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Formulation Design And Invitro Evaluation Of Sustained Release Matrix Tablets Of Losartan Potassium Using HPMC Polymers

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Abstract : The present research work is aimed at developing a sustained release tablet dosage form of Losartan potassium, a drug of choice in hypertension. It acts as an angiotensin receptor antagonist. It is the drug with lesser side effects so used widely. Because of its high solubility, short half-life and therapeutic use in such diseases, it is considered as an ideal drug candidate for the design of oral controlled release dosage form. It has been studied that a matrix tablet containing hydroxyl propyl methyl cellulose polymers for oral controlled delivery of Losartan Potassium has been formulated with greater significance; hence it was decided to check the *in-vitro* drug-polymer study in formulating a sustained release tablet for Losartan Potassium. Direct compression method was employed for blending of drug with polymers in the given ratio as 9 formulations. The prepared powder blends were then compressed into tablets using the necessary excipients. The tablets were evaluated for hardness, thickness, friability and drug content and were subjected to a 12 hour *in vitro* drug release studies (USP dissolution rate test apparatus II, 50 rpm, 37^0C $\pm 0.5^0$C) using 0.1N hydrochloric acid for first 2hrs, phosphate buffer, pH 6.8 as a dissolution medium (900ml) for the next 10 hrs. The amount of Losartan Potassium released from the tablet formulations at different time intervals was estimated using a UV spectroscopy method. The formulations that showed a considerable retardation of the drug release are considered promising. Among the nine formulations, F7 formulation containing Drug to HPMC K100 in ratio 1:1 is optimized based on its ability to sustain drug release till 12 hours of dissolution study, release kinetics were applied to optimized formulation showed that the pattern of release was First order and mechanism of drug release was fitted to higuchi's model.
Key Words: Losartan potassium, Sustained release, hypertension, Kinetics.

1) INTRODUCTION :

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drug via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance, and cost effective manufacturing process.

Various types of modified release formulations have been developed to improve the patient compliance and also clinical efficacy of the drug. The sustained release oral dosage forms have been demonstrated to improve therapeutic efficacy by maintaining steady state drug plasma concentration. Hydroxypropyl methyl cellulose (Hypromellose, HPMC) polymers have been widely studied for their application in oral sustained release formulations [1]. Such hydrophilic polymers are most popular because of their flexibility to get a desirable drug release profile, cost effectiveness and broad regulatory acceptance [2]. HPMC has always been a first choice for formulation of hydrophilic matrix systems, because of providing robust mechanism, choice of viscosity grades, nonionic nature, consistent reproducible release profiles, cost effectiveness and utilization of existing conventional equipment and methods [3]. HPMC most widely used as the gel forming agent in the formulations of solid, liquid, semisolid and controlled release dosage forms. The adjustment of the polymer concentration, the viscosity grades and the addition of different types and levels of excipients to the HPMC matrix can modify the drug release rates [4].

The hypertensive patients are more prone to morning surge in blood pressure and hypertensive attacks during morning hours between 5 a.m. to 9 a.m. The development sustained release tablets of enalapril are expected to avoid acute overdose, and to prevent morning hypertension [5]. The other advantages of sustained release dosage forms are patient compliance, reduction of local and systemic side effects, minimization of peaks and valleys in drug blood levels [6].

Losartan potassium is a potent, highly specific angiotensin II type 1 receptor antagonist with antihypertensive activity. It is readily absorbed from the gastrointestinal tract with oral bioavailability of about 33% and a plasma elimination half-life ranging from 1.5 to 2.5 hours. Administration of Losartan Potassium in a sustained release dosage form would be more desirable by maintaining the plasma concentrations of the drug well above the therapeutic concentration.[7]

2) MATERIALS AND METHODS:

2.1) Materials:

Losartan potassium was obtained from Bright labs, Hyderabad. HPMC grades were received as gift samples from Baris Pharmaceuticals Pvt. Ltd., Hyderabad. Other materials were purchased from yarrow chem products, Mumbai, India.

2.2) Methodology:

2.2.1) Preformulation Studies:

2.2.1.1) Standardization of losartan potassium by UV-Visible spectrophotometry:

a) In 0.1 N Hcl Solution:

i) Preparation of stock solution: Stock solution 100µg/ml of Losartan potassium was prepared in 0.1N Hcl solution. This solution was approximately diluted with 0.1N Hcl to obtain a concentration of 10µg/ml. The resultant solution was scanned in range of 200- 400nm using UV double beam spectrophotometer (Lab India UV-3000+).

ii) Standard calibration of Losartan potassium in 0.1N Hcl:

100mg of Losartan potassium was accurately weighed and dissolved in100ml of 0.1N Hcl to obtain a concentration of 1000µg/ml. From the above 10ml was withdrawn and diluted to 100ml to obtain a concentration of 100µg/ml. From this stock solution aliquots of 0.5ml, 1ml, 1.5ml, 2ml and 2.5ml were diluted in 10ml volumetric flask with phosphate buffer to give concentrations in range of 5µg/ml to 25µg/ml respectively, absorbance was measured at 220nm.

b) In pH 6.8 Buffer:

i) Preparation of stock solution: Stock solution 100µg/ml of Losartan potassium was prepared in phosphate buffer of pH 6.8. This solution was approximately diluted with phosphate buffer of pH 6.8 to obtain a concentration of 10µg/ml. The resultant solution was scanned in range of 200- 400nm using UV double beam spectrophotometer (Lab India UV-3000+).

ii) Standard calibration of Losartan potassium in phosphate buffer of pH 6.8:

100mg of Losartan potassium was accurately weighed and dissolved in100ml of pH 6.8 phosphate buffer to obtain a concentration of 1000µg/ml. From the above 10ml was withdrawn and diluted to 100ml to obtain a concentration of 100µg/ml. From this stock solution aliquots of 0.5ml, 1ml, 1.5ml, 2ml and 2.5ml were diluted in 10ml volumetric flask with phosphate buffer to give concentrations in range of 5µg/ml to 25µg/ml respectively, absorbance was measured at 224nm.

2.2.1.2) Drug- Excipient Compatibility by FTIR studies:

In the preparation of SR tablet, drug and polymer may interact as they are in close contact with each other, which could lead to instability of drug. Preformulation studies regarding drug-polymer interactions are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy (BRUKER ALPHA-T) was employed to ascertain the compatibility between losartan potassium and selected polymers. The individual drug and drug with excipients were scanned separately.

Procedure: Potassium bromide was mixed with drug and polymer in the ratio of 100:1 and pellet was prepared using KBr pellet press (HORIZON WC-56) and spectrum was taken using FTIR (BRUKER Alpha-T). FT-IR spectrum of losartan potassium was compared with spectrum of losartan potassium and polymer. Disappearance of losartan potassium peaks or shifting of peak in any of the spectra was studied.

2.2.1.3) Angle of repose

The angle of repose of blends was determined by the funnel method. The accurately weighed blend was taken in funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the blend. The blend was allowed to flow from the funnel on the surface. The diameter and height of the heap formed from the blend was measured. The angle of repose was calculated using following formula

$\tan \Theta = h/r$ …… Eqn.(1)

Where, "h" is height of the heap and "r" is the radius of the heap of granules.

2.2.1.4) Carr's compressibility index

The Carr's compressibility Index was calculated from Bulk density and tapped density of the blend. A quantity of 2g of blend from each formulation, filled into a 10mL of measuring cylinder. Initial bulk volume was measured, and cylinder was allowed to tap from the height of 2.5cm. The tapped frequency was 25±2 per min to measure the tapped volume of the blend. The bulk density and tapped density were calculated by using the bulk volume and tapped volume.

Carr's compressibility index was calculated by using following formula:

Carr's compressibility index (%) =

[(Tapped density-Bulk density) X100]/Tapped density ….. Eqn.(2)

2.3) Preparation of tablets

Different tablets formulations were prepared by direct compression technique. All powders were passed through 60 mesh. Required quantities of drug and polymers were mixed thoroughly Magnesium stearate was added as lubricant. Aerosil was used as glidant. Micro crystalline cellulose was used as diluent. Finally the powder mix was subjected to compression after mixing uniformly in a polybag. Prior to compression, the blends were

evaluated for several tests. In all formulations, the amount of the active ingredient is equivalent to 50mg of losartan potassium (Table 1).

Table 1: Formulation Chart

Sno	Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Losartan	50	50	50	50	50	50	50	50	50
2	HPMC K4M	50	100	150	-----	-----	-----	-----	-----	-----
3	HPMC K15M	-----	-----	-----	50	100	150	-----	-----	-----
4	HPMC K100M	-----	-----	-----	-----	-----	-----	50	100	150
5	Mg.Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
6	Aerosil	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
7	MCC	195	145	95	195	145	95	195	145	95
	Total weight	300	300	300	300	300	300	300	300	300

2.4) Evaluation of tablets

The weight of tablets was evaluated on 20 tablets using an electronic balance. Friability was determined using 6 tablets in Roche friability tester at 25rpm. Hardness of the tablets was evaluated using an Monsanto hardness tester. The hardness of all the formulation was between 4-6kg/cm^2.

2.5) In vitro dissolution studies

In vitro drug release studies from the prepared matrix tablets were conducted using USP type II apparatus at 37°C at 50rpm. Dissolution mediums used were 900mL of 0.1N HCl and phosphate buffer of pH 6.8. The release rates from matrix tablets were conducted in HCl solution (pH 1.2) for 2h and changed to phosphate buffer (pH 6.8) for further time periods. The samples were withdrawn at desired time periods from dissolution media and the same were replaced with fresh dissolution media of respective pH. The samples were analyzed by UV-Visible Spectrophotometer (Lab India 3000+). The amounts of drug present in the samples were calculated with the help of appropriate calibration curves constructed from reference standards. Drug dissolved at specified time periods was plotted as percent release versus time curve.

2.6) Dependent-model method (Data analysis)

In order to describe the losartan potassium release kinetics from individual tablet formulations, the corresponding dissolution data were fitted in various kinetic dissolution models: zero order, first order, Higuchi, Korsmeyer Peppas. When these models are used and analyzed in the preparation, the rate constant obtained from these models is an apparent rate constant. The release of drugs from the matrix tablets can be analysed by release kinetic theories. To study the kinetics of drug release from matrix system, the release data were fitted into Zero order as cumulative amount of drug release vs. time (Eqn.3), first order as log cumulative percentage of drug remaining vs. time (Eqn.4), Higuchi model as cumulative percent drug release vs. square root of time (Eqn.5). To describe the release behavior from the polymeric systems, data were fitted according to well known exponential Korsmeyer – Peppas equation as log cumulative percent drug release vs log of time equation (Eqn.6).

(i) Zero order kinetics

$$Qt=K0t \quad \text{.....Eqn.(3)}$$

Where,
Q= Amount of drug release in time t
K0 = Zero order rate constant expressed in unit of concentration /time
t = Release time

(ii) First order kinetics

Log Q=Log Q0-kt/2.303……Eqn.(4)

Where,
Q0= is the initial concentration of drug
k= is the first order rate constant, t =release time

(iii) Higuchi kinetics

Q=kt1/2……...…Eqn.(5)

Where,
k= Release rate constant
t=release time, Hence the release rate is proportional to the reciprocal of the square root of time.

(iv) Korsmeyer-Peppas

First 60% *in vitro* release data was fitted in equation of Korsmeyer et al. to determine the release behavior from controlled release polymer matrix system. The equation is also called as power law,

Mt /M∞ =Kt n …… Eqn.(6)
Where,
Mt = amount of drug released at time t
M∞ = amount of drug released after infinite time
Mt /M∞ = fraction solute release
t = release time
K = kinetic constant incorporating structural and geometric characteristics of the polymer system
n = diffusional exponent that characterizes the mechanism of the release of traces.

The magnitude of the release exponent "n" indicates the release mechanism (i.e. Fickian diffusion, Non Fickian, supercase II release). For matrix tablets, values of n of near 0.5 indicates Fickian diffusion controlled drug release, and an n value of near 1.0 indicates erosion or relaxational control (case II relaxational release transport, non Fickian, zero order release) [8-16]. Values of n between 0.5 and 1 regarded as an indicator of both diffusion and erosion as overall release mechanism commonly called as anomalous release mechanism [17].

3. RESULTS AND DISCUSSION

3.1. Preformulation characteristics:

The drug Losartan potassium was standardized by UV method in 0.1N Hcl and pH 6.8 Buffer separately. The lamba max were 220nm and 224 nm in 0.1N Hcl and pH 6.8 buffer respectively (Fig 1 and Fig 2) and the linearity range was 5-25 mcg/ml in both the media.

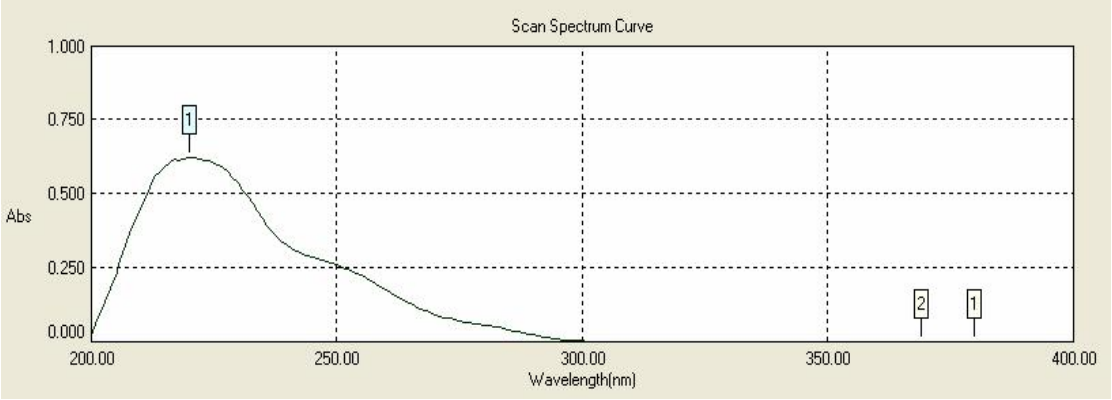


Fig: 1)Lambda Max of Losartan potassium in 0.1 N Hcl (220nm)

Standard graph of Losartan Potassium in 0.1 N Hcl

Table 2: Standard graph of Losartan Potassium in 0.1 N Hcl

Sno	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

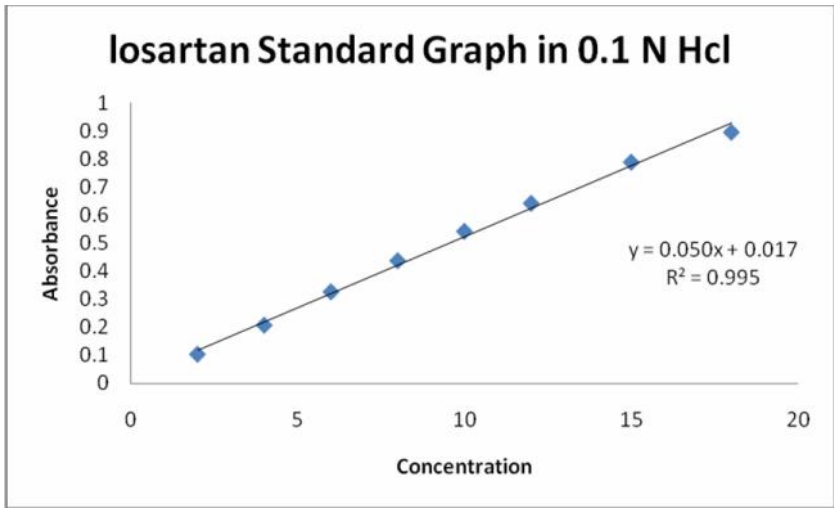


Fig 2 : Standard graph of Losartan Potassium in 0.1 N Hcl

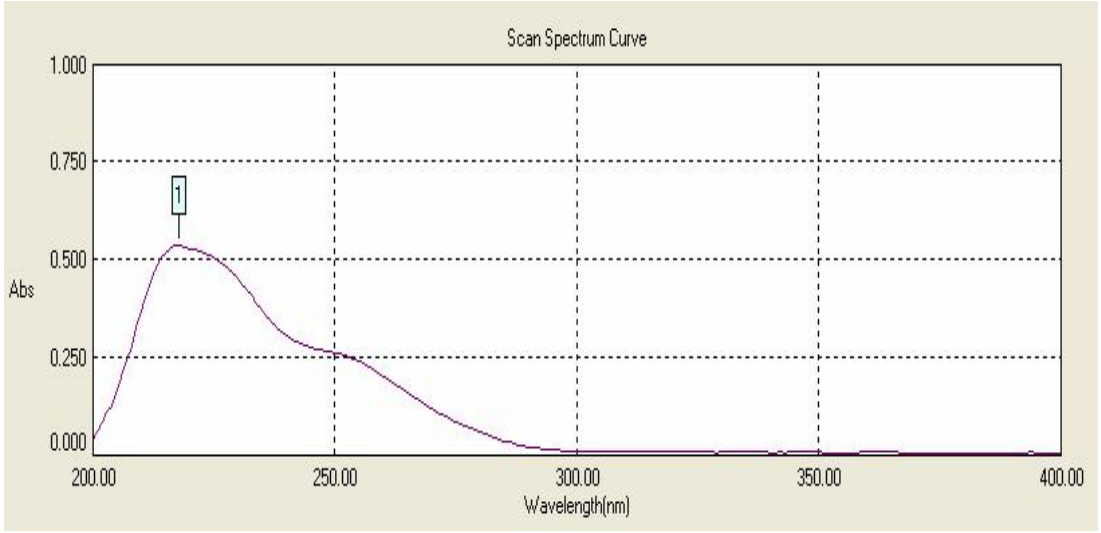


Fig 3: Lambda Max of Losartan potassium in pH 6.8 Buffer (224 nm)

Table 3: Standard graph of Losartan Potassium in pH 6.8 Buffer

Sno	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

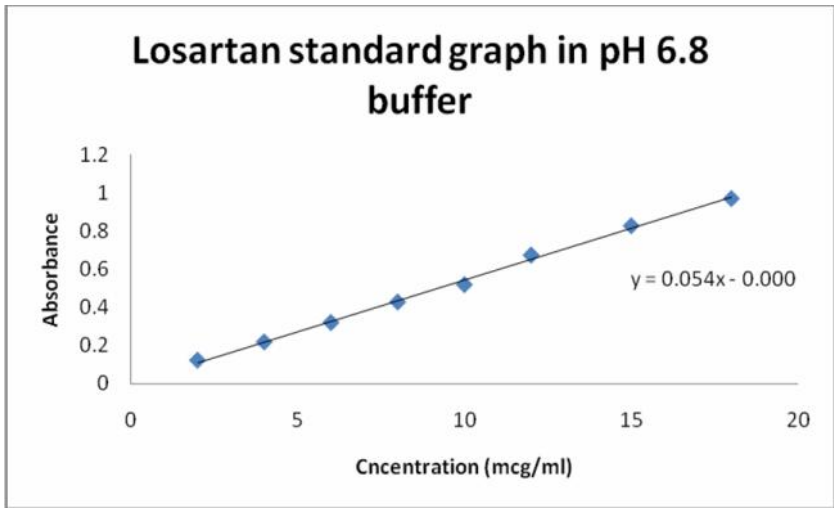


Fig 4: Standard graph of losartan potassium in pH 6.8 Buffer

3.2. Drug: Excipient Compatibility studies- FTIR:

Drug-Excipient compatibility studies by FTIR revealed no interaction between drug and the polymers used in the formulation thus showing compatibility.

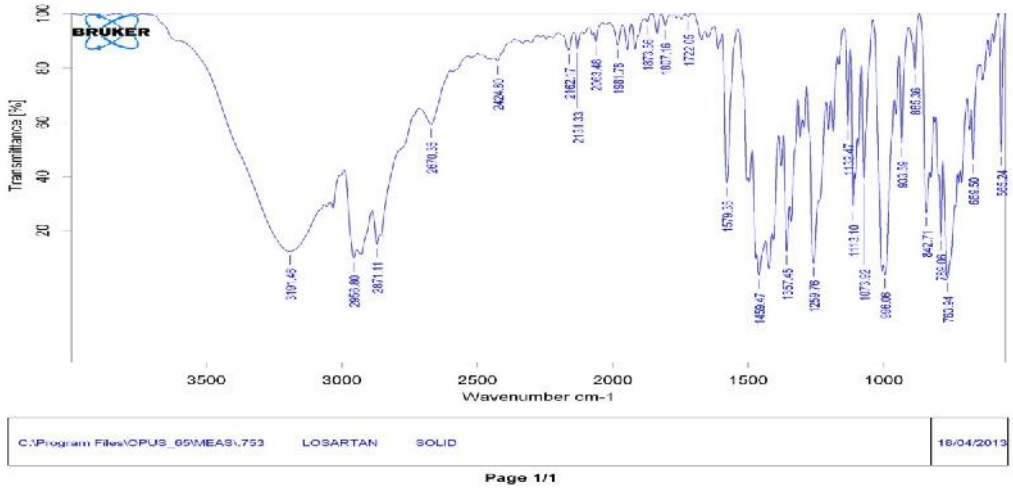


Fig 5: FTIR Spectrum of Pure Drug

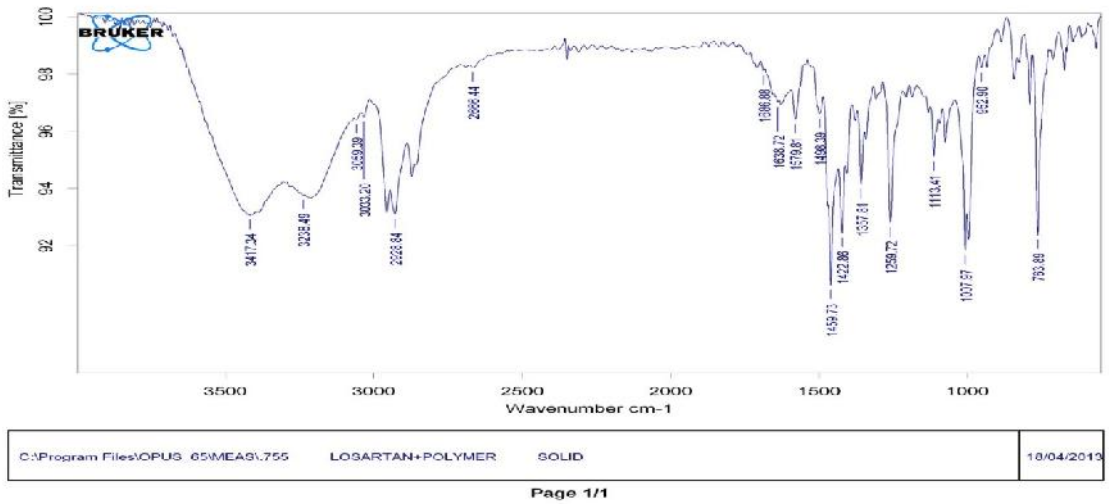


Fig 6: FTIR Spectrum of Drug+ Polymer

3.3. Physical characteristics of blends and tablets

The blends of different formulations were evaluated for angle of repose, Carr's compressibility index etc., (Table 4). The results of Angle of repose and Carr's compressibility Index (%) ranged from 16-28 and 14-16, respectively which showed that blends from all the formulations having good flow property. The hardness and percentage friability ranged from 4-5kg/cm2 and 0.18-0.35% respectively.

Precompression Parameters :

Formulation No	Angle of repose (Ɵ)	Bulk density(gm/cm3)	Tapped density(gm/cm3)	Carr's index (%)
F1	19	0.5144	0.5896	14.61
F2	18	0.5102	0.5952	16.66
F3	16	0.5122	0.5814	14.03
F4	14	0.5208	0.5966	14.60
F5	34	0.5081	0.6053	19.13
F6	17	0.5091	0.5924	16.36
F7	28	0.5197	0.5966	14.79
F8	19	0.5144	0.5980	16.26
F9	18	0.5319	0.6024	13.25

Post Compression Parameters:

Formulation No	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Assay (%)
F1	300 ± 1.06	4.5 ± 0.2	3.62	0.27	98.51
F2	300 ± 2.43	4.0 ± 0.3	3.67	0.35	97.82
F3	299.9 ± 1.78	4.0 ± 0.3	3.63	0.24	98.91
F4	300.2 ± 1.1	4.0 ± 0.5	3.70	0.30	98.20
F5	300.5± 1.25	4.0 ± 0.3	3.64	0.32	97.04
F6	299.5± 1.75	4.0 ± 0.2	3.67	0.27	98.28
F7	299.8 ± 1.83	4.0± 0.2	3.67	0.18	99.50
F8	300.5 ± 1.24	4.0 ± 0.4	3.68	0.19	99.62
F9	300.0± 1.56	4.0 ± 0.3	3.67	0.18	99.11

3.2. In vitro dissolution studies

Losartan potassium sustained release tablets were prepared by using HPMC polymers. The release profiles of losartan potassium sustained release tablets were plotted as Fig.7-9. The release rate of losartan potassium mainly controlled by the hydration and swelling properties of HPMC which forms a gel layer that controls the water penetration and drug diffusion. The effect of polymer concentration on drug release could be clearly seen from the variation of the dissolution profiles. It was found that drug release from F1-F6 composed of HPMC K4M and HPMC K15M polymers was no longer than 8h and significantly higher drug release rate than other formulation which were prepared by using HPMC K100 M. Formulation F7 containing HPMC K100 M in ratio of 1: 1 could retard drug for relatively 12 hr compared to all other formulations. On applying release kinetics, the formulation F7 was following First order kinetics and Higuchi's model of drug release.

Table 6 : Dissolution release profiles of Formulations F1-F9

Sno	Time (Hrs)	% Cumulative Drug Release								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	**0**	0	0	0	0	0	0	**0**	0	0
2	**0.5**	22.4	26.2	20.3	39.5	32.1	29.5	**14.1**	9	6
3	**1**	40.1	56.9	45.1	53.3	47.8	43.1	**28.3**	29	16
4	**2**	74.6	78.4	66.9	77.2	66.2	67.3	**41.4**	38	34
5	**4**	98.7	92.1	80.6	89.0	88.5	83.8	**54.6**	49	42
6	**6**	-----	99.8	87.1	98.9	96.3	88.2	**78.9**	68	60
7	**8**	-----	-----	98.5	-----	99.1	92.1	**90.2**	82	75
8	**10**	-----	-----	-----	-----	-----	99.3	**96.0**	88	86
9	**12**	-----	-----	-----	-----	-----	-----	**101.0**	92	90

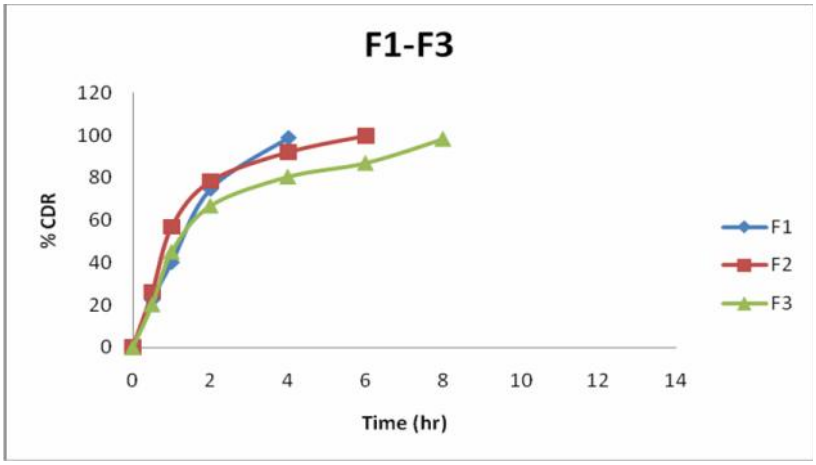


Fig 7: Dissolution profiles of Formulations F1-F3 (Using HPMC K4M)

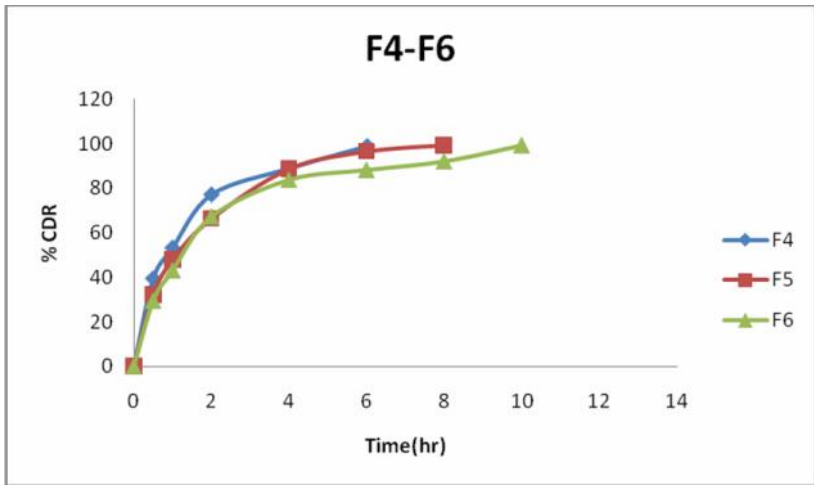


Fig 8: Dissolution profiles of Formulations F4-F6 (Using HPMC K15M)

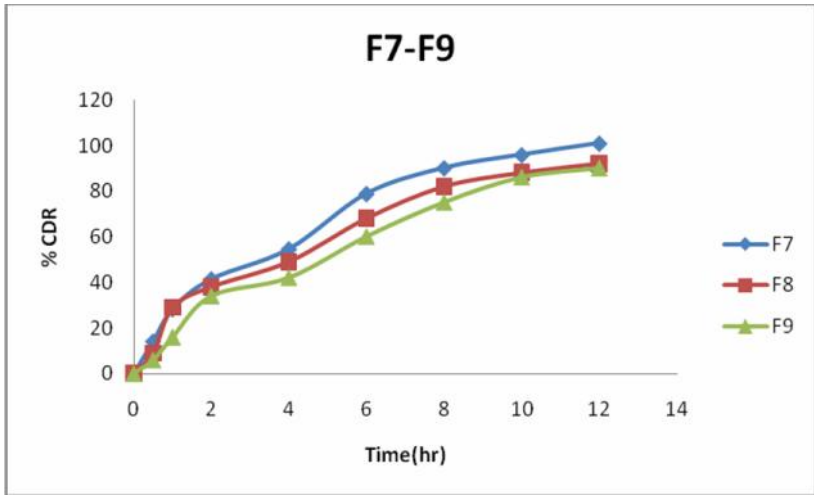
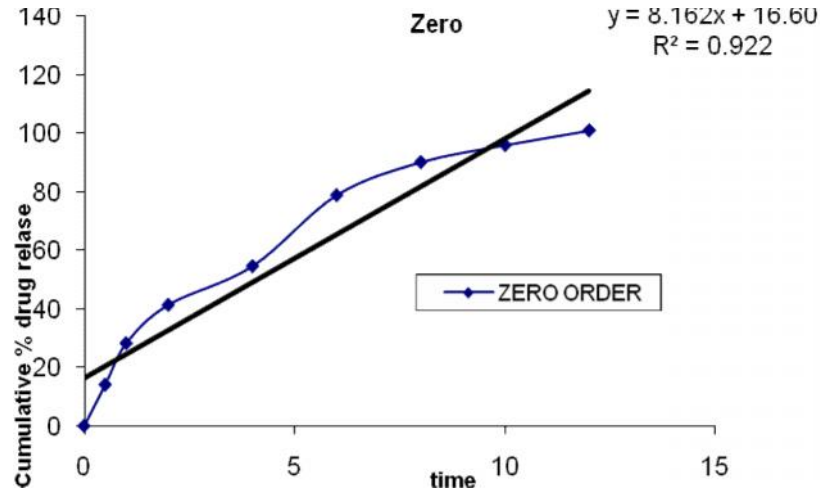


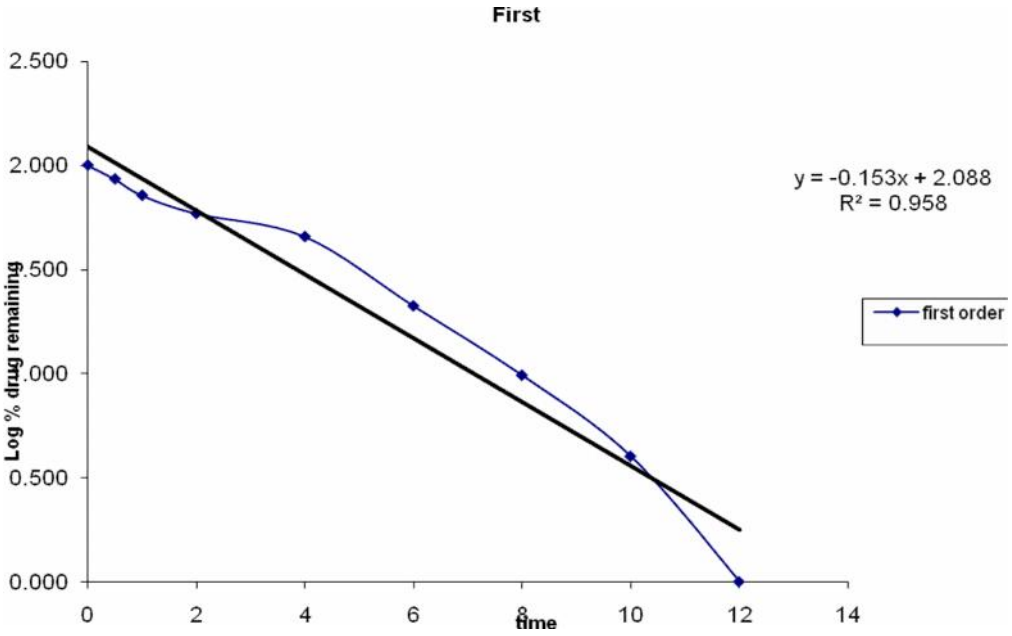
Fig 9: Dissolution profiles of Formulations F7-F9 (Using HPMC K100M)

Release Kinetics of optimized formulation F7:

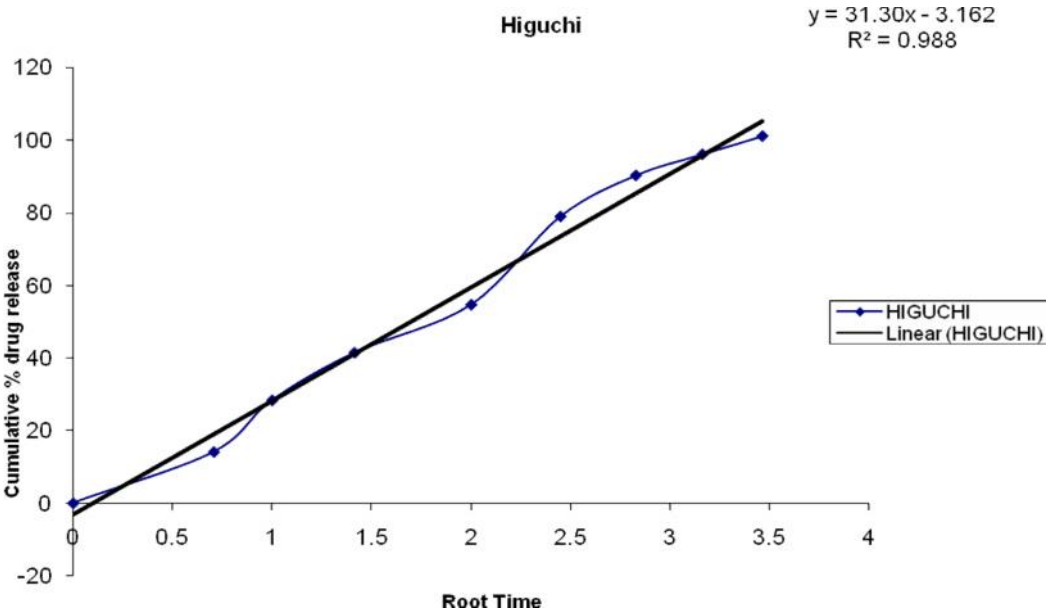
Zero Order



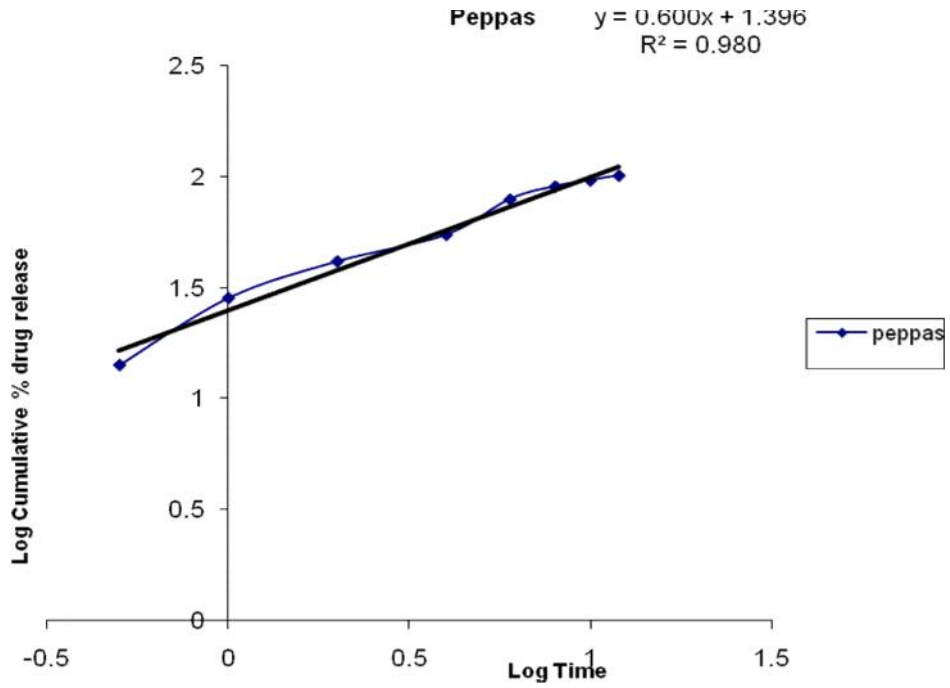
First Order



Higuchi:



Korsemeyer Peppas



4. CONCLUSIONS

The sustained release tablets of losartan potassium were prepared successfully using HPMC polymer of different viscosity. According to *in vitro* release studies, the release rate was decreased with increasing viscosity and amount of polymer. The results of the study clearly demonstrated that HPMC matrix tablet formulation is an effective and promising drug delivery system for once daily administration of losartan potassium.The analysis of the release profiles in the light of distinct kinetic models (zero order, first order, Higuchi, Korsmeyer Peppas) led to the conclusion that, the drug release characteristics from HPMC polymer matrices follows Higuchi square root time kinetics and the mechanism of drug release was both diffusion and erosion.

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