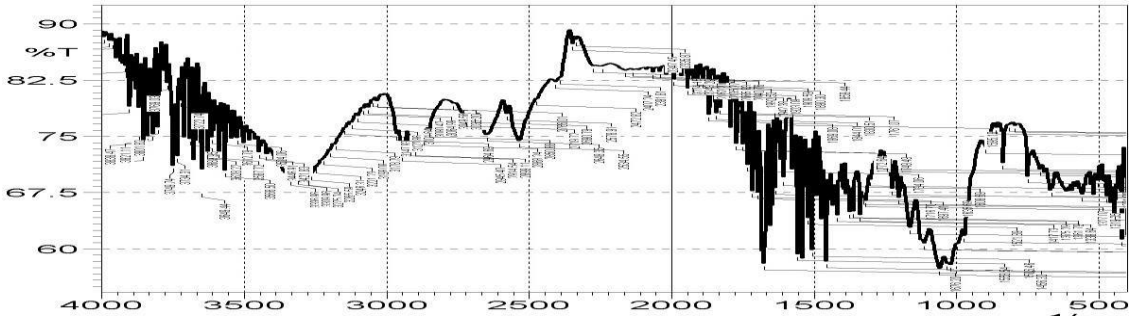

Figure 4: FTIR spectrum of HPMC K4M

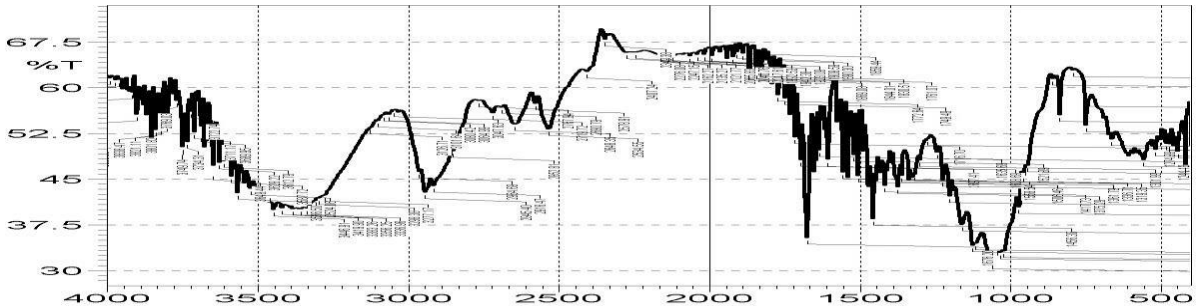

Figure 5: FTIR spectrum of drug+ xanthan gum

Table 5: In vitro cumulative % drug release

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1hr	7.5	6.9	7.2	7.4	6.7	7.1	7.9	8.2	8.8	8.8	8.1	7.9
2hr	15.2	14.1	13.9	15.2	15.9	14.4	13.2	17.4	16.4	15.2	16.4	17.8
3hr	22.8	23.4	23.2	21.9	22.8	24.1	23.2	28.1	25.6	24.2	25.1	24.1
4hr	34.0	30.2	32.2	33.8	30.9	35.8	36.2	39.8	34.5	37.2	33.9	35.8
5hr	42.8	45.4	44.8	41.7	40.0	43.7	42.9	42.4	46.1	44.6	42.5	43.8
6hr	53.0	51.9	52.4	49.6	48.8	50.1	51.2	54.0	58.8	52.0	55.1	50.0
7hr	60.9	59.2	59.8	54.6	57.8	58.8	60.0	61.2	64.0	59.0	62.3	59.4
8hr	69.1	68.0	67.5	62.1	65.5	64.3	68.9	68.4	70.2	67.4	69.4	68.6
9hr	74.6	75.6	74.8	71.2	73.4	72.8	70.8	75.8	78.4	75.0	74.0	74.2
10hr	76.8	81.4	81.0	80.0	79.8	80.4	78.6	81.0	83.5	81.2	82.0	79.9
11hr	82.4	90.8	86.8	88.4	84.6	87.5	86.1	87.8	90.2	88.8	89.7	87.6
12hr	94.2	98.5	95.7	95.6	92.8	94.3	96.8	95.1	98.8	96.2	97.8	95.5

Table 6: In-vitro and Kinetic data of F9

Cumulative % Drug Release Plot		Higuchi's Plot		Peppa's Plot		First Order Plot	
Time in hours	**Cumulative % Drug Release**	**Sq.root of time**	**Cumulative % Drug Release**	**Log time**	**Log Cumulative % Drug Release**	**Time in hours**	**Log Cumulative % Drug Release**
1	8.82	1.00	8.82	0.00	0.95	1	1.96
2	16.44	1.41	16.44	0.30	1.22	2	1.92
3	25.65	1.73	25.65	0.48	1.41	3	1.87
4	34.52	2.00	34.52	0.60	1.54	4	1.82
5	46.14	2.24	46.14	0.70	1.66	5	1.73
6	58.80	2.45	58.80	0.78	1.77	6	1.61
7	64.02	2.65	64.02	0.85	1.81	7	1.56
8	70.25	2.83	70.25	0.90	1.85	8	1.47
9	78.45	3.00	78.45	0.95	1.89	9	1.33
10	83.54	3.16	83.54	1.00	1.92	10	1.22
11	90.24	3.32	90.24	1.04	1.96	11	0.99
12	98.89	3.46	98.89	1.08	2.00	12	0.05

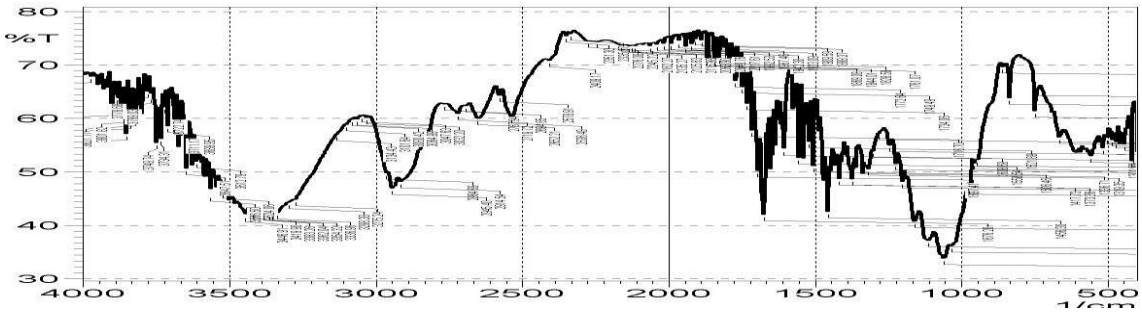

Figure 6: FTIR spectrum of drug+ carbopol 971p

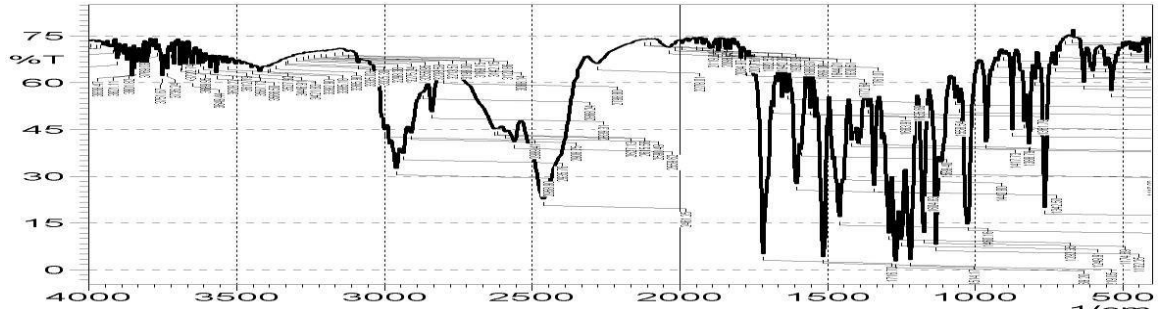

Figure 7: FTIR spectrum of drug +HPMC K4M

Table 7: Comparison of dissolution profile of F9 and market product

Time (H)	Market product (Alsartan 50mg)	Optimized formulationF9
1	8.6	8.8
2	15.1	16.4
3	23.6	25.6
4	33.4	34.5
5	42.1	46.1
6	50.9	58.8
7	59.9	64.0
8	65.0	70.0
9	72.1	78.4
10	79.8	83.5
11	86.8	90.2
12	97.9	98.8

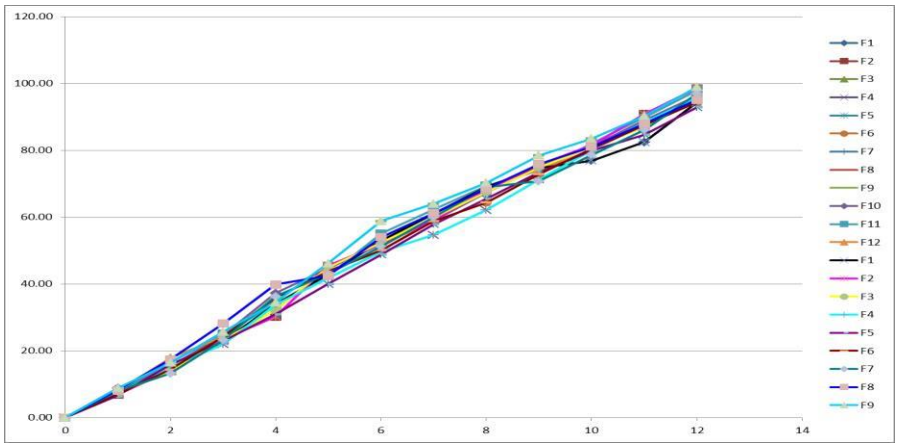

Figure 8: In-vitro dissolution profile of all formulations

Table 8: stability studies of drug content of optimized formulation F9

Time in month	Drug content	
	25±2°C/60%	40±2°C/75%RH
initial	101.58	101.26
1	99.23	99.14
2	97.55	97.36
3	95.78	95.52

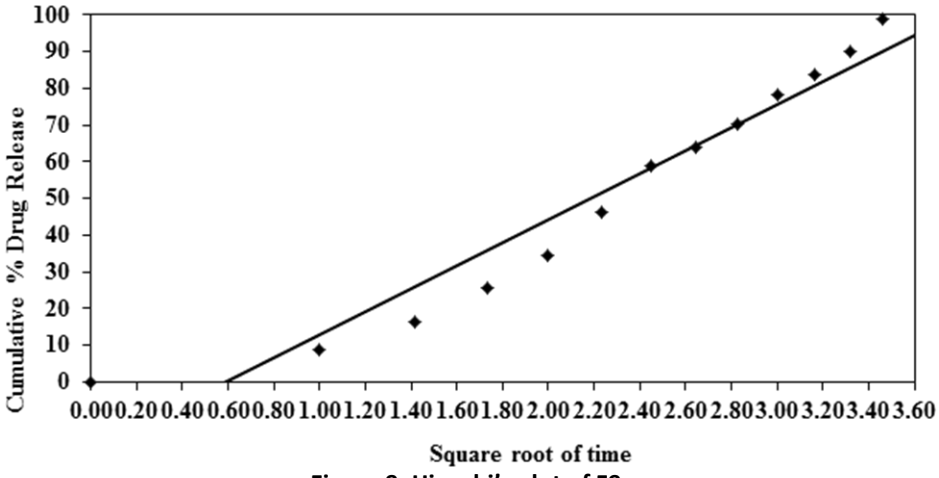

Figure 9: Higuchi's plot of F9

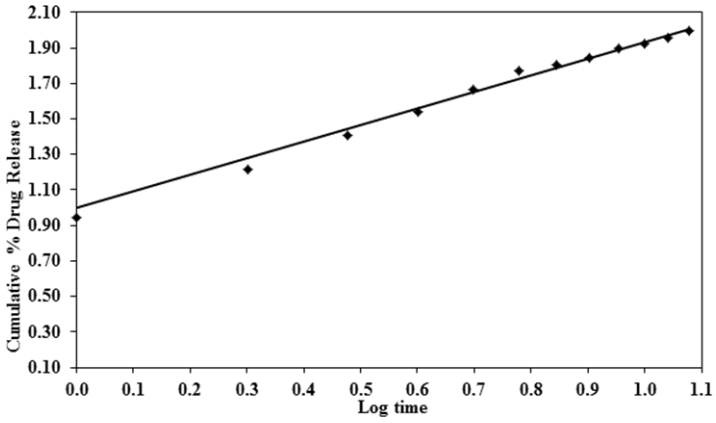

Figure 10: Peppa's plot of F9

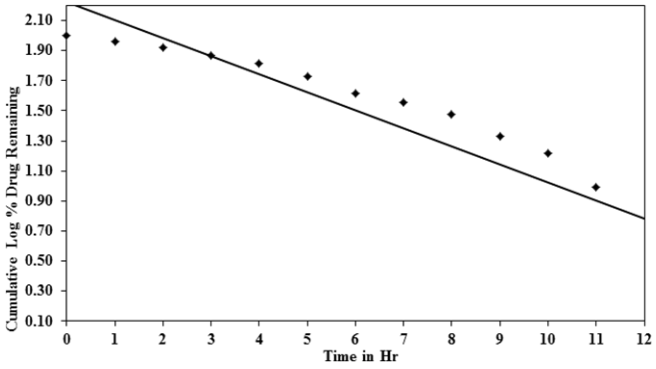

Figure 11: First order plot of F9

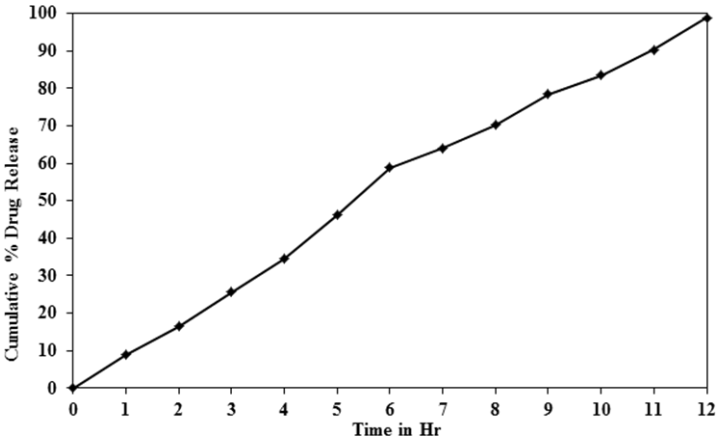

Figure 12: cumulative % drug release of F9

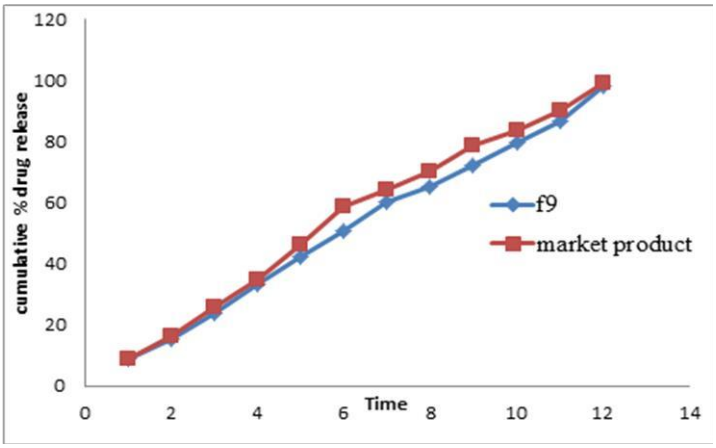

Figure 13: comparison study of F9 and market product graph

time point and sample was replaced with fresh medium. The sample was filtered with Whitman filter paper No 40. The dissolution media at different time intervals at 2, 4, 6, 8 , 10,12 and 14 hours and absorbance of solution were measured at 280nm using UV – spectrophotometer. It is used blank 0.1N hydrochloride.

7. Stability study: The selected formulations were packed in their final containers and are tightly closed with cap. They were stored at three months. Samples were analyzed for drug content at the end 1st, 2nd and 3rd months.

8. Drug release kinetics: kinetics studies were conducted for F1-F12 formulations. Zero order, fast order, higuchi, and korsmeyer-peppas were plotted for all formulation, based on the regression coefficient values obtained kinetics of all formulations were studied.

DISCUSSION

Drug and polymer compatibility studies: compatibility of losartan potassium and polymers was determined by FTIR spectroscopy. FTIR spectra are shown in figures 2-8 respectively.

In vitro drug release studies: The in-vitro dissolution study of losartan potassium tablet is tested by using 0.1N HCL dissolution medium. F1-F12 formulation cumulative % drug release range 94.2% to 98.8%. Among all the formulations F9 has shown maximum drug release. So the raft-forming technique for losartan potassium tablets with xanthan gum may fulfill our objective.

Drug content: percentage drug content of losartan potassium tablets all formulations were determined by UV-spectrophotometric method. The drug content values for all the formulation in the range of 96.74% to 101.58%.

Stability studies: The optimized formulation was subjected to the different temperature and different humidity conditions up to three month and analysis the every one month condition for drug content release studies shown in table no.6

CONCLUSION

In the present study was to develop and evaluation losartan potassium tablets to give improve the bioavailability and patient compliance. Pre-formulation study was carried out for powder and evaluated for bulk density, tapped density, carr's index and hausner's ratio and angle of repose. All the formulations have shown good flow properties. There was no interaction between drug and polymers, this indicates both drug and polymers were compatible. Losartan potassium tablets were prepared direct compression method. Formulated tablets gave satisfactory results for various physicochemical evaluation parameter like hardness, thickness, friability and weight variation, drug content, all the formulation were found within the permissible range. Then tablets were evaluated for *in-vitro* dissolution studies. Among the all formulations F1-F12, an optimized batch F9 shows good *In-vitro* drug release characteristics, lag time and floating time. It was concluded that F9 was considered as best formulation which may fulfill the objectives.

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