ejpmr, 2020,7(1), 445-453

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

COMPARATIVE STUDY OF LOSARTAN POTASSIUM WITH MARKETED MATRIX TABLET AS CONTROLLED RELEASE

Rina G. Maskare*, Nitin H. Indurwade and Vijaya Patle

Manoharbhai Patel Institute of Pharmacy (B-Pharm), Gondia, Maharashtra, 441614.

***Corresponding Author: Rina G. Maskare**

Manoharbhai Patel Institute of Pharmacy (B-Pharm), Gondia, Maharashtra, 441614.

Article Received on 21/11/2019 **Article Revised on 11/12/2019** **Article Accepted on 31/12/2019**

ABSTRACT

The objective of the present study was to develop hydrophilic polymer and hydrophobic polymer based matrix Losartan potassium controlled release tablets which can release the drug up to time of 12 hrs in predetermined rate using 3^2 factorial design. The CR (controlled release) tablets of Losartan potassium were prepared employing different concentrations of HPMC K100 and ethyl cellulose in different combinations as rate retardants by Direct Compression technique. Statistical elucidations of polynomials were established for all the responses. The formulations were evaluated for pre compression and post compression parameters. The results demonstrated the effectiveness of the proposed design for development of Losartan potassium sustained release tablets with optimized properties. The formulation was fabricated with a very less polymer ratio and show a very a good release profile at the end of 20th hours.

KEYWORDS: Losartan Potassium, Controlled Release, 3^2 Factorial Design, direct compression.

INTRODUCTION

The main aim of formulator to develop a product with maximum efficiency by keeping the excipients to a minimum in number, minimize the quantity of each excipients and multifunctional excipients may be given preference unifunctional excipients. Excipients play a crucial role in design of the delivery system, determining its quantity and performance.

Oral drug delivery system should have advantage of single dose for whole duration of the treatment and it should deliver the drug directly at specific site. Scientists have succeeded to develop a system that can be as near to an ideal system and it encourages the scientists to develop controlled release system. The design of oral sustain drug delivery system should be primarily aimed to achieve the more predictability and reproducibility to control the drug release, 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.

Controlled drug delivery systems can include the maintenance of drug levels within a desired range, the need for fewer administrations, optimal use of the drug in question, and increased patient compliance. While these advantages can be significant, the potential disadvantages cannot be ignored like the possible toxicity or non-biocompatibility of the materials used, undesirable by-products of degradation, any surgery required to implant or remove the system, the chance of patient discomfort from the delivery device, and the higher cost of controlled-release systems compared with traditional pharmaceutical formulations.

The ideal drug delivery system should be inert, biocompatible, mechanically strong, comfortable for the patient, capable of achieving high drug loading, safe from accidental release, simple to administer and remove, and easy to fabricate and sterilize. The goal of many of the original controlled-release systems was to achieve a delivery profile that would yield a high blood level of the drug over a long period of time. With traditional drug delivery systems, the drug level in the blood follows the in which the level rises after each administration of the drug and then decreases until the next administration. The key point with traditional drug administration is that the blood level of the agent should remain between a maximum value, which may represent a toxic level, and a minimum value, below which the drug is no longer effective.[1]

Losartan potassium is an orally active angiotensin-II receptor antagonist used in the treatment of hypertension due to mainly blockade of AT1 receptor. It is freely soluble in water, slightly soluble in acetonitrile, and soluble in isopropyl alcohol. It is readily absorbed from the gastrointestinal tract with oral bioavailability of about 33 per cent and a plasma elimination half-life ranging from 1.5 to 2.5 hours Administration of losartan potassium in a sustained release dosage form with dual characteristics, that is, burst release, followed by an

extended release over 8 hours would be more desirable; as these characteristics would al-low a rapid onset followed by protracted anti-hypertensive effect by maintaining the plasma concentration of the drug. Previously, several studies were conducted onlosartan potassium by using various hydrophilic and hydrophobic polymers for their in-vitro evaluation.[2]

The objective of the present study was to develop hydrophilic polymer and hydrophobic polymer based matrix Losartan potassium controlled release tablets which can release the drug up to time of 12 hrs in predetermined rate using 3^2 factorial design. The CR (controlled release) tablets of Losartan potassium were prepared employing different concentrations of HPMC K100 and ethyl cellulose in different combinations as rate retardants by Direct Compression technique.

MATERIAL AND METHODS

Material

Losartan Potassium was kindly supplied by Zim Laboratory, Nagpur, Maharashtra, India, as a gift sample. HPMC K 4 M+, HPMC K 100 M was procured from Glenmark Pharmaceutical. Potassium di-hydrogen phosphate (Merck, Darmstadt, Germany), and sodium hydroxide (Merck, Darmstadt, Germany) were used as dissolution medium. Microcrystalline cellulose, lactose, talc, Magnesium stearate (Taj Laboratories Ltd.), and starch were obtained from Loba Chemicals, India. Solvents and all other chemicals were of analytical grade.

Methods

Preparation of Matrix Tablet

The tablets were prepared by direct compression method. The corresponding amount of drug and excipients such as HPMC K4M CR, HPMC K100M CR, lactose monohydrate, microcrystalline cellulose, talc, magnesium stearate, starch were accurately weighed and mixed properly and the matrix tablets were prepared by direct compression using single station tablet press. Each tablet contains 100 mg of Losartan potassium and other pharmaceutical ingredients as listed in table 1.[3]

Table 1: Composition of controlled matrix formulations.

	Quantity per Batch (mg/tab)				
Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**
Losartan Potassium	100	100	100	100	100
HPMC K4M	95	90	70	45	54
HPMC K100M	95	80	80	45	36
Lactose Monohydrate	108	128	148	158	158
MCC	45	45	45	45	45
Talc	4.5	4.5	4.5	4.5	4.5
Magnesium Stearate	2.5	2.5	2.5	2.5	2.5
Starch	-	-	-	50	50
Total	450	450	450	450	450

Micromeritic properties of powder[4]

The flow properties for bulk density (Loose bulk density and tapped bulk density), Angle of repose, Hausner's ratio, percentage compressibility were evaluated.

Evaluation of losartan potassium matrix tablet[5]

Thickness

Thickness of the tablets was determined using a Vernier caliper.

Weight Variation Test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance and the test was performed according to the official method.

Hardness

Hardness of the tablets was determined using a hardness testing apparatus (Monseto Type). A tablet hardness of about 5-6 kg/cm2 is considered adequate for mechanical stability. It was found that all the formulations showed uniform thickness. The average percentage of deviation of all tablet formulations was found to be within the limit.

Friability

The tablets were tested for friability testing using a Roche Friabilator. For this test, six tablets were weighed and subjected to a combined effect of abrasion and shock in the plastic chamber of the Friabilator revolving at 25 r.p.m. For 4 min and the tablets were then dusted and re-weighed.

In this study the percentage friability for all the formulations was below 1%, indicating that the friability was within the prescribed limits. All the tablet formulations are complied with the specifications for weight variation, drug content, hardness and friability.

Drug content uniformity

Drug content was determined by taking an accurately weighted amount of powdered Losartan potassium with water and solution was filtered through 45µ membrane. The absorbance was measured at 205nm by UV visible spectrophotometer.

Dissolution Studies

The In-vitro drug release study was performed for all the tablets using USP type II dissolution apparatus under the

following conditions.

Dissolution test parameters
Medium: 900 ml of 0.1 N HCL, buffer solution, pH 6.8
Temperature: 37°C (± 0.5°C)
RPM: 100
Sampling volume: 10 ml
Sampling time: 1, 2, 4, 8, 10, 12, 24 hours

Procedure: In *vitro* drug release studies of the matrix tablets were carried out using a six-station USP XXII type II dissolution test apparatus at 37°C (± 0.5°C) and 100 rpm speed in 900 ml of 0.1 N hydrochloric acid (gastric simulated fluid, pH 1.3) as a dissolution medium for first 2 hours and next 3 to 24 hours in intestinal simulated fluid (buffer solution, pH 6.8). The amount of drug dissolved after 1hr, 2hr, 4hr, 8hr, 10hr, 12hr and 24hr in the surrounding dissolution medium were determined by UV visible spectrophotometer at 205 nm.

Kinetic analysis of release data and mechanism of drug release
In order to evaluate the kinetics and the mechanism of drug release from the formulations, the data obtained from the in vitro drug release studies were analyzed by zero order, first order, Higuchi, Korsemeyer-Peppas and Hixson-Crowell models.

Zero order
To determine the mechanism of drug release from the formulations the zero order equation expressed as cumulative amount of drug release vs time.

First order
To determine the mechanism of drug release from the formulations the first order equation expressed as log cumulative amount of drug remaining vs time.

Higuchi square root law
The Higuchi release model describe as cumulative percentage of drug release vs square root of time.

Korsemeyer-Peppas model
The dissolution data were also fitted according to the well-known exponential equation of *Peppas et al* which is often used to describe drug release behavior from polymeric systems.
$Mt / M\infty = Ktn$ ---------- (3)

Where, $Mt / M\infty$ is the fraction of drug released at time, t, k is the kinetic constant, and n is the diffusional exponent for drug release.

Hixson-Crowell cube root law
It is the law that provides idea about the evaluation of drug release pattern changes with the surface area and the diameter of the particles. The diffusional exponent, n, is dependent on the geometry of the device as well as the physical mechanism for release. A value of n = 0.45 indicates Fickian (case I) release; > 0.45 but < 0.89 for non-Fickian (anomalous) release; and > 0.89 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled drug release.

RESULTS

Table 2: Standard graph of Losartan Potassium in 0.1 N HCL.

Sr. No.	Concentration(mcg/ml)	Absorbance
1.	2	0.102
2.	4	0.206
3.	6	0.325
4.	8	0.436
5.	10	0.541
6.	12	0.641
7.	15	0.788
8.	18	0.895

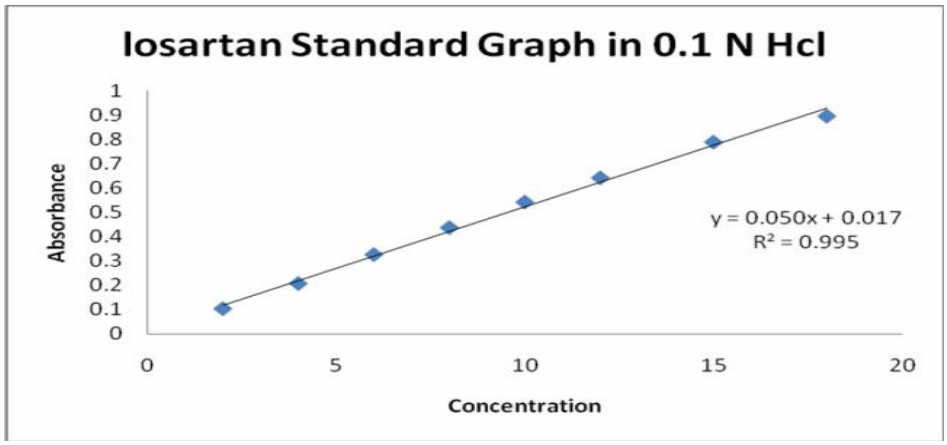

Fig 1: Standard graph of Losartan Potassium in 0.1 N HCl.

Table 3: Standard graph of Losartan potassium in pH 6.8 buffer.

Sr.no	Concentration (mcg/ml)	Absorbance
1	2	0.120
2	4	0.216
3	6	0.318
4	8	0.426
5	10	0.517
6	12	0.672
7	15	0.826
8	18	0.969

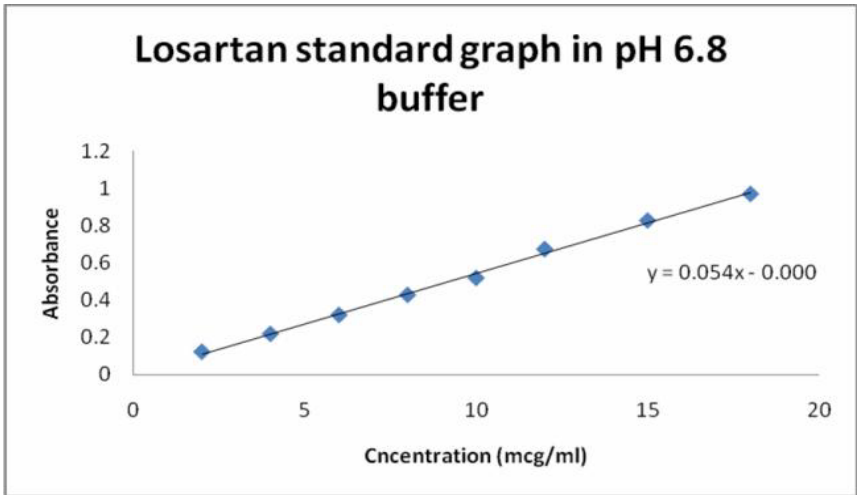

Fig. 2: Standard graph of losartan potassium in pH 6.8 Buffer.

Drug Excipients Compatibility

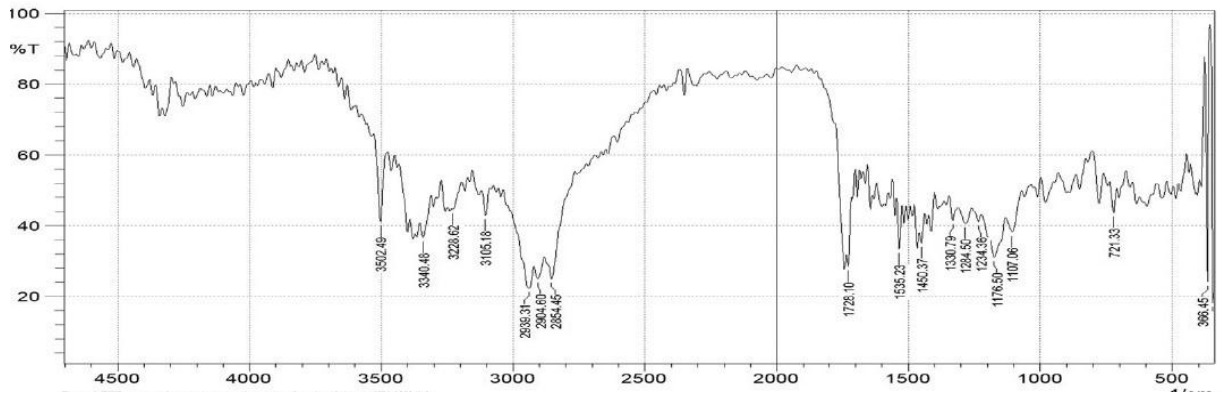

Fig. 3: FT-IR spectrum of pure drug.

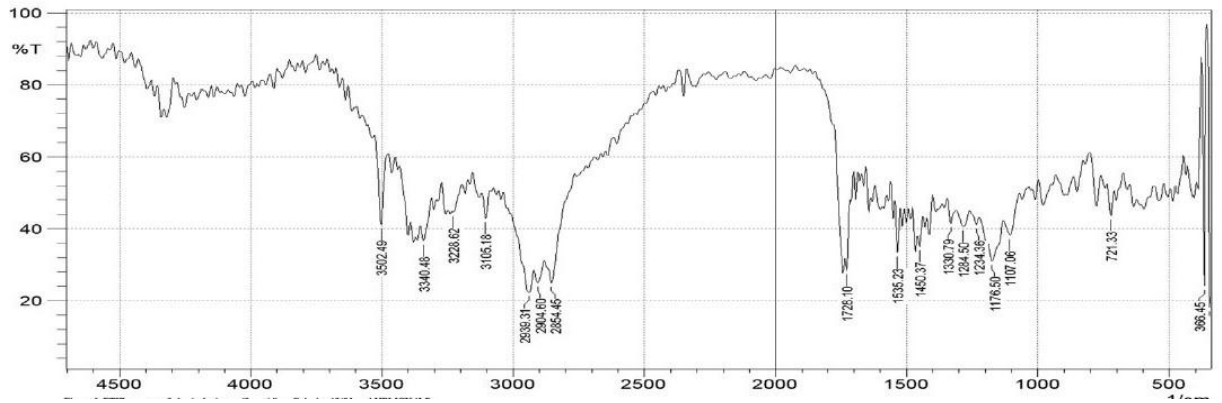

Fig. 4: FT-IR spectrum of drug and excipients.

Table 4: Evaluation of pre-compression parameter of powder blend.

Formulation Code	Bulk Density(gm/ml)	Tapped Density(gm/ml)	Angle of repose	Hauser's Ratio	Compressibility Index(%)
F1	0.5384 ± 0.191	0.5833 ± 0.272	25.260 ± 0.672	1.0833	7.6923
F2	0.5599 ± 0.0281	0.6087 ± 0.293	26.290 ± 0.587	1.0869	8.0000
F3	0.6087 ± 0.281	0.6363 ± 0.321	26.450 ± 0.652	1.0454	4.3478
F4	0.5381 ± 0.191	0.6087 ± 0.293	27.040 ± 0.498	1.0400	3.8461
F5	0.5519 ± 0.221	0.6363 ± 0.321	25.140 ± 0.622	1.0869	8.0000

Table 5: Post compression parameter.

Formulation code	Tablet Weight(mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (% loss)
F1	450.40 ± 4.85	3.84	4.39 ± 0.038	0.27
F2	449.90 ± 1.25	3.59	4.4 ± 0.041	0.18
F3	448.72 ± 2.20	3.62	4.46 ± 0.047	0.19
F4	449.98 ± 1.02	3.60	4.42 ± 0.040	0.30
F5	448.90 ± 1.98	3.54	4.24 ± 0.045	0.21
F6(marketed)	449.72 ± 2.55	3.57	4.46 ± 0.041	0.19

Table 6: Data of drug Dissolution.

Time	Cummulative Drug Released(%)					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
1	4.9	6.8	3.4	14.1	7.7	17
4	39.4	34.	39.2	58.3	34.1	58.3
8	63.2	54.3	58.6	55.7	58.6	55.7
16	62.7	65.7	71.3	60.6	62.9	60.6
20	83.5	93.9	93.9	92.1	97	92.1

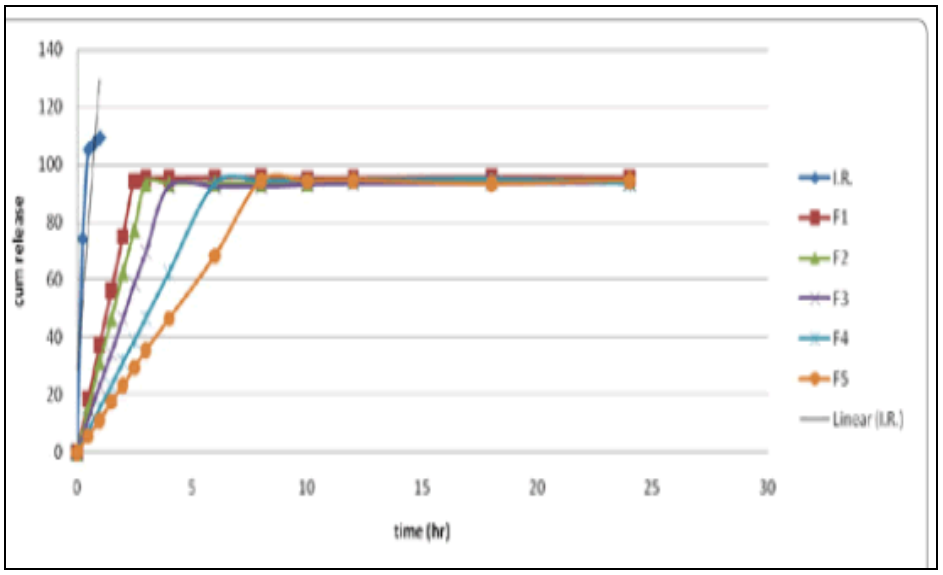

Fig. 5: Dissolution Kinetic Plot.

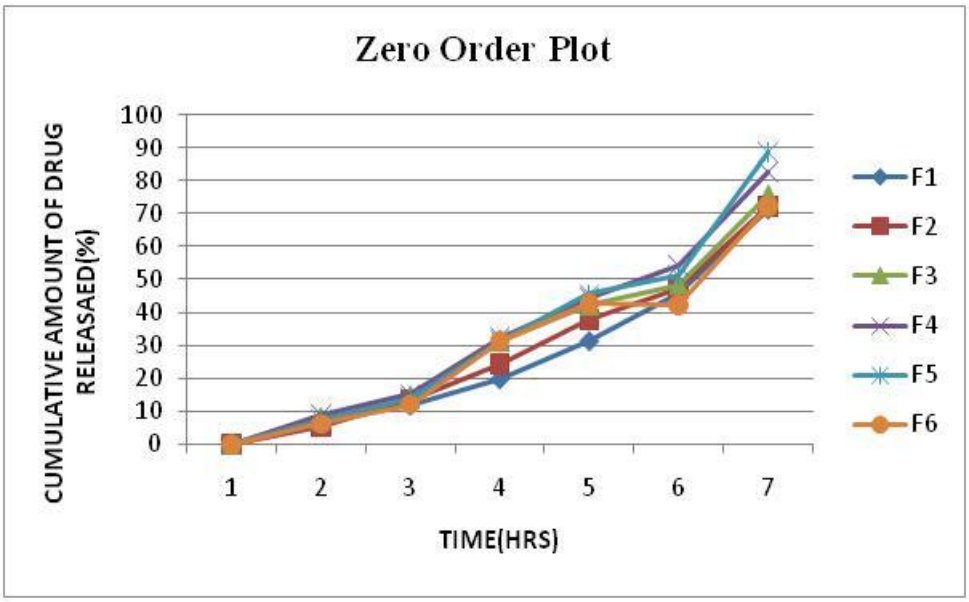

Fig. 6: Zero Order Plot of Release Kinetic.

Fig. 7: Zero Order Plot of Release Kinetic.

Table 7: Data Higuchi Release Kinetic.

SQRT Time(hrs)	Cummulative amount of drug released(%)					
	F1	**F2**	**F3**	**F4**	**F5**	**F6(marketed)**
0	0	0	0	0	0	0
1	7.23	9.43	8.36	9.37	8.93	7.46
1.41	11.89	13.71	14.91	15.32	14.44	15.32
2	19.89	24.36	31.34	32.54	34.36	32.73
2.83	31.46	37.45	42.63	44.71	51.34	47.56
3.46	45.86	47.24	48.59	52.36	60.57	59.46
4.90	71.39	72.36	75.81	82.93	88.76	85.39

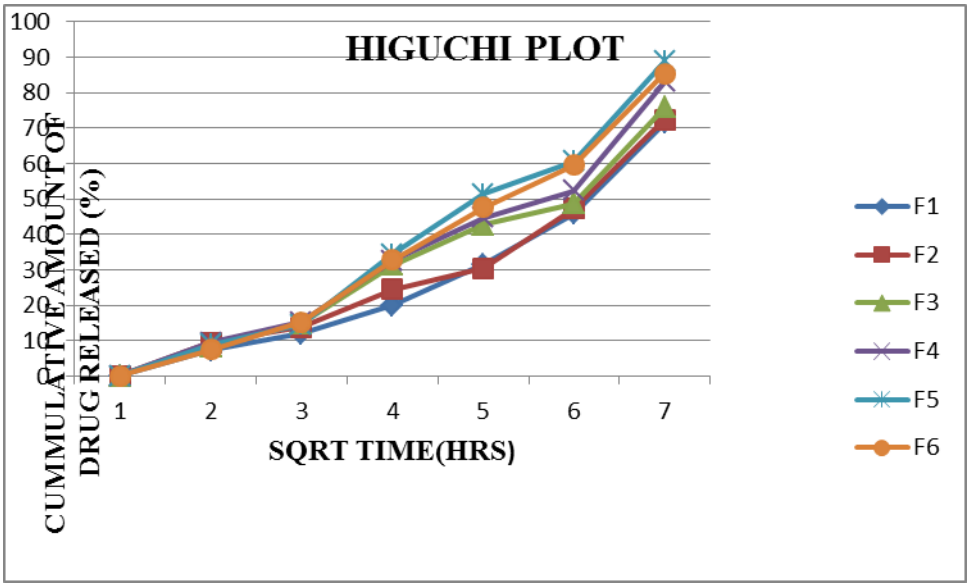

Fig. 8: Higuchi Plot of Release Kinetic.

Table 8: Korsemeyer peppas release kinetic.

Log of time(hrs)	Log fraction released(%)					
	F1	F2	F3	F4	F5	F6(marketed)
0	0.86	0.97	0.92	0.91	1.01	0.97
0.30	1.08	1.14	1.17	1.16	1.24	1.22
0.60	1.30	1.39	1.50	1.51	1.54	1.51
0.90	1.50	1.57	1.63	1.65	1.71	1.68
1.08	1.66	1.67	1.69	1.72	1.78	1.77
1.38	1.85	1.86	1.88	1.92	1.95	1.94

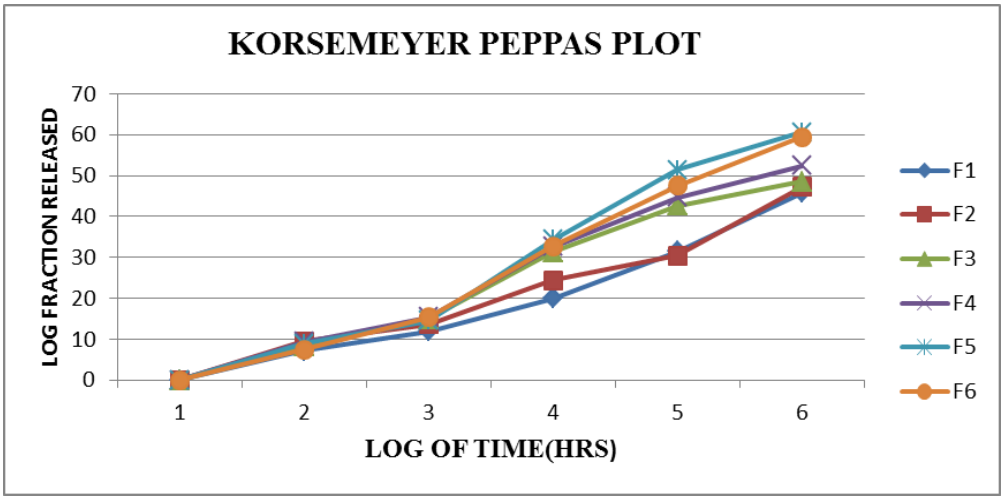

Fig. 9: Korsemeyer Peppas plot of release kinetic.

Table 9: Data for Hixson Crowell release kinetic.

Time(hrs)	Cubic root of drug remaining(%)					
	F1	F2	F3	F4	F5	F6(marketed)
0	4.46	4.64	4.64	4.64	4.64	4.64
1	4.53	4.49	4.51	4.52	4.48	4.49
2	4.45	4.42	4.39	4.40	4.35	4.37
4	4.31	4.23	4.09	4.07	4.03	4.07
8	4.09	3.97	3.85	3.81	3.65	3.74
12	3.78	3.75	3.72	3.62	3.40	3.43
24	3.06	3.02	2.89	2.57	2.24	2.39

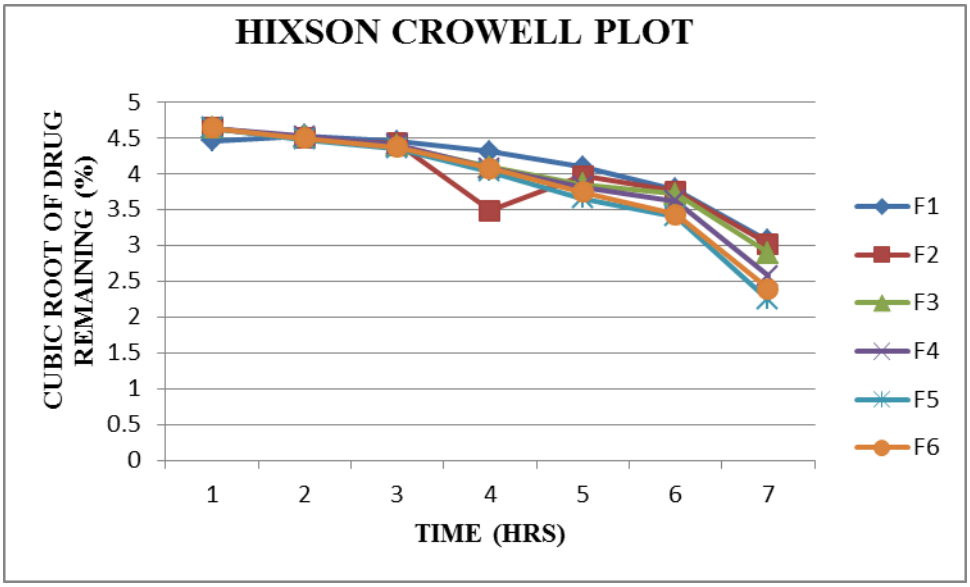

Fig. 10: Hixson Crowell Plot Of Release Kinetic.

Table 10: Release Rate Constant and R^2 Values.

Formulation	Zero order		First order		Higuchi		Korsemeyer peppas		Hixson crowell	
	Ka	R^2	Ka	R^2	Ka	R^2	Ka	R^2	Ka	R^2
F1	2.903	0.9755	-0.0223	0.9978	14 .986	0.9722	0.7255	0.999	-0.0648	0.9973
F2	2.8773	0.9536	-0.0226	0.9971	15.151	0.9887	0.6537	0.6981	-0.0653	0.9911
F3	2.9816	0.9213	-0.0247	0.9861	15.935	0.9842	0 .6837	0.9708	-0.0697	0.9738
F4	3.5433	0.9209	-0.0384	0.9924	18.985	0.9887	0.6844	0.982	-0.0972	0.9902
F5	3.4044	0.9424	-0.0336	0.9885	17.999	0.9852	0.7089	0.9833	-0.0885	0.9914
F6	3.3004	0.943	-0.0307	0.9868	17.402	0.9804	0.7418	0.9738	-0.0828	0.9874

DISCUSSION

The present investigation was undertaken to formulate losartan potassium controlled release matrix tablets for the treatment of hypertension. Formulations were evaluated for pre and post compression parameter.

The compatibility studies for the drug and excipients used in the formulation were carried out. The FT-IR spectral analysis showed that there was no change in characteristic peaks of pure drug. Losartan potassium and excipients which confirmed that the absence of chemical interaction between the drug and excipients.

Six formulations were formulated by using different proportions of polymers. All the formulations were prepared by direct compression. The blend of different formulations were evaluated for angle of repose, bulk density and tapped density, Hausner's ratio, and compressibility index. The results showed that all the formulations of powders were within the limits and thus it confirmed that the powders have a very good flow property.

The results of post compression such as thickness, hardness, friability, weight variation and drug content for the prepared formulation were within the limits.

In the formulations F1, F2, F3, F4 and F6 the polymer ratio is used in much quality and the results in less release of drug is seen at the time of dissolution where as the drug coated with less polymer containing formulation F-5 show a very good release dissolution release profile rate than other formulations and given best results. The result is shown in Table. No.6.

In the formulation F5 prepared with HPMC E15 200mg and MCC 65mg in sufficient quantity showed maximum (97%) in-vitro drug release at the end of 20 hrs. Although all the formulations shown a good release in-vitro release profiles even more than 90%.

In the present work efforts have been made to developed Losartan potassium controlled release matrix tablets was depend upon polymer. The results showed that the in vitro drug release depend upon the concentration of polymer. The best (F-5) formulation contains sufficient quantity of HPMC E15 and MCC and *in-vitro* drug release is compared with the Marketed formulations.

CONCLUSION

It can be concluded that controlled release tablets of Losartan potassium can be performed by direct compression method. All the formulas show a very good drug release profiles and shown better controlled action till the end of last hour (24^{th} hrs). And hence will improve patient compliance and increase in bioavailability.

ACKNOWLEDGEMENT

The author thanks the Management and Principal Dr. N. H. Indurwade of Manoharbhai Patel Institute of Pharmacy (B-Pharm), Gondia, Maharashtra for providing various facilities to complete the work.

REFERENCES

1. Vyas SP, Khar RK. Controlled drug delivery concepts and advances. vallabh prakashan, 2002; 1: 411-47.
2. Chithaluru K, Tadikonda R, Gollapudi R, KANDULA KK. Formulation and invitro evaluation of sustained release matrix tablets of losartan potassium. Asian J. Pharm. Clin. Res., 2011; 4(3): 18-22.
3. Prajapati BG, Patel KR. Once-Daily sustained release matrix tablets of losartan potassium: Formulation and in vitro evaluation. International Journal of Medical and Clinical Research, 2010; 1(1): 1-7.
4. Iqbal Z, Khan R, Nasir F, KHAN JA, Rashid A, Khan A, Khan A. Preparation and in-vitro in-vivo evaluation of sustained release matrix diclofenac sodium tablets using PVP-K90 and natural gums. Pakistan journal of pharmaceutical sciences, 2011 Oct 1; 24(4).
5. Jaimini M, Tanwar YS, Srivastava B. Formulation and characterization of gastroretentive drug delivery system of losartan potassium. International Current Pharmaceutical Journal, 2012 Dec 8; 2(1): 11-7.
6. Enayatifard R, Saeedi M, Akbari J, Tabatabaee YH. Effect of hydroxypropyl methylcellulose and ethyl cellulose content on release profile and kinetics of diltiazem HCl from matrices. Tropical Journal of Pharmaceutical Research, 2009; 8(5).
7. Nalle S, Sarpate R, Setty M, Pathan I, Deshmukh A. Controlled release nateglinide tablets using Na-CMC and HPC hydrophilic polymer. Research Journal of Pharmacy and Technology, 2010; 3(1): 87-91.
8. Rajendran NN, Natarajan R, Sakthikumar T. Effect of processing and polymer variables on invitro release of metoprolol succinate extended release tablets. International Journal of Pharmaceutical Sciences and Research, 2011 Dec 1; 2(12): 3136.
9. Enayatifard R, Saeedi M, Akbari J, Tabatabaee YH. Effect of hydroxypropyl methylcellulose and ethyl cellulose content on release profile and kinetics of diltiazem HCl from matrices. Tropical Journal of Pharmaceutical Research, 2009; 8(5).
10. Iqbal Z, Khan R, Nasir F, KHAN JA, Rashid A, Khan A, Khan A. Preparation and in-vitro in-vivo evaluation of sustained release matrix diclofenac sodium tablets using PVP-K90 and natural gums. Pakistan journal of pharmaceutical sciences, 2011 Oct 1; 24(4).
11. Koland M, Charyulu RN, Prabhu P. Mucoadhesive films of losartan potassium for buccal delivery: design and characterization. Indian J Pharm Educ Res., 2010 Oct 1; 44(4): 315-23.