International Journal of Farmacia

Journal Home page: www.ijfjournal.com

Development, optimization and invitro characterization of Losartan potassium gastroretentive bioadhesive tablets

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ABSTRACT

Losartan bioadhesive tablets were prepared by direct compression method. The tablets were evaluated for pre compression and post compression parameters, swelling studies and in-vitro drug release. The formulation with desired drug release was tested for stability. The formulation F8 was selected as the best formulation, as the release of Losartan from the formulation was found to be zero order kinetics and Korsmeyer-Peppas model. The optimized formulation was found to have good mucoadhesive strength in sheep gastric mucosa and showed drug release up to 12 hours (99.8 %).Therefore, bimodal drug release pattern was successfully achieved through the formulation of bioadhesive tablets in this study. Formulating bioadhesive tablets of losartan increased the bioavailability to 99.8 % with the use of polymer carbopol.

Keywords: Gastro retentive, Bioadhesive, HPMC K4M, Carbopol 974 P, Losartan, zero order kinetics and Korsmeyer-Peppas model.

INTRODUCTION

Historically, oral drug administration has been the predominant route for drug delivery due to the ease of administration, patient convenience and flexibility in formulations [3]. However, it is a well-accepted fact today that drug absorption throughout the GI tract is not uniform. Using currently utilized release technology, oral drug delivery for 12 or even 24 hours is possible for many drugs that are absorbed uniformly from GI tract [5]. Nevertheless this approach is not suitable for a variety of important drugs characterized by narrow absorption window in the upper part of GI tract i.e., stomach and small intestine [1]. The design of oral controlled drug delivery systems (OCDDS) should be primarily aimed to achieve the more predictability and reproducibility to control the drug release [6], drug concentration in the target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose [2].

Controlled release system

Controlled release dosage forms cover a wide range of prolonged action formulations which provide continuous release of their active ingredients at a predetermined rate and predetermined time [7]. The most important objective for the development of these systems is to furnish an extended duration of action and thus assure greater patient compliance [8]. Ideally,

the optimization of therapeutic efficacy and safety may be attained as a result of providing nearly a constant pharmacological response [9], thereby avoiding the normal peak and valley pattern associated with multiple dosing of conventional drug products [4]. To improve the efficacy of oral administration, some recent studies have reported that controlled oral drug delivery system with prolonged gastric residence time [10], such as bioadhesive dosage system have been proved to be advantages. Approaches to gastric retention [11].

1. Floating Systems
2. Bio/Muco-adhesive Systems
3. Swelling and Expanding Systems
4. High Density Systems
5. Incorporation of Passage Delaying Food Agents
6. Ion Exchange Resins
7. Osmotic Regulated Systems

Losartan is a selective, competitive angiotensin II receptor type 1 (AT1) receptor antagonist [12], reducing the end organ responses to angiotensin II. Losartan administration results in a decrease in total peripheral resistance (afterload) and cardiac venous return (preload) [13]. All of the physiological effects of angiotensin II, including release of aldosterone, are antagonized in the presence of losartan [14]. Reduction in blood pressure occurs independently of the status of the renin-angiotensin system [15]. As a result of losartan dosing, plasma renin activity increases due to removal of the angiotensin II feedback [16].

MATERIALS AND METHODS

Losartan USP grade, Lactose monohydrate, Micro crystalline cellulose, HPMC K4M, ethyl cellulose, Carbopol 974 P and Magnesium stearate [17].

Formulation of bioadhesive tablet of Losartan Potassium

The bioadhesive tablets of losartan potassium was prepared by blending the drug with different concentrations of polymers [18], physical mixture was then compressed by direct compression method. Nine formulations were prepared [19].

FTIR studies of losartan with excipients

Infrared spectrum of losartan, excipients was determined by Fourier transform infrared spectrophotometer using KBr pellet method [20].

Table 1: Formulation of Losartan Bioadhesive tablets

Ingredients (mg)	Losartan	Lactose monohydrate	Micro crystalline cellulose	HPMCK4M	Ethyl cellulose	Carbopol	Mg. stearate	Total
F1	25	86.25	86.25	50	-	-	2.5	250
F2	25	61.25	61.25	100	-	-	2.5	250
F3	25	36.25	36.25	150	-	-	2.5	250
F4	25	86.25	86.25	-	50	-	2.5	250
F5	25	61.25	61.25	-	100	-	2.5	250
F6	25	36.25	36.25	-	150	-	2.5	250
F7	25	86.25	86.25	-	-	50	2.5	250
F8	25	61.25	61.25	-	-	100	2.5	250
F9	25	36.25	36.25	-	-	150	2.5	250

Post formulation studies

The tablets of the proposed formulations F1 to F9 were evaluated for hardness by using Monsanto hardness tester [21], weight variation, and thickness by using Vernier calipers, friability by using Roche friabilator and drug content. Losartan tablets should contain not less than 90.0 percent and not more than 110.0 percent [22, 23].

In-vitro drug release studies

The USP II dissolution test apparatus is used. The whole assembly is kept in a jacketed vessel of water maintained at 37± 1^0 C. Bio adhesive tablet is stuck on to the bottom of the flask (so as to allow one sided release from the tablet).The beaker is filled with 900ml of phosphate buffer. The vessel is maintained at 100 rpm under stirring conditions by means of a

paddle fabricated for the purpose in a dissolution apparatus [24, 25]. At various time intervals samples of dissolution medium are withdrawn and filtered through whatman filter paper. It is replaced immediately with an equal amount of fresh buffer. The samples are then analyzed in UV spectrophotometer at 234 nm. Absorbance measured and % drug release is determined.

Swelling studies

The tablets of each formulation were weighed individually (designated as W_1) and placed separately in petri dishes containing 2 % agar gel. At regular intervals of 1, 2, 3, 4, 5, 6, 7 and 8 hours, the tablets were removed from the petri dishes and excess water was removed carefully by using filter paper. The swollen tablets were reweighed (W_2), the swelling index of each formulation was calculated using the formula,

Evaluation of bioadhesive strength

Detachment force measurement

Method

Immediately after slaughter, the intestines was removed from the goat and transported to laboratory in tyrode solution is (g/litre); (sodium chloride 8 gm; potassium chloride 0.2 gm; calcium chloride $2H_2O$ 0.134 gm; sodium bicarbonate 1.0 gm; sodium dihydrogen phosphate 0.05 gm and glucose H_2O 1gm). During this experiment take the intestine in a specified area and place it on one glass slide and tie it. The glass slide with the intestine was affixed on one side floor below the modified physical balance. Already prepared 200 mg plain polymer tablet was pasted in another glass slide and it balanced in the assembled physical balance with a beaker in other side which is used to hold the water. Now the balance was calibrated.

$$Force\ of\ Adhesion\ (N) = Mucoadhesive\ strength \times 9.8/1000$$

$$Bond\ Strength\ (N/m^2) = Force\ of\ Adhesion/Surface\ Area.$$

RESULTS AND DISCUSSION

Pre-formulation studies

The loose bulk density and tapped bulk density of all the batches varied from 0.343±0.030 to 0.446±0.006g/ml and 0.372±0.012 to 0.507±0.010 g/ml. Carr's consolidation index ranged from 4.76±0.001to 13.63±0.005. Results clearly showed that flow- ability of all the formulations is good and has good compressibility (Table 2).

Pre-compression parameters of Losartan tablets blend

Table 3: Pre-compression parameters of Losartan tablets blend F1-F9

F. code	Angle of Repose (^{0})	Bulk Density (gm / ml)	Tapped Density (gm / ml)	Compressbility Index (%)	Hausner Ratio
F1	19.77±1.04	0.394±0.00	0.416±0.01	5.263±3.29	1.055±0.03
F2	20.01±0.87	0.399±0.00	0.446±0.00	10.526±0.42	1.117±0.00
F3	20.54±0.41	0.357±0.02	0.375±0.04	4.761±3.65	1.050±0.04
F4	19.35±1.34	0.375±0.01	0.416±0.01	10.000±0.05	1.111±0.00
F5	22.86±1.13	0.340±0.03	0.394±0.03	13.636±2.62	1.157±0.03
F6	21.53±0.19	0.441±0.03	0.500±0.04	11.764±1.29	1.133±0.01
F7	21.37±0.08	0.416±0.01	0.468±0.02	11.111±0.83	1.125±0.00
F8	22.53±0.73	0.441±0.03	0.500±0.04	11.764±1.29	1.133±0.015
F9	23.32±1.46	0.394±0.00	0.441±0.00	10.526±0.42	1.117±0.00

Standard curve of losartan potassium in 0.1 N HCL

Table 4: Standard curve of Losartan

Concentration (µg/ml)	Absorbance at 234 nm
0	0
10	0.1414
20	0.2968
30	0.4539
40	0.6085
50	0.7686

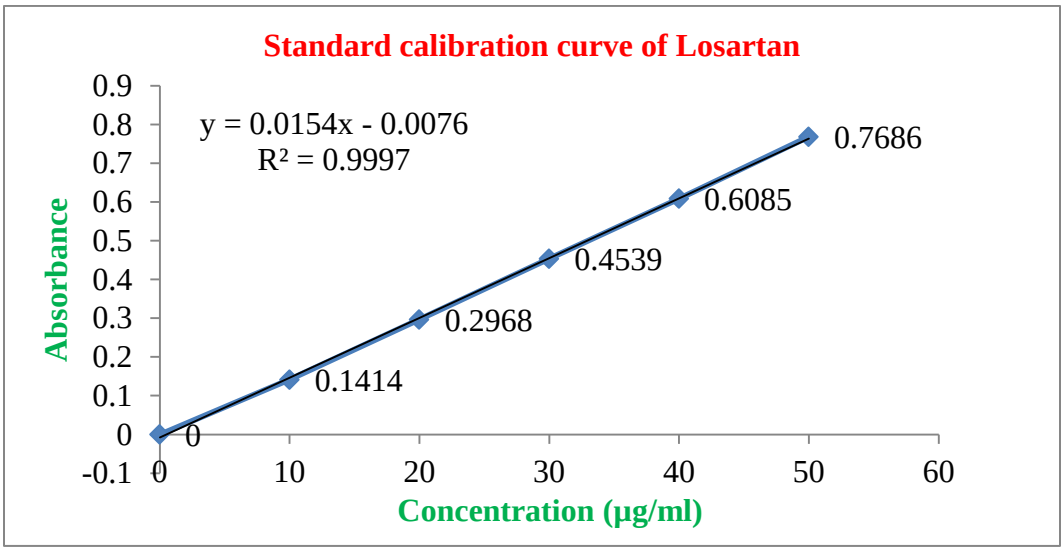

Fig. 1: Standard calibration curve of Losartan

Post formulation studies

The tablets of the proposed formulations F1 to F9 were evaluated for hardness, weight variation, thickness, friability and drug content. The thickness for tablets (n=3, mean ± SD) ranged from 4.0 ± 0.04 to 4.10 ± 0.02 mm. The hardness and friability (n=3, mean ± SD) of the tablets was found to be ranging from 4.7±0.20 to 6.5±0.20 kg/cm^2 respectively. All the tablets passed the weight variation test i.e., they were within the Pharmacopoeia limits of ±5%. Content uniformity ranged from 99.0±0.54to 100.47±0.34, meets the USP specification of 90-100 %. All the batches of the fabricated tablets were of good quality with regard to hardness, friability and drug content (Table 5).

Table 5: Post formulation studies of F1-F9

Form.	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Drug content (%)	Muco adhesion force
F1	248±0.02	4.1±0.10	4.7±0.06	0.17±0.0001	99±0.157	1.867±0.022
F2	249±0.74	4.2±0.03	5.4±0.47	0.20±0.0003	100±0.549	2.060±0.114
F3	248±0.96	4.2±0.17	6.5±0.58	0.14±0.0001	99±0.157	2.142±0.172
F4	251±0.14	4.1±0.17	5.5±0.12	0.14±0.0001	100±0.549	1.968±0.048
F5	250±0.46	4.3±0.10	6.2±0.22	0.36±0.0014	99±0.157	2.130±0.183
F6	250±0.72	4.4±0.25	5.1±0.47	0.21±0.0009	99±0.157	2.158±0.183
F7	250±0.51	4.2±0.39	6.1±0.72	0.19±0.0002	98±0.864	1.569±0.233

F8	251±0.12	4.1±0.10	5.2±0.01	0.18±0.0005	100±0.549	1.573±0.230
F9	251±0.71	4.1±0.10	6.2±0.22	0.19±0.0004	99±0.157	1.621±0.196

In vitro drug release study

F8 was selected as optimized formulation since it released maximum amount of the drug in 12 hours compared to other batch formulations. The mechanism of drug release of F8 was found to be non Fickian diffusion, zero order as evident from release exponent (n) value (Table 6, fig.2).

Table 6: In vitro drug release study of Formulations F1-F9

Time (hrs.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0±23.03	0±32.2	0±30.9	0±35.0	0±32.3	0±33.9	0±35.35	0±34.64	0±34.04
2	10±15.9	21±17.3	19±17.4	24±18.0	13±23.1	23±17.6	28±15.55	20±20.50	21±19.19
4	17±11.0	27±13.1	29±10.4	31±13.1	33±8.99	44±2.82	34±11.31	38±7.77	36±8.58
6	22±7.47	51±3.8	45±0.90	53±2.42	50±3.03	48±0.98	52±1.41	54±3.53	55±4.84
8	39±4.54	61±10.9	59±10.8	72±15.85	65±13.6	63±10.60	66±11.31	62±9.19	60±8.38
10	66±23.63	73±19.3	71±19.2	78±20.1	72±18.5	70±15.55	77±19.09	84±17.67	75±18.9
12	74±29.29	86±28.5	83±27.7	89±27.8	87±29.1	88±28.28	93±30.40	99±32.52	90±29.59

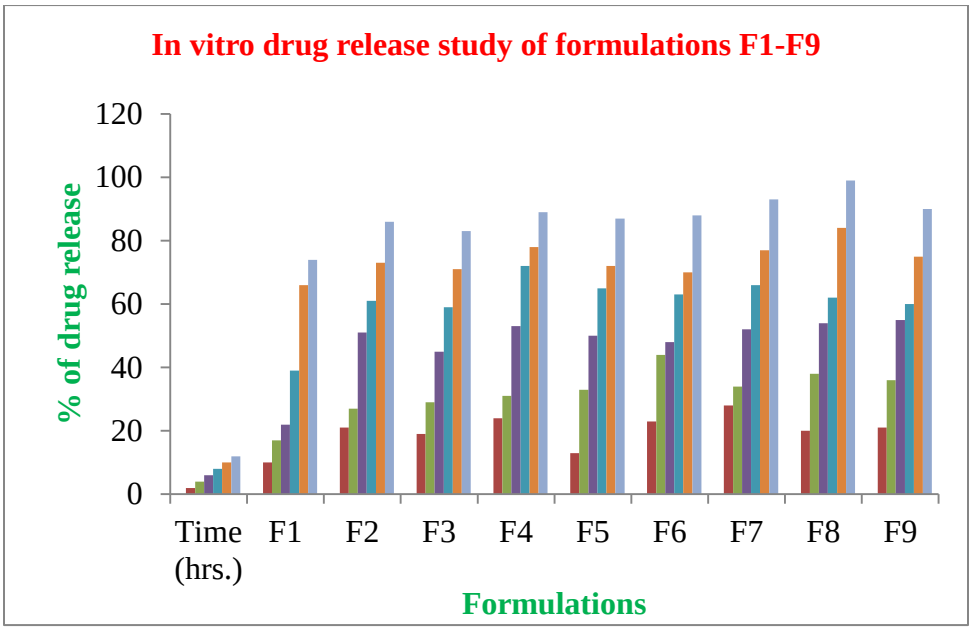

Fig 2: In vitro drug release study of formulations F1-F9

Swelling studies

The swelling index of bioadhesive tablets for a period of 8 hours was studied. The values obtained are shown in table. It is evident that an increase amount of HPMC K 4 M , Carbopol causes increase in swelling index and depending on the concentration the drug release will vary. Among all the formulation carbapol showed highest and HPMC K 4 M and ethyl cellulose showed lowest swelling index value (Table 7).

Table 7: Swelling studies of formulations F1-F9

Time (hrs.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	51.38±6.3	30.14±13.92	24.54±11.16	49.27±7.32	30.06±13.6	32.55±19.0	43.15±11.8	29.06±14.9	31.15±19.7
2	61.77±0.9	47.33±1.76	32.51±5.52	60.51±0.62	44.18±3.69	49.92±6.71	62.30±1.65	45.12±3.61	48.21±7.70
3	79.56±13.5	54.83±3.53	39.83±0.35	76.81±12.1	51.34±1.37	67.37±5.62	77.74±12.5	52.39±1.52	66.72±5.38
4	89.92±20.8	65.44±11.03	46.41±4.30	88.56±20.4	64.29±10.5	77.11±12.0	89.28±20.7	66.30±11.35	78.29±13.5
5	88.21±19.6	78.33±20.15	50.10±6.911	88.17±20.1	76.14±18.9	82.54±16.3	88.41±20.1	78.52±19.9	83.45±17.21
6	63.11±1.90	55.42±3.95	48.23±5.58	63.43±2.6	57.55±5.7	76.44±12.03	66.40±4.55	59.21±6.34	71.30±8.62
7	32.15±19.98	39.22±7.50	41.11±0.55	32.98±18.8	42.18±5.10	59.15±0.19	34.12±18.2	43.15±5.01	62.26±2.23
8	17.18±30.5	27.93±15.4	39.87±0.32	17.26±29.9	29.46±14.0	30.29±20.5	18.31±29.4	28.16±15.6	31.42±19.5

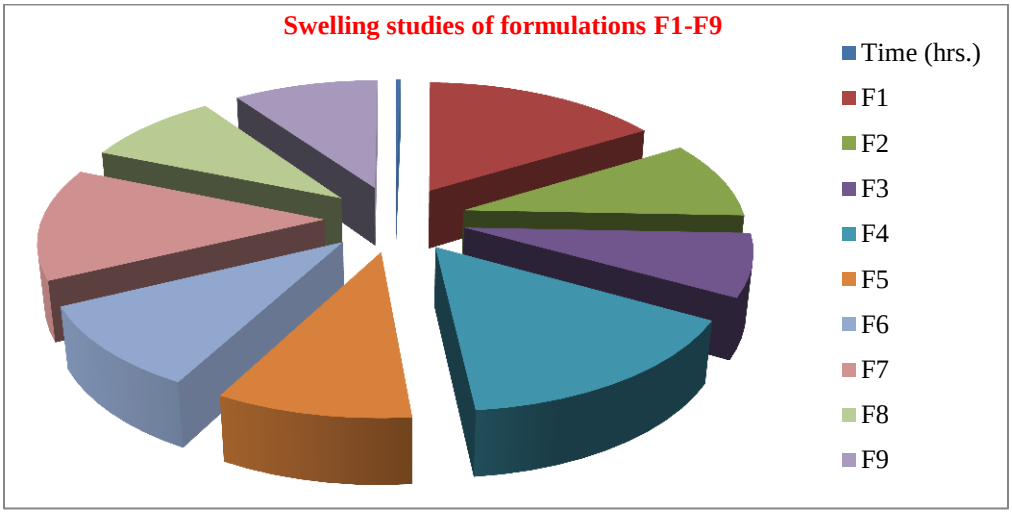

Fig 3: Swelling studies of formulations F1-F9

Fourier transform infrared spectroscopy

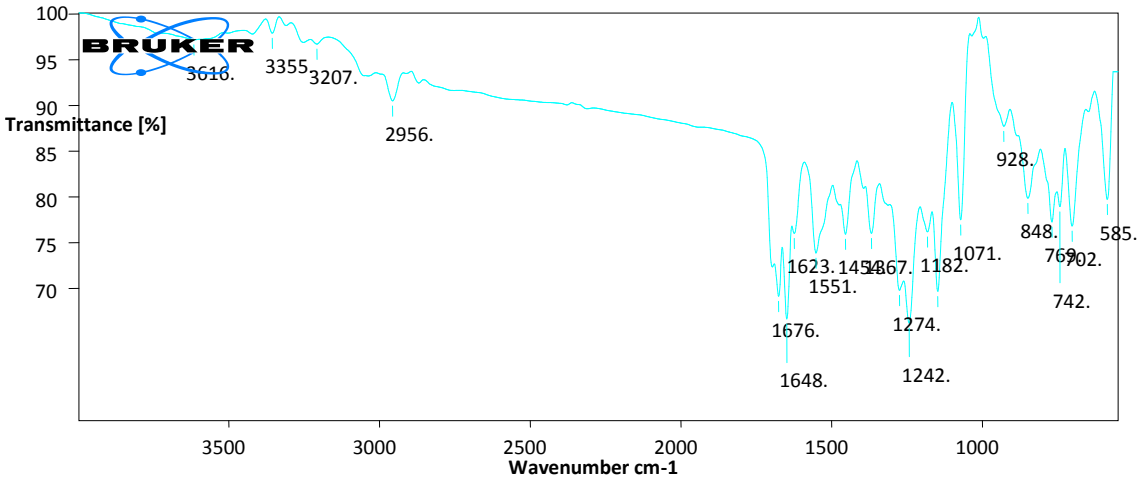

Fig 4: FTIR spectra of pure drug Losart

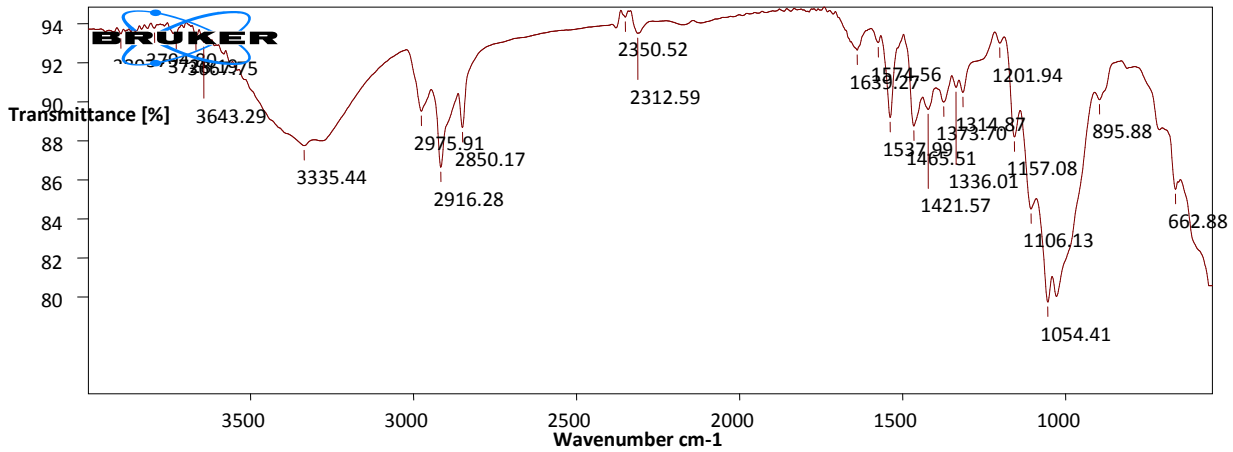

Fig 5: FTIR spectra of micro crystalline cellulose

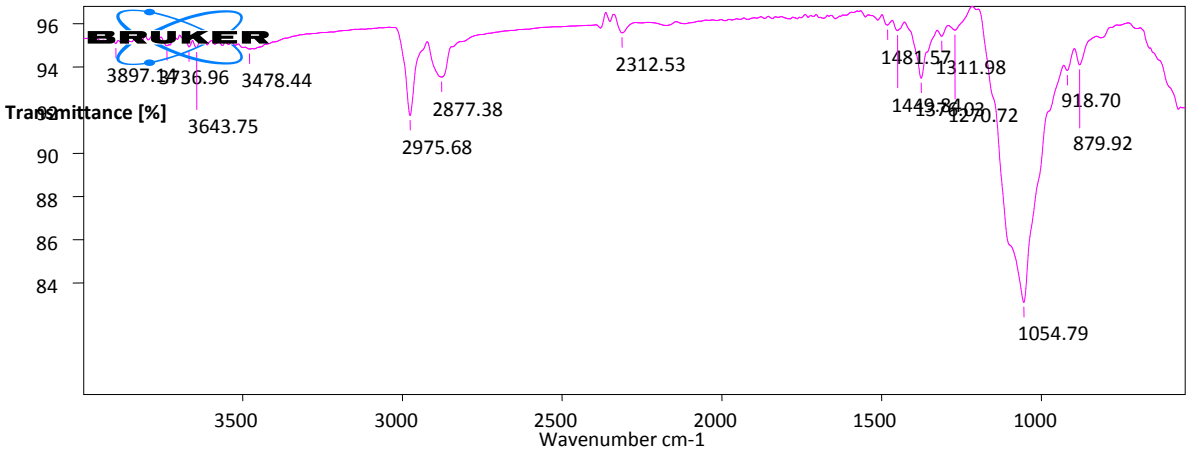

Fig 6: FTIR spectra of Drug + Carbopol

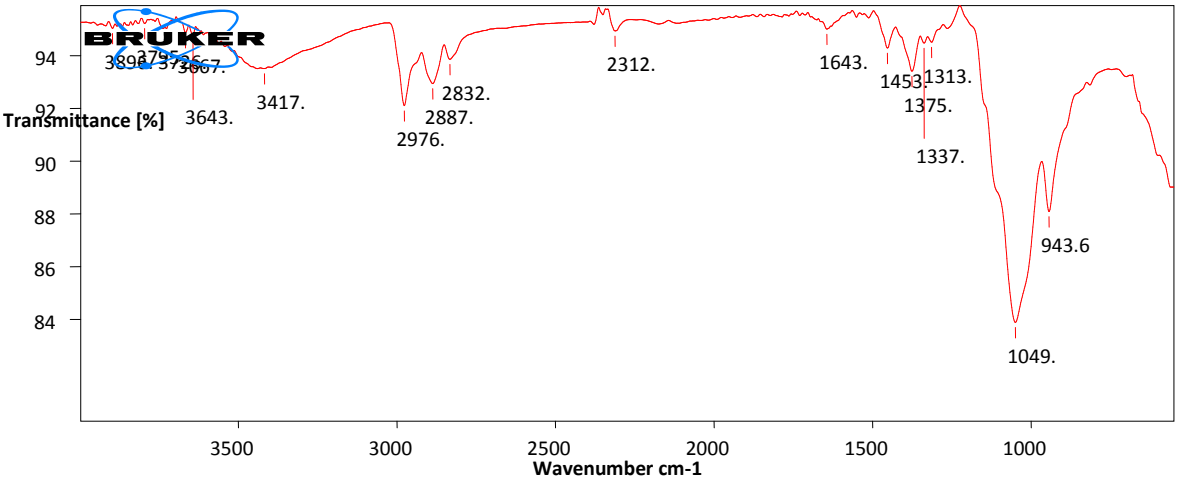

Fig 7: FTIR spectra of drug + HPMC K4M

The FTIR spectra of pure losartan and optimized formulation does not show any significant changes in peaks, indicating no incompatibility. Thus, confirms the structure of Losartan drug.

Stability study

It was done only for selected formulation F8. The storage conditions were at $40^{O}C \pm 2\ ^{O}C$ / 75% RH±5% for 30 days. The friability was 0.09% and hardness 4.5 ± 0.1 Kg/cm^2 after 30 days, indicating no significant changes. Dissolution study also showed no significant changes in drug release (Table 8).

Table 8: Dissolution studies after stability studies for F8

Time in Hours	% of drug release of F8	
	Day 1	After 30 days

2	23	22
4	30	28
6	48	45
8	56	59
10	77	82
12	94	92

Drug release kinetics

To investigate the mechanism of drug release from tablets, various kinetic models like zero order, first order, Higuchi, Korsmeyer- Peppas equations were applied to the *in vitro* release data obtained from different formulations. Diffusion exponents (n) were determined for all the formulations. From the observations it was concluded that the optimized formulation F8 was best explained by zero order (R^2=0.990) and Korsmeyer - Peppas (R^2=0.995). The drug release was proportional to the square root of time indicating that the drug release was diffusion controlled. The kinetic release data also suggest the diffusion mechanism to be non Fickian diffusion since it indicates a good linearity (Table 9 and fig. 8, 9, 10 and 11).

Table 9: Kinetics of drug release for F8

Time	**Log Time**	**Square root of Time**	**Cumulative % Drug Released**	**Log Cumulative %Drug Released**	**Cumulative %Drug Remained**	Log Cumulative %Drug Remained
0	0	1	-	1	100	2
2	1.414214	0.30103	20	1.30103	80	1.903089987
4	2	0.60206	38	1.5797836	62	1.792391689
6	2.44949	0.778151	50	1.69897	50	1.698970004
8	2.828427	0.90309	72	1.8573325	28	1.447158031
10	3.162278	1	80	1.90309	20	1.301029996
12	3.464102	1.079181	95	1.9777236	5	0.698970004

Fig 8: Zero order plot for F8

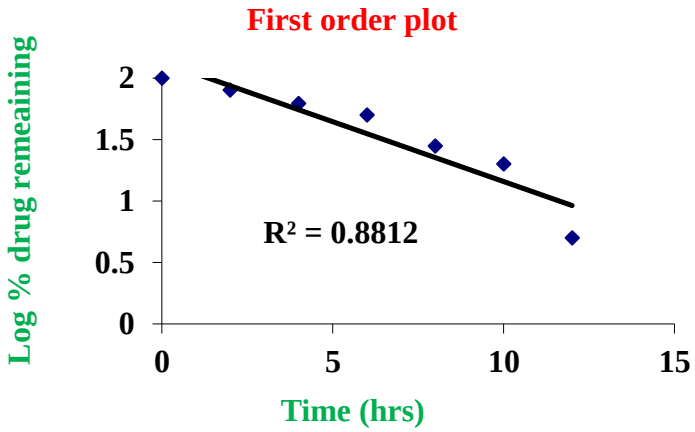

Fig 9: First order plot for F8

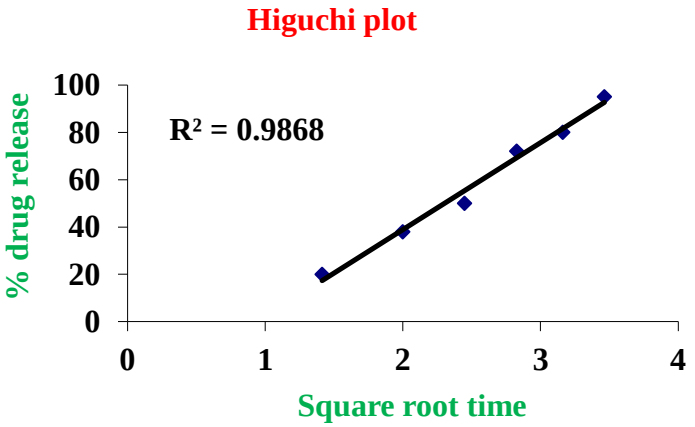

Fig 10: Higuchi plot for F8

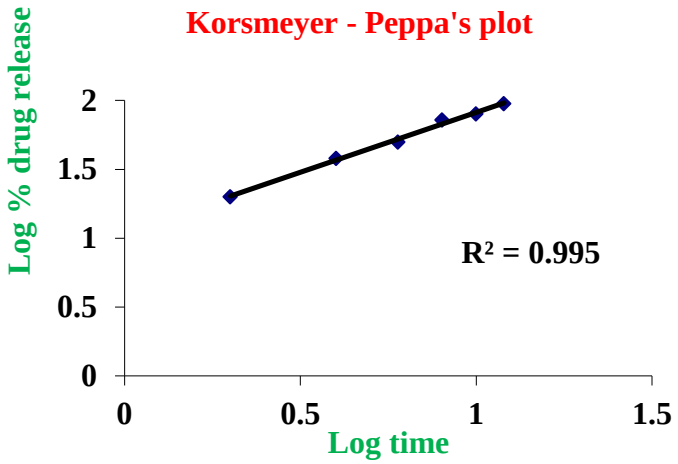

Fig 11: Korsmeyer - Peppa's plot for F8

CONCLUSION

The present study was conducted to develop gastro retentive bioadhesive tablets of Losartan containing HPMC K4M, ethyl cellulose, Carbopol polymers in different concentrations along with the excepients lactose monohydrate and magnesium stearate. The polymers were used in the ratio of 2:4:6. Formulation noF8 sowed optimum release upto 12 hours (99%) with the polymer cabopol. Optimized formulation F8 showed an excellent bimodal drug release pattern. This could be advantageous in terms of increased bioavailability. The drug release from the formulation followed both zero order and kormeyer peppas model which indicates anamolous fickian diffusion. Stability studies were conducted which revelead that no significant changes occurred in the formulation.

REFERENCES

[1]. Brahmankar D.M, Jaiswal S.B, Biopharmaceutics and Pharmacokinetics a treatise, 1st ed. Vallabh prakashan; New Delhi: 1995, 64-70.

[2]. M.D.Chavanpatil, P. Jain, S. Chaudri, R Shear and P R Vavia, Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin, Int J. Pharm. 316, 2006, 86-92.

[3]. Roma Patel, Priyesh Malviya, "Recent Development in Floating Drug Delivery System, for Gastric retention", An Review, School of Pharmacy D.A.V.V., Indore.

[4]. Rajesh A, Gayatri Ramya M, Surendra Y, Design and development of sustained release gastro retentive drug delivery system for ofloxacin, IJPBS |2(3), 2012, 408-423.

[5]. Satyabrata Bhanja, Parthasarathi Mishra, Sudhakar Muvvala, Formulation and in-vitro evaluation of sustained release matrix tablets of levofloxacin, Bhanja, et al. Int J Pharm 3(3), 2013, 556-564.

[6]. Singh BN and Kim H. Floating drug delivery system an approach to control delivery via gastric retention, J. Cont. Rel., 63, 2000, 235-259.

[7]. Timmermans J and Moes AJ. The cut off size for gastric emptying of dosage forms, J Pharm Sci. 82, 1993, 854.

[8]. Ichikawa M, Watanabe S and Miyake Y. A new multiple-unit oral floating dosage system: Preparation and in-vitro evaluation of floating and sustained-release characteristics. J Pharm Sci.80, 1991, 1062-1066.

[9]. Ozdemir N, Ordu S and Ozkan Y. Studies of floating dosage forms of Furosemide: in-vitro and in vivo evaluations of bilayer tablet formulations, Drug DevInd Pharm.26, 2000, 857-866.

[10]. Streubel A, Siepmann J and Bodmeier R. Floating matrix tablets based on low density foam powder: effects of formulation and processing parameters on drug release. Eur J Pharm Sci.18, 2003, 37-45.

[11]. Nur OA and Zhang JS. Captopril floating and/or bioadhesive tablets: design and release kinetics. Drug DevInd Pharm., 26, 2000, 965-969.
[12]. Shah S, Quaqish R, Patel V, Amiji M. Evaluation of the factors influencing stomach specific delivery of antibacterial agents for H.pyloriinfections. J Pharm Pharmacol. 51, 1999, 667-672.
[13]. Hilton AK and Deasy BP, In vitro and in vivo evaluation of an oral sustained-release floating dosage form of Amoxycillin trihydrate. IntJ Pharm. 86, 1992, 79-88.
[14]. Basak SC. Development and in vitro evaluation of oral matrix floating tablets formulation of Ciprofloxacin. Ind J Pharm Sci. 66, 2004, 313-316.
[15]. Himasankar K. Design and Biopharmaceutical evaluation of gastric floating drug delivery system of Metformin HCl. Ind J Pharm Edu Res. 40, 2006, 369-382.
[16]. Dave BS, Amin AF and Patel MM.Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and in-vitro evaluation. AAPS Pharm Sci Tech.5, 2004, 1-6.
[17]. Cooper J, Gunn C, Powder flow and compaction, In: Carter SJ, eds. Tutorial Pharmacy. New Delhi, India: CBS Publishers and Distributors; 1986, 211-233.
[18]. Leon Lachman, Herbert A. Liberman, the Theory and Practice of Industrial Pharmacy: 293-302.
[19]. Robinson Jr, Lee V.H.L, Controlled drug delivery: Fundamentals and Applications, 2nd edn. Marcel Dekker, New york: 1978, 24-36.
[20]. Wilson K.R.W, Waugh A. Anatomy and physiology in Health and Illness, 9th ed. Churchill Livingstone: London: 1996, 342-345.
[21]. Garima Chawla, Gupta, Pharmaceutical technology, July 23(9), 2003, 39-48.
[22]. Desai S, Bolton S. A Floating Controlled Release System: In-vitro and In-vivo evaluation, J. Pharm. Res., 10, 1993, 1321-1325.
[23]. Roop K. Khar, Controlled Drug Delivery, Gastroretentive system 4,. 202-203
[24]. Hradman J.G, Limbrid, Goodman Gilman's, The Pharmacological Basis of Therapeutics, Newyork 10, 2001, 1765.
[25]. Thripati K.D, Essential of Medical Pharmacology, New Delhi: 5, 2003, 248-49.