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FORMULATION AND IN-VITRO EVALUATION OF BILAYER TABLET OF LOSARTAN POTASSIUM AND *TRIGONELLA FOENUM GRAECUM* FOR THE TREATMENT OF HYPERTENSION

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ABSTRACT

Aim of the study was to formulate and evaluate Bilayer tablet of Losartan potassium and *Trigonella foenum graecum* for the treatment of Hypertension. By utilizing the concept of bilayer tablet system an attempt was made to improve bioavailability, reduced dosing frequency and to get maximum therapeutic benefits and patient compliance. Bilayer tablet were prepared by direct compression technique. The bilayer tablets consist of two layers one is immediate release (IR) and other is sustained release layer (SR). The I.R release layer of losartan potassium was developed for sudden onset of action using microcrystalline cellulose, cross carmellose sodium and sustained release layer of *Trigonella foenum graecum* was developed using polymers HPMC-K4M and carbopol 940-P in the ratio of 1:1 gave an initial burst effect and followed by sustained release of drug. Based on in-vitro release studies formulations were optimized. The Optimized formulation F4 showed 93.2% release of losartan potassium and 92.45 % release of *Trigonella foenum graecum* respectively. Drug content was found to be 98.2% of losartan potassium and 96.22 of *Trigonella foenum graecum* respectively. The *in-vitro* studies concluded that the immediate layer releases Losartan potassium within 30 minutes and sustained release layer was capable to retard the release of *Trigonella foenum graecum* for 12 hours.

Keywords: Losartan potassium, *Trigonella foenum graecum*, bilayer tablet, matrix tablet, HPMC, carbopol

INTRODUCTION

Oral drug delivery has been used as most widely utilized route of administration among all the route for the systemic delivery of drug via various pharmaceutical product of different dosage form. The real issue in the development of oral drug delivery systems is to prolong the residence time of the dosage form in the stomach or upper gastrointestinal tract until the drug is completely released and absorbed [1]. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules [2].

Oral drug delivery systems (DDS) are comprises of two systems: immediate release and modified release systems. Immediate release DDS are intended to disintegrate rapidly, and exhibit instant drug release [3]. Controlled/sustained release preparations delayed the drug release using various approaches and alternating routes but oral route is still more preferable one [4]. Bilayer tablets are the tablets which are made by compressing the two different layers, one on top of another. Each layer comes from a separate feed frame with individual weight control. Rotary tablet presses can be set up for two or three layers. Ideally, a slight compression of each layer and individual layer ejection permits weight checking for control purposes [5, 6].

Hypertension is a disorder in which force exerted by the blood against the walls of blood vessels, and the magnitude of this force depends on the cardiac output and the resistance of the blood vessels. Hypertension also known as high blood pressure (HBP), is a long term medical condition in which the blood pressure in the arteries is persistently elevated[7]**.** Losartan potassium is a non-peptide molecule and its empirical formula is $C_{22}H_{23}ClKN_6O$. Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland) [8, 9]. ***Trigonella foenum-graecum*** (Fenugreek) seeds which belong to Fabaceae family showed antihypertensive activities . It is reported that the antihypertensive action is mediated through serotonergic antagonistic property via 5 HT_2 receptor [10], reduce systolic blood pressure [11] and showed diuretic activity by increasing the levels of Na+/K+ ions ratio [12].

By considering the above factors, an attempt has been made to formulate and evaluate Bilayer tablet of Losartan potassium and *Trigonella foenum graecum* for the treatment of Hypertension to improve bioavailability, reduced dosing

frequency and to get maximum therapeutic benefits and patient compliance.

MATERIAL AND METHODS:

Material used: The authentified extract of ***Trigonella foenum-graecum*** (Fenugreek) was purchased from Sri Herbasia Biotech, Amritsar, India. Losartan potassium, was a gift sample from Meridian Pharmaceuticals, Solan, Hydroxypropyl methyl cellulose K4M was purchased from Central Drug House Pvt. Ltd., New Delhi, India, Carbopol 940P was from Qualikems fine chemicals Pvt. Ltd., New Delhi and drug excipients, chemicals such as Polyvinyl pyrrolidone K-30, Micro Crystalline Cellulose, Talc, Magnesium stearate, Lactose, Cross carmellose sodium were purchased from S. D. Fine Chemicals Ltd., Mumbai, India.

PREFORMULATION STUDIES

Determination of λmax: Stock solution (1000µg/ml) of losartan potassium and *Trigonella foenum graecum* was prepared in 0.1N HCl and pH 6.8 (phosphate buffer). This solution was apparently diluted with same solvent to obtain concentration of 100 µg/ml. The resultant solution was scanned in the range of 200-400 nm on double beam UV-spectrophotometer. The resultant was plotted on chart.

Solubility: The solubility of both the drugs in various solvents was measured. Solubility was determined by taking 10 mg of drug sample in 10 ml of solvent as Acetone, Methanol, Ethanol, pH buffer 6.8 in small test tubes and well solubilized by shaking. The solution was taken and filtered through Whatman filter paper. The filtrate was solubilized in suitable solvent, diluted with the pH 6.8 buffer and the concentration of drug extracts were determined using UV-Visible spectrophotometer at suitable wavelength.

Formulation of Bilayer tablets of Losartan potassium and *Trigonella foenum graecum* [13]: The bilayer tablets of Losartan potassium and *Trigonella foenum graecum* were formulated by Direct Compression Technique. The bilayered tablets consist of two layers one is immediate release (IR) and other is Controlled release layer (CR). The drug and polymers for both IR and CR layer were passed through a # 60 sieve before their use in the formulation. The composition is shown in table 1.

Compression of Bilayer Tablets: The sustain release blend of *Trigonella foenum graecum* (750 mg) was compressed lightly using single punch tablet machine equipped with 12mm circular, flat and plain punches. Over this compressed layer, the immediate release layer of Losartan Potassium (200mg) was placed and compressed to form a bi-layered matrix tablet of 950 mg. The composition is shown in table 2.

Table 1: Composition of immediate layer of bilayer tablet

Formulation code	Losartan potassium (mg)	Microcrystalline cellulose (mg)	Cross carmellose sodium (mg)	Magnesium stearate (mg)
F1	50	130	8	12
F2	50	130	12	8
F3	50	130	10	12
F4	50	130	16	4
F5	50	130	14	10

Table 2: Composition of varying proportions of polymers for Sustain Release layer

Formulation code	*Trigonella graecum* (mg)	HPMC (mg)	Carbopol (mg)	Poly vinyl pyrrolidone (mg)	Lactose (mg)	Talc (mg)	Magnesium stearate (mg)
F1	400	200	50	50	30	10	10
F2	400	175	75	50	30	10	10
F3	400	150	100	50	30	10	10
F4	400	125	125	50	30	10	10
F5	400	100	150	50	30	10	10

Figure 1: Formulated Bilayer tablet

Evaluation of tablet [14]

Pre-compression studies: The flow properties of granules (before compression) of both the layers were characterized in terms of bulk density, tapped density, Carr's index, Hausner ratio and Angle of repose.

Bulk Density: It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume was called the bulk volume. From this the bulk density was calculated according to the formula mentioned below. It is expressed in gm/ml and is given by

Bulk density= M/ V

Where, M and V are mass of powder and bulk volume of the powder respectively

Tapped Density: It is the ratio of total mass of the powder to the tapped volume of the powder. A known quantity of granules was taken in a measuring cylinder and tapped on mechanical tapping apparatus for 5 mins. The initial and final volumes were noted. It is expressed in gm/ml and is given by

Tapped density = M/V

Where, M and V are mass of powder and tapped volume of the powder respectively

Hausner's Ratio: Hausner's Ratio is an ease of index of powder flow. It is calculated by using the following formula:

Hausner's Ratio = Tapped Density/ Bulk Density

Angle of Repose: The frictional forces in a loose powder or granules can be measured by angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The value of angle of repose are calculated by using the following formula,

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

Where, θ = Angle of repose, h = height of the heap, r = radius of the heap

Compressibility index: The compressibility index and the closely related Hausner ratio have become the simple, fast and popular methods of predicting granules flow characteristics. The compressibility index and Hausner ratio were determined by measuring both the Bulk density and tapped density of granules.

Compressibility index = Tapped density − Bulk density/ Tapped density X 100

Post compression evaluation of Tablets: The prepared bilayer tablets were evaluated forquality control tests like weight variation, hardness, thickness, friability and content uniformity [14].

General appearance: The general appearance of all tablets, its visual identity and overall elegance is essential for consumer acceptance. The formulated tablets were evaluated for size, shape, organoleptic characters such as, color, odor and taste.

Thickness: The dimensions of the tablet like thickness, length were measured using Vernier-calipers. Ten tablets were selected randomly for this test and the average value was reported.

Weight Variation: The weight variation test was run by weighing 20 tablets individually and compared individual weight to average weight. The tablets meet the USP test, if no more than two tablets are outside the percentage limit and if no tablet differs by more than 2 time the percentage limit.

Hardness of tablet: Hardness of tablet was determined by Monsanto hardness tester. 6 tablets were randomly selected from each formulation and the pressure at which each tablet crushed was recorded.

Friability test: The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (W_0 initial) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The % friability was then calculated by

Percentage friability = $\frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100$

Drug Content Uniformity: Ten tablets were finely powdered and an amount equivalent to 100 mg was accurately weighed and transferred to a 100 ml volumetric flask, then phosphate buffer of pH 6.8 was added. The flask was shaken for 10 minutes. Finally, the volume was made up to the mark with the same buffer solution. The resultant solution was then filtered through Whatman filter paper (No.41) and 1 ml of the filtrate was suitably diluted up to 100 ml with same buffer solution and analyzed for losartan potassium content at 213.5 nm and *Trigonella foenum graecum* at 223.3 nm using a double beam UV/Visible spectrophotometer (Shimadzu 1800, Japan) and phosphate buffer of pH 6.8 as blank.

Swelling Index: Measurement of the swelling index was carried out to gain an insight into the phenomenon of polymer hydration and to evaluate the extent of media penetration within the tablets. The swelling index was determined by equilibrium weight gain method. The tablets were accurately weighed, placed in dissolution basket, immersed in HCL (for 2 hrs.) and phosphate buffer (pH 6.8) and maintained at 37±0.50C in the dissolution vessel. At regular intervals of 2, 4, 6, 8, 10 up to 24 hrs. The weighted basket matrix system was withdrawn from the dissolution vessel, lightly blotted with the tissue paper to remove excess test liquid and re-weighed. The swelling index (SI) of each tablet was calculated according to the following equation.

S.I. = {(Wt-W0) / W0} ×100

Where- W0 = initial weight, Wt. = final weight

Disintegration studies: Disintegration test is a method to evaluate the rate of disintegration of tablets. It is also defined as break down of solid dosage form into smaller particles when it is disintegrated. Place 1 tablet in each of the 6 tubes and added a disc to each tube. Maintain the temperature of the disintegration media at 37±2ºC as specified in the monographs. At the end of time limit specified, left the basket from fluid and observe the tablets. If 1 or 2 tablets fail to disintegrate completely repeat the test on 12 additional tablets. Not less than 16 out of 18 tablets tested disintegrate completely.

***In-Vitro* Dissolution Studies:** Dissolution studies of formulation was carried out using USP type 2 dissolution apparatus for 24 hours in 900 ml of simulated pH1.2 for the first 2 h and then in phosphate buffer (pH 6.8) from 3 to 24h at 100 rpm maintaining the temperature at 37 ± 0.5°C. Samples of 5ml of each was collected over a period of 24h. The withdrawn sample was immediately replaced by equal volume of fresh medium. Collected samples were analyzed spectrophotometrically on a UV-

Vis spectrophotometer (Systronic Double beam) at measured wavelength of Losartan potassium and *Trigonella foenum graecum*, and cumulative percent drug release was calculated. A plot of cumulative % drug release versus time in hours was plotted.

Kinetic Modeling of Drug Release [15] The dissolution profile of all the batches was fitted to Zero order, first-order, Higuchi, Korsemeyer Peppas to ascertain the kinetic modeling of drug release.

RESULT AND DISCUSSION:

Preformulation study: Standard plot of Losartan Potassium was prepared in 0.1N HCl and phosphate buffer pH 6.8 at λmax 205 nm and 213.5 nm. Standard plot of *Trigonella foenum graecum* extract was prepared in 0.1N HCl and phosphate buffer pH 6.8 at λ_{max} 223.5nm and 223.3 nm. The results are shown in figure 2 and figure 3. The solubility studies of Losartan Potassium and *Trigonella foenum graecum* extracts was studied. It was found that the solubility of both the drug was highest in Distilled water as compared to other solvents. Solubility of Losartan Potassium and Trigonella foenum graecum drug extracts were found to be 970±0.3µg/ml & 330.67±0.5 µg/ml respectively in distilled water as shown in table 3.

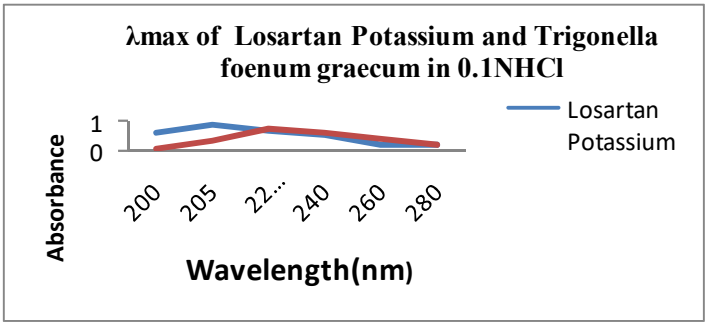

Figure 2: Maximum wavelength of Losartan Potassium and *Trigonella foenum graecum* in 0.1N

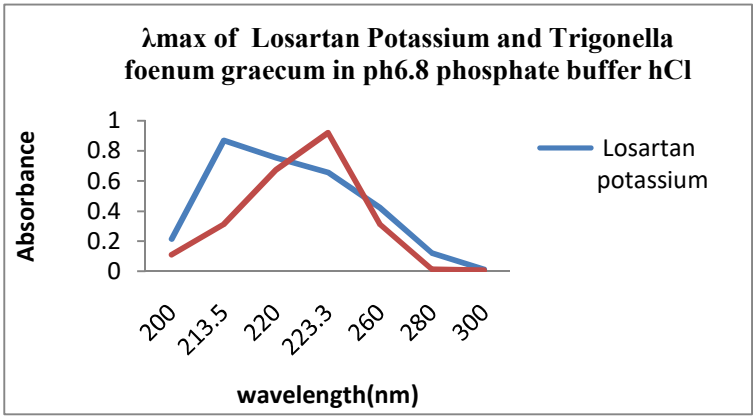

Figure 3: Maximum wavelength of Losartan Potassium and *Trigonella foenum graecum* in pH6.8 phosphate buffer

Table 3: Solubility of Losartan Potassium and *Trigonella foenum graecum* in different

Sr. No.	Solution	Solubility(µg/ml)	
		Losartan Potassium	Trigonella foenum graecum
1	Distilled water	970±0.3	330.67±0.5
2	HCl	457±0.02	326.56±0.6
3	Ethanol	617±0.5	166.22±0.09
4	Phosphate Buffer	934±0.4	211.56±0.2
5	Methanol	458±0.1	158±0.7

Evaluation of pre compressional blend:

Angle of repose was determined by fixed funnel method. Angle of repose was found to be in range of 23.56º - 28.34º for different powder blend batches, which indicates good to passable powder flow as shown in table 4. Bulk and tapped density was found to be 0.680-0.751 gm/ml and 0.731 -0.932 gm/ml respectively (Table 4). This shows good repacking ability of powder blend. The Carr's index of the ingredients was found to be in the range of 16.00- 18.72% and Hauser's ratio in the range of 1.18- 1.23 as shown in table. These findings concluded that the composition of ingredients for compression possess good compression property and good flow property.

Table 4: Evaluation of pre compressional powder blend of immediate release layer of Losartan Potassium:

Formulations	Angle of repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's Index (%)	Hausner' Ratio
F1	26.24º±0.22	0.690±0.014	0.840±0.001	17.85±0.014	1.21±0.06
F2	28.34º±0.19	0.742±0.001	0.913±0.002	18.72±0.001	1.23±0.01
F3	25.88º±0.59	0.680±0.01	0.821±0.001	17.17±0.01	1.20±0.02
F4	23.56º±0.29	0.751±0.001	0.893±0.001	16.00±0.22	1.18±0.01
F5	27.52º±0.48	0.702±0.002	0.862±0.002	18.56±0.001	1.22±0.03

All values are expressed as mean± standard deviation, n=10

Table 5: Evaluation of physical properties of powder blend of Sustain release layer of Trigonella foenum graecum:

Formulations	Angle of repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's Index (%)	Hausner' Ratio
F1	30.12º ±1.04	0.435±0.0202	0.546±0.0434	20.32±0.02	1.25±0.02
F2	29.12º ±1.42	0.449±0.002	0.623±0.002	27.92±0.001	1.38±0.01
F3	30.42º ±1.04	0.468±0.0226	0.592±0.0346	20.94±0.02	1.26±0.2
F4	26.51º±0.78	0.440±0.0134	0.528±0.0254	16.66±0.02	1.20±0.02
F5	28.14º±0.29	0.484±0.001	0.671±0.002	27.86±0.001	1.38±0.03

All values are expressed as mean± standard deviation, n=10

Evaluation of Post-compression parameter:

All values are expressed as mean ± standard deviation. The thickness and diameter of tablets was measured by Vernier calipers and was ranged between 8.22 to 8.56 mm. The hardness of the tablets was measured by Monsanto tester and was in between 14.10 to 14.30 kg/cm2. The friability was measured by Friabilator and was found to be 0.321 to 0.527%, which is an indication of satisfactory mechanical resistance of the tablets. The drug content estimations showed values in the range of 61.32 to 98.20 % which reflects good uniformity in drug content

among different formulations. All the tablets passed weight variation test as the % weight variation was within the Pharmacopoeial limits of ±5% of the weight. All the formulations showed values within the prescribed limits for tests like hardness, friability and weight variation which indicate that the prepared tablets are of standard quality as shown in table 6.

Table 6: Evaluation of physical properties of Bilayer tablet:

Formulation	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Avg wt. (mg)	Swelling index	Drug content (%)	
						Losartan potassium	Trigonella graecum
F1	14.30±0.20	8.22	0.527	1000	89.54	70.80	62.75
F2	14.20±0.50	8.40	0.321	940	91.35	61.32	59.86
F3	14.30±0.50	8.56	0.323	970	95.16	83.5	86.43
F4	14.10±0.50	8.35	0.345	950	97.02	98.2	96.22
F5	14.20±0.20	8.40	0.321	1010	94.63	53.65	50.45

All values are expressed as mean ± standard deviation

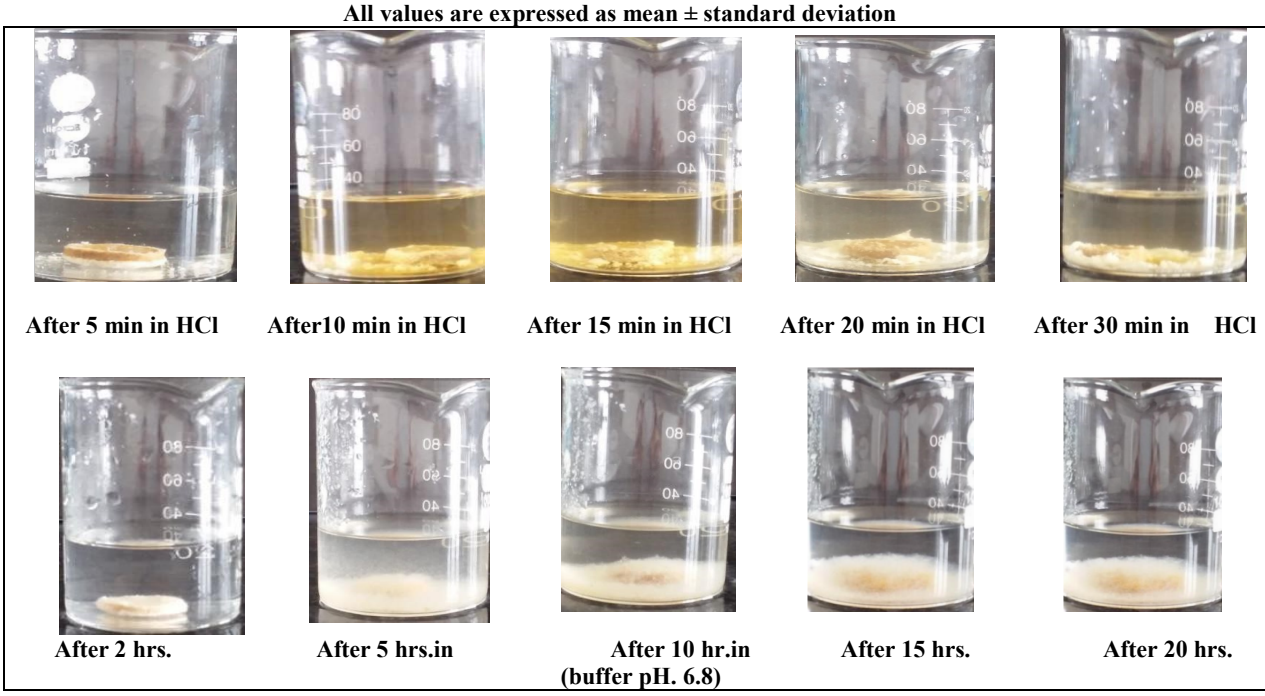

Figure 8: Swelling index of bilayer tablet

Kinetics of swelling is important because the gel barrier is formed with water penetration. The swelling index of matrix tablets of F4 is shown in table 6. Tablets containing equal concentration of Carbopol 940P and HPMC showed constant increasing in swelling index up to 12 hours. Tablet containing more concentration of HPMC resulted in a higher swelling index. The reason for this appeared to be its high viscosity and high water retention property. Initially tablet remained intact for 12 hr. With respect to time swelling index of the tablet increased. Tablet was disintegrated within 20 hrs. The highest release was found to be 93.20 % of Losartan potassium in case of formulation F4 can be detected by performing dissolution studies for 19 hours. F4 showed better release rate in comparison to other 4 different formulations as shown table 7.

Time (min)	% CDR of Immediate release layer of Losartan potassium				
	F1	F2	F3	F4	F5
5	7.89	19.04	29.13	22.5	31.40
10	19.86	24.22	41.66	50.1	36.07
15	27.89	34.83	55.90	54.6	46.89
20	36.5	48.50	63.34	77.41	51.52
25	49.9	57.43	71.95	82.4	50.38
30	56.68	67.15	85.53	93.2	63.49

Table 7: % CDR from Immediate release layer of Losartan potassium

Table 8: % CDR from sustained layer of *Trigonella graecum*

Time (min)	% CDR of *Trigonella foenum graecum*				
	F1	F2	F3	F4	F5
5	8.54	9.02	9.38	3.95	6.57
30	12.50	13.42	18.25	9.98	14.51
60	21.30	21.96	23.45	12.18	21.72
120	23.51	27.46	25.01	17.85	29.16
180	29.98	31.45	29.41	22.35	38.36
240	30.89	33.71	35.66	26.75	41.40
300	31.11	35.14	38.89	31.38	43.29
360	31.82	36.41	41.91	35.77	45.74
420	32.43	38.74	45.98	40.66	47.86
480	33.41	40.43	47.33	48.33	49.50
540	33.85	41.52	51.00	55.78	50.46
600	35.24	42.82	52.11	61.53	54.13
660	36.66	44.43	54.55	65.18	54.92
720	37.05	45.37	56.43	70.92	55.28
780	38.48	47.16	63.54	74.78	57.54
840	40.37	48.75	65.21	79.58	59.92
900	42.84	50.65	68.92	83.84	60.75
960	44.71	53.73	72.74	89.63	61.98
1020	47.32	55.59	77.50	91.01	64.72
1080	53.91	57.39	85.22	92.45	66.56

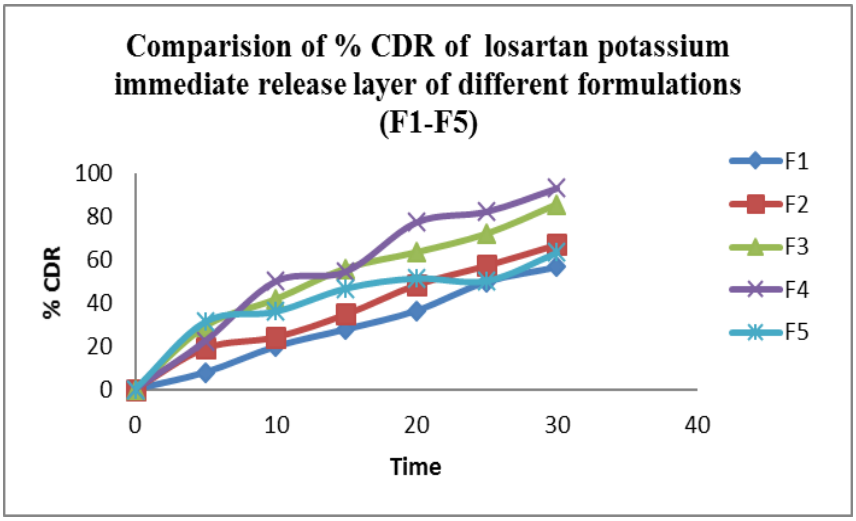

Figure 9: Comparison of % CDR of Immediate Release layer containing Losartan potassium of different formulations (F1-F5)

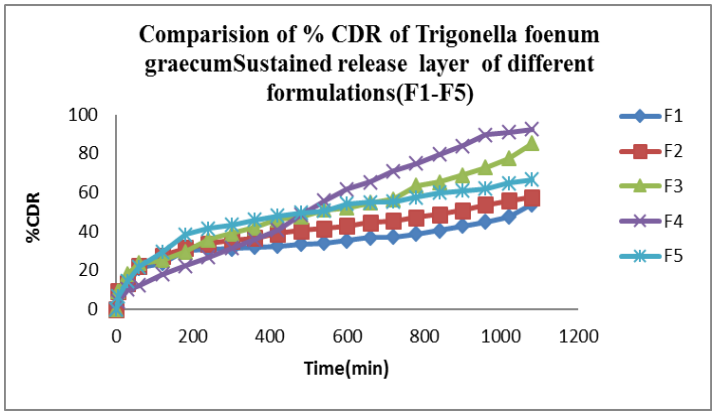

Figure 10: Comparison of % CDR of *Trigonella foenum graecum* Sustained release layer of different formulations (F1-F5)

Regression coefficient of *Trigonella foenum graecum for* zero order release plot was found to be 0.993. Regression coefficient of *Trigonella foenum graecum*for Higuchi Plot was found to be 0.959. Regression coefficient of *Trigonella foenum graecum*for Korsemeyer- Pappas Model was found to be 0.971. The Regression coefficient of zero order release plot of *Trigonella foenum graecum* was found to be highest among all plots thus, the formulation showed zero order release kinetics.

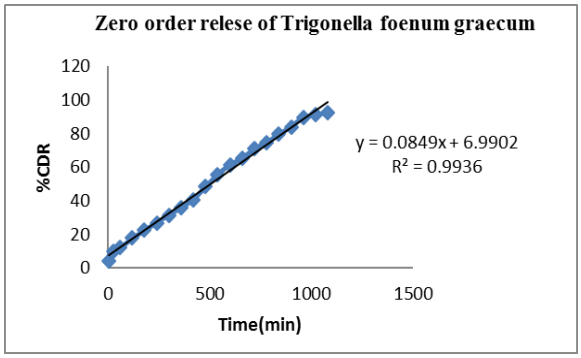

Figure 11: Zero order release of *Trigonella foenum graecum* of F4 formulation

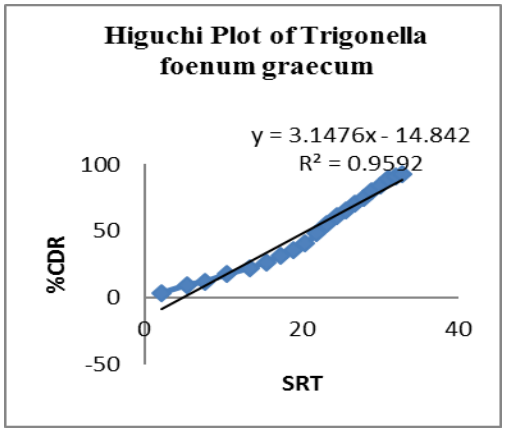

Figure 12: Higuchi Plot of *T. graecum* F4 formulation

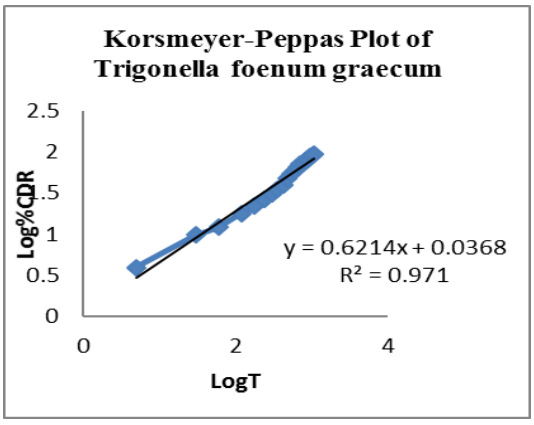

Figure 13: Korsemeyer-Peppas Plot of *T. graecum* of F4 formulation

CONCLUSION:

In the present investigation, controlled release Bilayer tablets of Losartan potassium and *Trigonella foenum graecum* were formulated by Direct Compression technique. Bilayer tablets comprise of IR for sudden onset of action formulated with microcrystalline cellulose, cross carmellose sodium and CR layer formulated with HPMC and Carbopol in order to sustain the drug release. The Pre-compressional parameters for IR, CR layer formulations i.e.; Angle of repose, Bulk density, tapped density, Compressibility index, Hausner's ratio were studied and found to be in satisfactory limits indicating that the Physical mixtures of the formulations are suitable to formulate the Bilayered tablets. The Post-compressional parameters for Bilayered tablets i.e.; Weight variation, Hardness, Friability, Drug content, were evaluated and the results obtained were satisfactory. The *in-vitro* drug dissolution studies were carried out for the formulations in pH 0.1N HCL for 2 hours and in phosphate buffer (pH 6.8) for 19hrs respectively and based on the *in-vitro* drug release profile. The formulation F4 comprising of HPMC and Carbopol sustained the drug release for a period of more than12 hrs. The above found formulations may be suitable for once a day administration. Hence *In-vitro* release profile indicated that there was zero order release of formulation. Further work is required to conduct in-vivo studies which estimate the therapeutic effective dose of drug.

REFERENCE:

[1] Gupta.H et al, Recent Trends in Oral Drug Delivery: A Review, RPDDF, 2009, 3(2), 162 173.

[2] Dandar. M et al, Bilayer tablet: a novel approach for immediate release of Telmisartan and hydrochlorothiazide combination, IJPT, 2012, 4(1), 70 -83.

[3] Kumar. K et al, Development and characterization of sustained release of Metformin and Gliclazide bi-layered tablets, IJBP, 2010, 1(2), 67-71.

[4] Brahhmankar. D.M et al, Biopharmaceutics and Pharmacokinetics, 2nd Edition, Vallabh Prakashan, Delhi, 2009, 399-401.

[5] Bhadange.D.et al, Bi-layer tablet technology-opening new ways in drug delivery system: an overview, WJPR, 2015, 4(1), 529-548.

[6] Panchal.H.et al, A Novel Approach of Bi-layer Tablet Technology- a review IRJP 2012, 3(5), 44-49.

[7] Keith. N et al, Some different types of essential hypertension: their course and prognosis, AJMS, 1939, 1(9), 332–343.

[8] Reddy R et al, Formulation and evaluation of bilayered tablets of losartan potassium, IPP 2014, (1), 312-320.

[9] http//:www.innpharmacotherapy.com

[10] Balaraman. R et al, Antihypertensive effect of *Trigonella foenum-graecum* seeds in experimentally induced hypertension in rats, PB, 2006, 44,568-575.

[11] Talpur. N et al, Effects of a novel formulation of essential oils on glucose-insulin metabolism in diabetic and hypertensive rats: a pilot study, DOM, 2005, 7(2), 193-199.

[12] Rohini.R et al, Diuretic effect of Trigonella Foenum Graecum seed extracts, IJAM, 2009, 6(2), 23-28.

[13] Carla M. Let al, Compressed Matrix Core Tablet as a Quick/Slow Dual-Component Delivery System Containing Ibuprofen, AAPST, 2007, 8(2), 13-20.

[14] Yuvraj.S et al, UV Spectrophotometric method developed for the simultaneous estimation of Amoxicillin trihydrate and Ranitidine bismuth citrate for Helicobacter Pylori infections, 2010, 1(3), 11-16.

[15] Abbaraju P et al, Formulation and Evaluation of Levofloxacin hemihydrates and Ambroxol HCl Bilayer Tablets. AJPCR 2012, 4(2), 273-277.