WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 10, 2115-2130. Research Article ISSN 2277– 7105

DIFFUSION SUSTAINED RELEASE MATRIX TABLETS OF LOSARTAN POTASSIUM BY SELECTING DIFFERENT GRADES OF HPMC AND GUAR GUM AS RETARDING POLYMERS.

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Article Received on
18 Aug 2015,

Revised on 11 Sept 2015,
Accepted on 02 Oct 2015

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ABSTRACT

In the present work, an attempt has been made to develop Diffusion sustained release matrix tablets of Losartan potassium by selecting different grades of HPMC and Guar gum as retarding polymers. All the formulations were prepared by direct compression method. The blend of all the formulations showed god flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F3 formulation showed maximum % drug release i.e., 97.3 % in 8 hours hence it is considered as optimized formulation. Whereas the formulation containing HPMCK100M showed more retarding with increasing concentration of polymer. The formulations with Guar gum were unable to produce the desired rug release pattern.

KEY WORDS: Losartan potassium, HPMC K15M, HPMC K100 M, Guar gum, Sustained release tablets.

Objectives of work

1. To formulate Diffusion Sustained release matrix tablets of Losartan potassium to improve its oral bioavailability and to reduce its dosing frequency.
2. To optimize optimum concentration of various Sustained release polymers.
3. To perform various quality control evaluation parameters for the prepared tablets.

6. Methodology

6.1 Determination OF UV Absorption maxima

Losartan potassium solution was prepared in 0.1 N HCL and diluted suitably. The UV spectrum of the solution was taken on Lab India 3200 UV/Vis double beam Spectrophotometer. The Solution exhibited UV maxima at 231 nm. The procedure was repeated with pH 6.8 phosphate buffer.

6.2 Preparation of Standard Calibration Curve of Losartan potassium:

100 mg of Losartan potassium was accurately weighed and dissolved in little amount of Methanol and make up the final volume up to 100 ml with 0.1 N HCl (pH 1.2) to prepare stock solution. The 10 ml of stock solution was further diluted with 0.1 N HCl (pH 1.2) in 100ml to get 100µg/ml (working standard). Then 0.2,0.4,0.6.0.8,and 1 ml of working standard was taken in 10 ml standard volumetric flask and made up the volume with 0.1N HCl to prepare 2µg,4µg,6µg,8µg, and 10µg drug per ml solution. Then the absorbance was measured in a UV spectrophotometer at 231 nm against 0.1 N HCl (pH 1.2) as blank. The absorbance so obtained was tabulated as in Table 7.1. Calibration curve was constructed and shown in Fig. 7.1.The procedure was repeated with pH 6.8 phosphate buffer and absorbance's were measured at 230 nm. The absorbances and standard graph were mentioned in Table 7.2 and figure 7.2 respectively.

6.3 Tablet formulation

Formulation of Losartan potassium Sustained release Tablet by Direct- Compression:

Composition of preliminary trials for Losartan potassium Sustained release Tablet by direct compression is shown in table 6.1. All the ingredients were weighed. Required quantity of drug and excipient mixed thoroughly in a polybag. The blend is compressed using Lab Press tablet machine-10 station with 10mm flat punch, B tooling. Each tablet contains 100mg of Losartan potassium and other pharmaceutical ingredients.

6.1. Formulation of Losartan potassium Sustained release tablets

INGREDIENT	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F10	F11	F12
Losartan potassium	100	100	100	100	100	100	100	100	100	100	100	100
HPMC K15M	50	100	150	200								
HPMC K100M					50	100	150	200				
GUAR GUM									50	100	150	200
Talc	5	5	5	5	5	5	5	5	5	5	5	5
Mg. Stearate	5	5	5	5	5	5	5	5	5	5	5	5
MCC pH102	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
TOTAL	500	500	500	500	500	500	500	500	500	500	500	500

All ingredients are expressed in mg only

6.4 Evaluation parameters

Precompression parameters

1. Bulk Density (D_b)

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

$$\mathbf{D_b = M / V_b}$$

Where, M is the mass of powder

V_b is the bulk volume of the powder.

2. Tapped Density (D_t)

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by,

$$\mathbf{D_t = M / V_t}$$

Where,

M is the mass of powder

V_t is the tapped volume of the powder.

3. Angle of Repose (Θ)

The friction forces in a loose powder can be measured by the angle of repose (q). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane

$$\mathbf{\tan(\Theta) = h / r}$$

$$\mathbf{\Theta = \tan^{-1} (h / r)}$$

Where,

Θ is the angle of repose.

h is the height in cm

r is the radius in cm

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel. Relationship between angle of repose and powder flow property.

Table 6.2 : Angle of Repose as an Indication of Powder Flow Properties

Sr. No.	Angle of Repose(^{0})	Type of Flow
1	<20	Excellent
2	20-30	Good
3	30-34	Passable
4	>34	Very Poor

4. Carr's index (or) % compressibility

It indicates powder flow properties. It is expressed in percentage and is give by,

$$I = \frac{D_t - D_b}{D_t} \times 100$$

Where,

Dt is the tapped density of the powder and

Db is the bulk density of the powder.

Table 6.3: Relationship between % compressibility and flow ability.

Sr no.	% Compressibility	Flow ability
1	5-12	Excellent
2	12-16	Good
3	18-21	Fair Passable
4	23-35	Poor
5	33-38	Very Poor
6	<40	Very Very Poor

5. Hausner ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner ratio} = \frac{D_t}{D_b}$$

Where, D_t is the tapped density, D_b is the bulk density.

Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Post compression parameters: [43, 44, 45, 46]

1. Weight variation:

20 tablets were selected randomly from the lot and weighted individually to check for weight variation. Weight variation specification as per I.P. is shown in table No.6.4

Table 6.4: Weight Variation Specification as per IP

Average Weight of Tablets	%Deviation
80 mg or less	±10
More than 80 mg but less than 250 mg	±7.5
250 mg or more	±5

2. Hardness

Hardness or tablet crushing strength (fc), the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm^2.

3. Thickness

Three tablets were selected randomly from each batch and thickness was measured by using Vernier Caliper.

4. Friability (F)

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at the height of 6 inches in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.]

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

5. In-Vitro drug release

Invitro dissolution studies were carried out by using 900ml of 0.1 N HCl in USP dissolution apparatus by using paddle method for about 2 hours. After 2 hours the dissolution medium

was withdrawn keeping the tablet in the dissolution basket. Then pH 6.8 phosphate buffer was added to the dissolution medium (900ml) and the dissolution was carried out for about 8 hours.The samples were withdrawn at regular time intervals of 30 min,1 hour,2 hr,3,5,5,6,7 & 8 hours respectively.

6. Assay

10 tablets were weighed and triturated. The tablet triturate equivalent to 10 mg of the drug was weighed accurately, dissolved in pH 1.2 buffer and diluted to 100 ml with the same. Further dilutions were done suitably to get a concentration of 10 µg/ ml with simulated gastric fluid pH 1.2. Absorbance was read at 210 nm against the reagent blank, and the concentrations of Losartan potassium in µg/ ml was determined by using the regression equation.

Y = absorbance/slope

Drug content in mg / tablet = conc. µg/ml * dilution factor

% Drug content = drug content in mg * 100 / label claim.

7. RESULTS & DISCUSSION

Standard Calibration curve of Losartan potassium:

Table 7.1: Concentration and absorbance obtained for calibration curve of Losartan potassiumS in 0.1 N hydrochloric acid buffer (pH 1.2)

S. No.	Concentration (µg/ml)	Absorbance* (at 217 nm)
0	0	0
1	2	0.15
2	4	0.31
3	6	0.45
4	8	0.579
5	10	0.71
Correlation Coefficient = 0.998 y = 0.071x + 0.011		

It was found that the estimation of Losartan potassium by UV spectrophotometric method at λ_{max} 231.0 nm in 0.1N Hydrochloric acid had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 2-10µg/ml. The regression equation generated was y = 0.063x + 0.075.

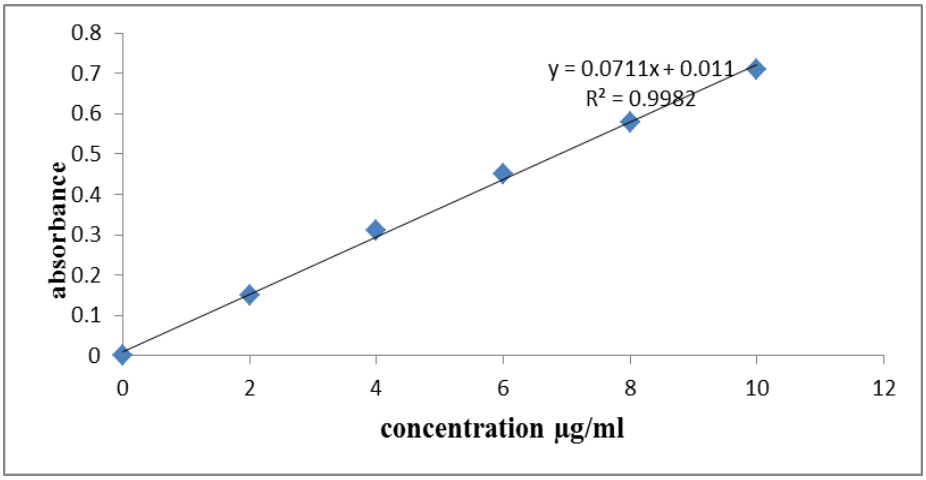

Fig 7.1 : Standard graph of Losartan potassium in 0.1 N HCl

Table 7.2: Concentration and absorbance obtained for calibration curve of Losartan potassium in pH 6.8 Phosphate buffer.

S. No.	Concentration (µg/ml)	Absorbance* (at 220 nm)
1	2	0.15
2	4	0.29
3	6	0.42
4	8	0.553
5	10	0.677
Correlation Coefficient = 0.999 y = 0.067x + 0.010		

It was found that the estimation of Losartan potassium by UV spectrophotometric method at λ_{max} 230.0 nm in pH 6.8 Phosphate buffer. had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 2-10µg/ml. The regression equation generated was y = 0.067x + 0.010.

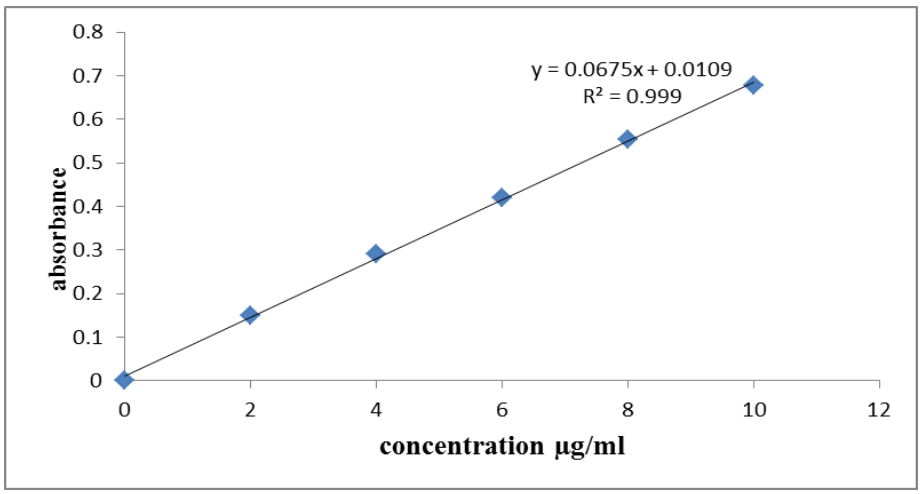

Fig 7.2: Standard graph of Losartan potassium in pH 6.8 Phosphate buffer

7.2 Evaluation Parameters for Sustained release tablets of Losartan potassium:

7.2.1 Pre-compression parameters

The data's were shown in Table 7.3.The values for angle of repose were found in the range of 25°-30°. Bulk densities and tapped densities of various formulations were found to be in the range of 0.41 to 0.50 (gm/cc) and 0.50 to 0.58 (gm/cc) respectively. Carr's index of the prepared blends fall in the range of 13.06% to 18.18%. The Hausner ration fall in range of 1.14 to 1.22. From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

Table 7.3: Pre-compression parameters

Formulations	Bulk Density (gm/cm^2)	Tap Density (gm/cm^2)	Carr's Index (%)	Hausner ratio	Angle Of Repose(Ɵ)
F_1	0.45	0.55	18.18	1.22	27.91
F_2	0.47	0.55	14.54	1.17	28.23
F_3	0.50	0.58	13.79	1.16	29.34
F_4	0.46	0.55	16.36	1.19	26.71
F_5	0.50	0.58	13.79	1.16	29.34
F_6	0.47	0.55	14.54	1.17	28.23
F_7	0.50	0.58	13.79	1.16	29.34
F_8	0.41	0.50	18	1.21	26.78
F_9	0.41	0.50	18	1.21	26.78
F10	0.42	0.51	18.24	1.20	26.68
F11	0.48	0.56	18.12	1.21	26.70
F12	0.41	0.54	18.11	1.22	26.71

7.2.2. Post compression Parameters

Weight variation test

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 7.4. The average weight of the tablet is approximately in range of 495 to 505 mg, so the permissible limit is ±5% (>220 mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test

Hardness of the three tablets of each batch was checked by using Pfizer hardness tester and the data's were shown in Table 7.4. The results showed that the hardness of the tablets is in range of 4 to 4.5 kg/cm^2, which was within IP limits.

Thickness

Thickness of three tablets of each batch was checked by using Vernier Caliper and data shown in Table-7.4 The result showed that thickness of the tablet is raging from 5.00 to 6.14 mm.

Friability

Tablets of each batch were evaluated for percentage friability and the data's were shown in the Table 7.4. The average friability of all the formulations lies in the range of 0.30 to 0.51% which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Table No:7.4.:Post Compression Parameters

7.4. Post-Compression parameters:					
FD	**Weight variation (mg)**	**Hardness (kg/cm^2)**	**Thickness (mm)**	**Friability (%)**	**Assay (%)**
F_1	494	4.5	5.5	0.43	97.23
F_2	504	4.3	5.5	0.34	98.55
F_3	510	4.2	5.5	0.49	98.16
F_4	495	4.2	5.4	0.47	99.34
F_5	502	4.3	5.5	0.49	98.16
F_6	508	4.3	5.5	0.34	98.55
F_7	510	4.4	5.4	0.49	98.16
F_8	494	4.5	5.5	0.34	99.25
F_9	506	4.4	5.5	0.34	99.25
F10	501	4.4	5.5	0.43	98.6
F11	502	4.3	5.5	0.54	98.7
F12	504	4.5	5.5	0.43	98.5

Assay: Assay studies were performed for the prepared formulations. From the assay studies it was concluded that all the formulations were showing the % drug content values within 97.23 -99.25 %.

***In-vitro* Dissolution studies**

In-vitro dissolution studies were carried out by using 900ml of 0.1 N HCl in USP dissolution apparatus by using paddle method for about 2 hours. After 2 hours the dissolution medium was withdrawn keeping the tablet in the dissolution basket. Then pH 6.8 phosphate buffer was added to the dissolution medium (900ml) and the dissolution was carried out for about 6 hours.The samples were withdrawn at regular time intervals of 30 min,1 hour,2 hr,3,5,5,6,7 & 8 hours respectively. The results were displayed in table 7.5.

Table 7.5: *In-vitro* dissolution data

Time(Hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0.5	25.5	20.1	16.4	11.4	15.4	10.4	9.4	8.5	49.5	38.2	26.4	18.9
1	46.7	39.4	26.7	18.6	29.4	16.5	15.6	14.5	78.8	41.9	38.2	28.3
2	76.5	55.3	34.6	29.5	38.5	28.6	21.4	18.4	96.9	62.4	43.4	36.4
3	98.4	75.3	42.4	39.5	55.4	39.5	36.7	23.4	96.1	78.2	59.3	49.5
4		87.3	55.4	49.6	68.4	48.5	42.4	28.2		81.4	76.3	69.3
5		99.4	67.4	57.4	87.1	59.4	49.6	34.8		96.8	88.4	78.1
6			85.4	69.3	98.3	69.2	55.3	40.2			95.4	89.7
7			91.5	78.5		74.5	60.3	44.8			98.5	97.5
8			97.3	82.3		82.3	72.8	50.4				

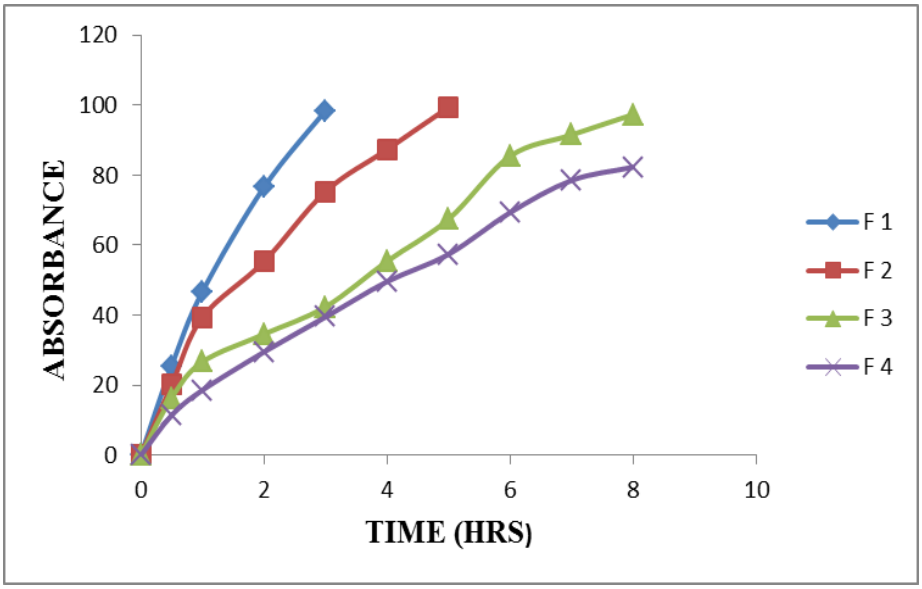

Fig 7.3: Dissolution profile of formulations prepared with HPMC K15M polymer

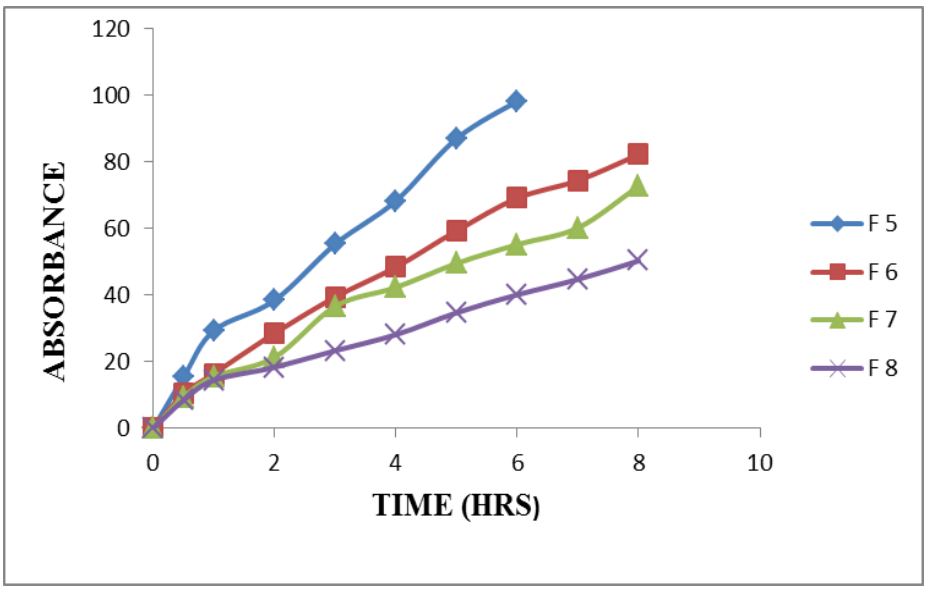

Fig 7.4: Dissolution profile of formulations prepared with HPMC K100M polymer

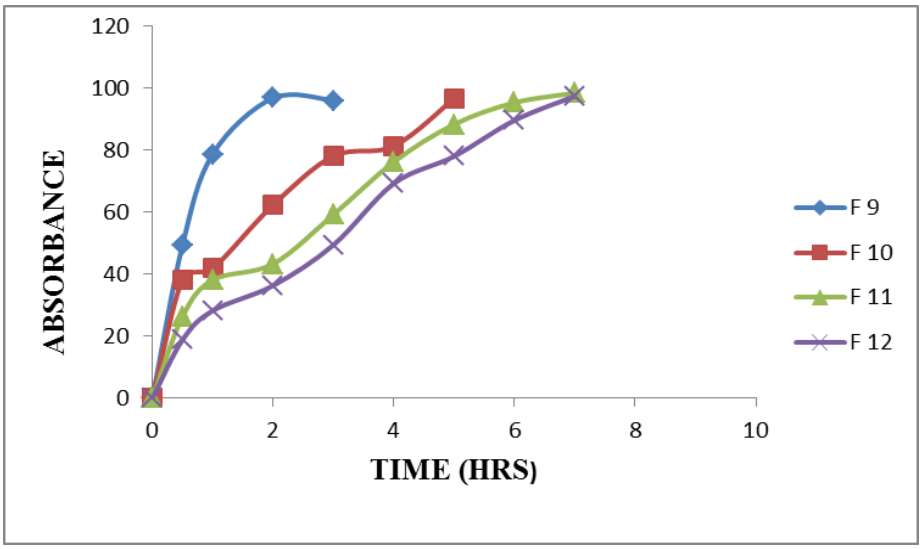

Fig 7.5: Dissolution profile of formulations prepared with Guar gum as polymer

From the tabular column 7.5 it was evident that the formulations prepared with HPMC K15M as retarding polymer in low concentrations the polymer was unable to produce the required retarding action to the tablets. As the concentration of polymer increases the retarding nature was also increased. HPMC K15 M in the concentration of 150 mg showed good % drug release i.e., 97.3 in 8 hours. Where as in the concentration of 200 mg it showed less drug release due to increased retarding nature of polymer.

Where as in case of formulations prepared with HPMC K100 M as retarding polymer, the formulations with 50 mg concentration of polymer showed complete drug release in 6 hours only, whereas the concentration of polymer increases the retarding nature also increased. The Formulation Containing HPMC K100M in 100 Mg Concentration Showed good retarding nature with required drug release in 8 hours i.e., 82.3%.

Where as in case formulations prepared with Guar gum as retarding polymer, as the concentration of polymer increases the retarding nature was also increased. When compared with HPMC polymers it was failed to produce desired drug release pattern. From the above results it was evident that the formulation F3 is best formulation with desired drug release pattern extended up to 8 hours.

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Table 7.6: Release kinetics data for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG (%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
16.4	0.5	0.707	1.215	-0.301	1.922	32.800	0.0610	-0.785	83.6	4.642	4.373	0.269
26.7	1	1.000	1.427	0.000	1.865	26.700	0.0375	-0.573	73.3	4.642	4.185	0.457
34.6	2	1.414	1.539	0.301	1.816	17.300	0.0289	-0.461	65.4	4.642	4.029	0.613
42.4	3	1.732	1.627	0.477	1.760	14.133	0.0236	-0.373	57.6	4.642	3.862	0.780
55.4	4	2.000	1.744	0.602	1.649	13.850	0.0181	-0.256	44.6	4.642	3.546	1.095
67.4	5	2.236	1.829	0.699	1.513	13.480	0.0148	-0.171	32.6	4.642	3.195	1.447
85.4	6	2.449	1.931	0.778	1.164	14.233	0.0117	-0.069	14.6	4.642	2.444	2.197
91.5	7	2.646	1.961	0.845	0.929	13.071	0.0109	-0.039	8.5	4.642	2.041	2.601
97.3	8	2.828	1.988	0.903	0.431	12.163	0.0103	-0.012	2.7	4.642	1.392	3.249

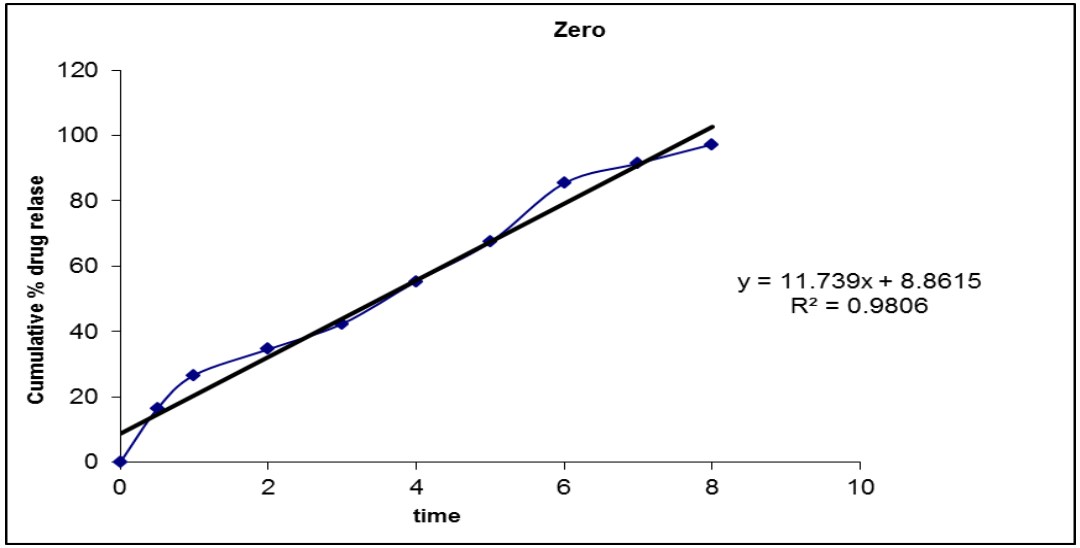

Fig 7.6 : Zero order release kinetics graph

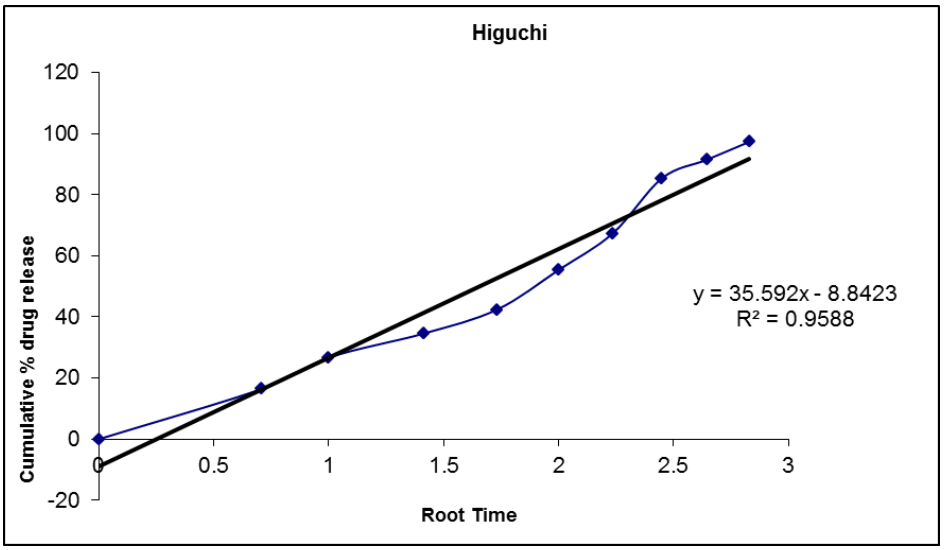

Fig 7.7: Higuchi release kinetics graph

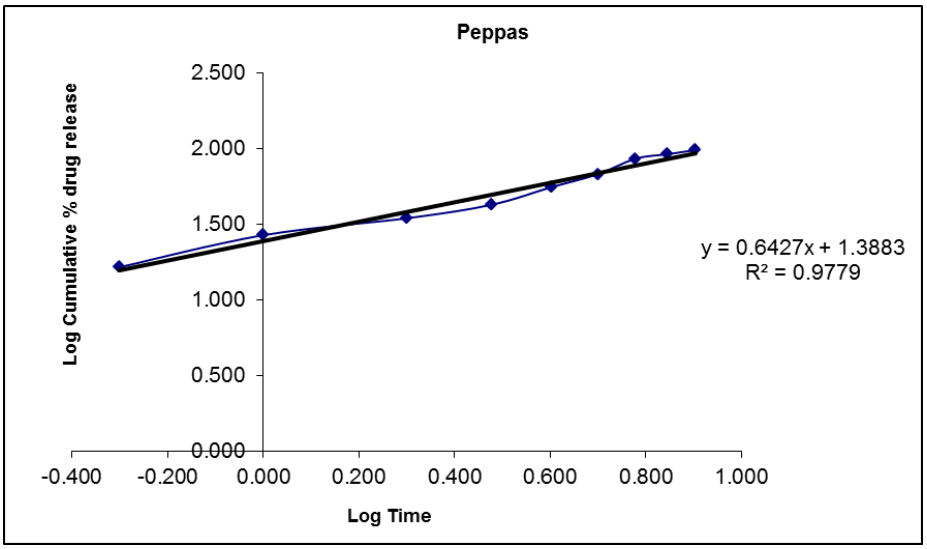

Fig 7.8: Kars mayer peppas graph

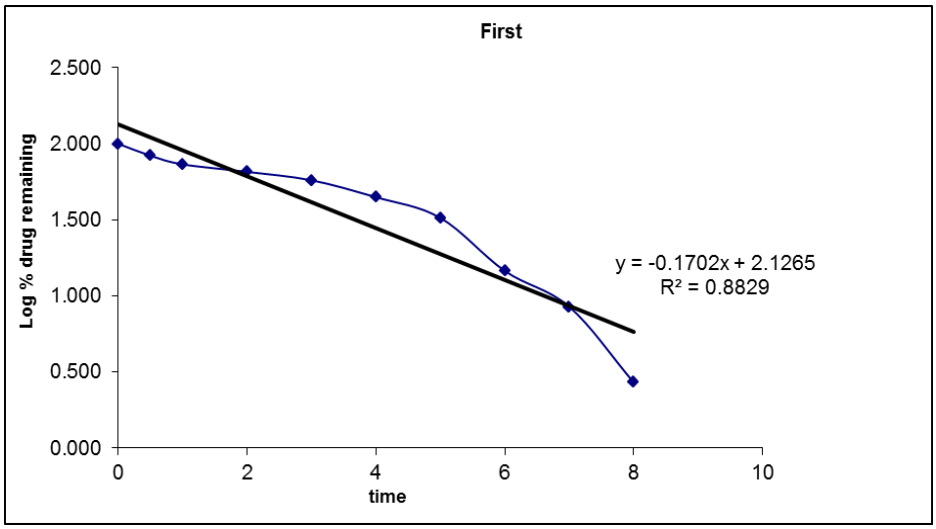

Fig 7.9: First order release kinetics graph

From the above graphs it was evident that the formulation F3 was followed Zero order release mechanism.

Drug – Excipient compatability studies

Fourier Transform-Infrared Spectroscopy

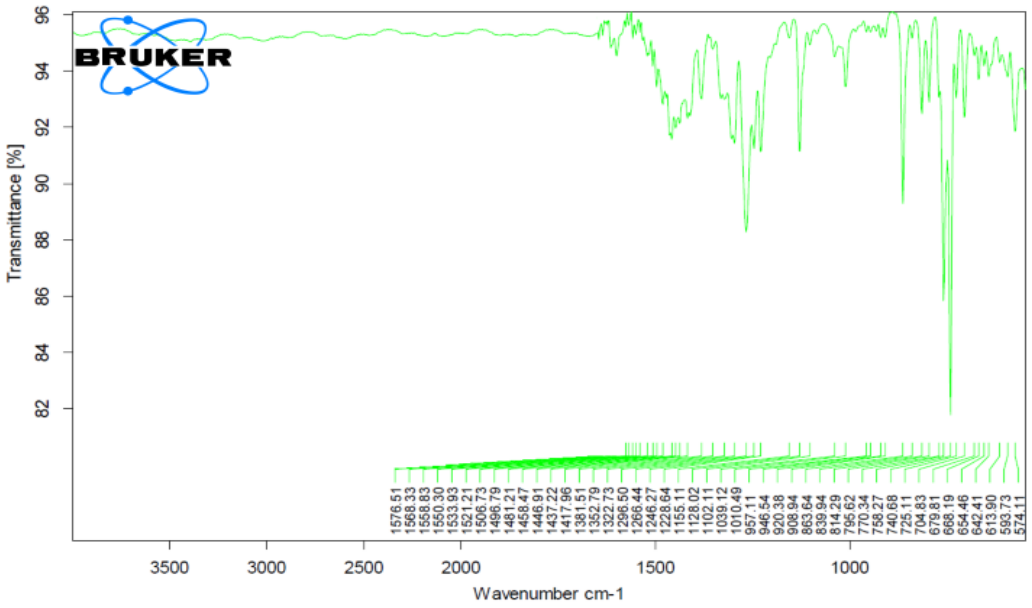

Fig no 7.10 : FT-TR Spectrum of Losartan potassium pure drug

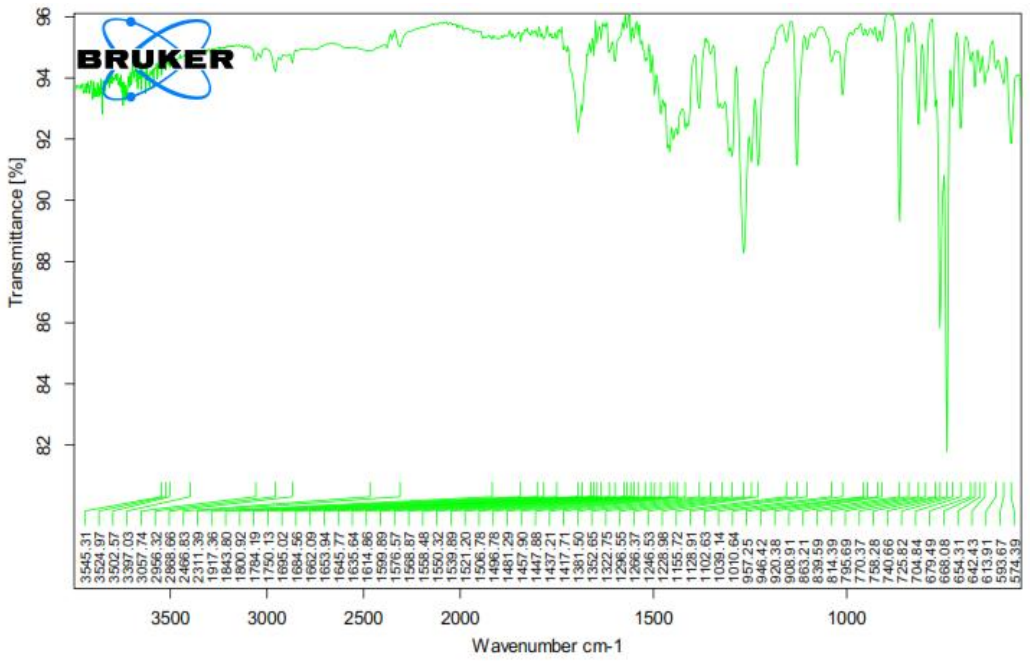

Figure 7.11: FT-IR Spectrum of Optimized Formulation

By using FTIR drug and excipient compatibility studies were carried out. FTIR results showed that the drug and excipients were compatible with each other.

CONCLUSION

In the present work, an attempt has been made to develop Sustained release tablets of Losratan potassium by selecting different grades of HPMC and Guar gum as retarding polymers. All the formulations were prepared by direct compression method using 12mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed god flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F3 formulation showed maximum % drug release i.e., 97.3 % in 8 hours hence it is considered as optimized formulation. Whereas the formulations containing HPMCK100M showed more retarding with increasing concentration of polymer. The formulations with Guar gum were unable to produce the desired rug release pattern.

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