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DESIGN, DEVELOPMENT AND CHARACTERIZATION OF LOSARTAN POTASSIUM SUSTAINED RELEASE MATRIX TABLET

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ABSTRACT

The aim of this research work was to formulate and develop a fixed Dose Combination product in a two different strength using same blend for both the strengths of tablet as a SR tablet formulation. In the tablet, Extended Release layer consist of Antihypertensive Drug belonging to class β-selective adrenergic blocking agent without partial agonist or membrane stabilizing properties. Extended release preparation provides sustained release and reduces the chances of tough related side effects. In selected cases of extended release preparation of this drug used in treatment of hypertension and congestive heart failure. The clinical studies have shown beneficial role of this drug as an extended release preparation. The main objective of the present study was to develop, formulate and evaluate a matrix tablet by using hydrophilic natural retardant polymers which would retard drug release in upper GI tract and should start releasing the drug when it reaches the alkaline environment of small intestine. Metolose 90 sh and xanthan gum were investigated as the model hydrophilic retardant polymers. Wet granulation method was used for preparation of sustained release matrix tablets. Nine batches of tablets were prepared. The prepared tablets were subjected for pharmacopoeial and non-pharmacopoeial evaluation parameters including loose and tapped bulk density, compressibility index, hausner ratio, angle of repose, friability, hardness, thickness, weight variation, % drug content and in-vitro drug release studies. It can be concluded that the combination of hydrophilic polymers that are retardant in nature are better suited for sustained and controlled drug delivery system than the hydrophilic polymer alone.

INTRODUCTION

Oral drug delivery, the fastest and more preferred route for drug administration is also the largest & oldest segment of the total drug delivery market. The concept to formulate oral extended release of drugs requires use of hydrophilic polymers to achieve steady state blood level or tissue level that is therapeutically effective and non-toxic for an extended period of time. To achieve better therapeutic action various types of drug delivery systems are available, out of which sustained release drug delivery system is gaining more importance because of their wide advantages over others like ease of administration, convenience and non-invasiveness. To overcome the problems like achieving steady state of therapeutic drug concentration encountered by conventional drug delivery system, sustained release drug delivery system was introduced three decades ago. The aim of present is to formulate and evaluate sustained release matrix tablets by using different rate retarding natural or synthetic polymers in alone or in combination. The objectives of present topics are to study and investigate the effect of concentration of different natural or synthetic polymers and their combination on release profile of drug from matrix system. Comparative evaluation and optimization of natural or synthetic polymers blends in the development of SR matrix tablet formulation. To develop the matrix system natural biodegradable polymer that retards release of drug in upper GI tract (stomach and small intestine) and the system gets degraded in lower part of the intestine to release the drug.

MATERIALS

Losartan potassium was obtained as a gift sample from Concept Pharma Aurangabad and other ingredients like Metolose 90 sh100000SR, Xanthan gum, magnesium stearate were gifted by Merck Chemical, Mumbai.

METHODS

For preparing the matrix tablets, Losartan potassium and various concentration of Metolose 90sh 10000SR and xanthan gum were used as a hydrophilic polymer.. The other excipient used was MCC for its diluent property. They were first sieved and then sufficient amount of Isopropyl alcohol was added and then wet mass was sieved through mesh no.20 and dried at 55 c for 1hr in an oven. The dried granules were passed through mesh no.16 and fractions of granules retained on the sieve were discarded. Finally 1% talc and0.5% magnesium stearate was mixed for lubrication of granules which were then compressed by cadmach single punch machine by using 9.5mm flat punch. The weight of tablet was adjusted to 250 mg and each

tablet contained 50 mg Losartan potassium. The compressed tablets of each type of polymer were then evaluated for tablet characteristics such as thickness, weight variation and friability. Preparation of matrix tablets by Wet Granulation method the sustained release matrix tablets of Losartan potassium tablet were prepared by wet granulation method. shows the composition of each matrix formulation. The formulation of each Losartan potassium sustained release matrix tablets is composed of two selected polymers i.e. Metolose 90 sh , and xanthan gum in alone or in combination. The other excipients used were MCC for its diluent property, PVP K-30 as a binder and magnesium stearate and talc. The weight of tablet was adjusted to 250 mg and each tablet contained 50 mg Losartan potassium.

Formulations of Losartan potassium matrix tablets.

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Losartan Potassium	50	50	50	50	50	50	50	50	50
Metolose 90sh 10000 sr	50	75	100				25	37.5	50
Xantan gum				50	75	100	25	37.5	50
MCC	135	115	85	135	115	85	135	115	85
PVP K-30	10	10	10	10	10	10	10	10	10
IPA	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Mag.Stearate	3	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2	2
Total Weight	250	250	250	250	250	250	250	250	250

RESULT and DISCUSSION

Loss on drying of losartan potassium

The pharmacopoeial limits for LOD of losartan potassium reported not more than 1% and the experimental values for given sample of losartan potassium where found to be 0.67% indicating good agreement between the reported and experimental value.

Table No.1 Evaluation of prepared Losartan potassium powder blend.

Formulation	LooseBulk Density(g/cm)	Tapped bulkdensity(g/cm^2)	Carr's index(%)	Hausner ratio	Angleof Repose (degrees)
F1	0.443±0.013	0.508±0.008	12.69±0.042	1.145±0.012	$31^0$02'±0.014
F2	0.466±0.009	0.528±0.017	11.76±0.031	1.133±0.009	$32^0$82'±0.019
F3	0.488±0.007	0.522±0.019	7.89±0.019	1.069±0.014	$29^0$75'±0.011
F4	0.455±0.011	0.495±0.013	8.68±0.024	1.089±0.004	$30^0$46'±0.008
F5	0.469±0.014	0.506±0.007	8.41±0.015	1.077±0.001	$29^0$64'±0.002
F6	0.434±0.008	0.498±0.021	11.35±0.021	1.148±0.009	$32^0$26'±0.009
F7	0.414±0.009	0.462±0.012	10.33±0.028	1.116±0.003	$32^0$45'±0.014
F8	0.472±0.015	0.532±0.014	11.31±0.035	1.127±0.015	$29^0$38'±0.026
F9	0.486±0.007	0.539±0.011	9.67±0.022	1.107±0.007	$33^0$18'±0.012

* **All the values represent mean ± standard (n=3)**

Compatibility studies

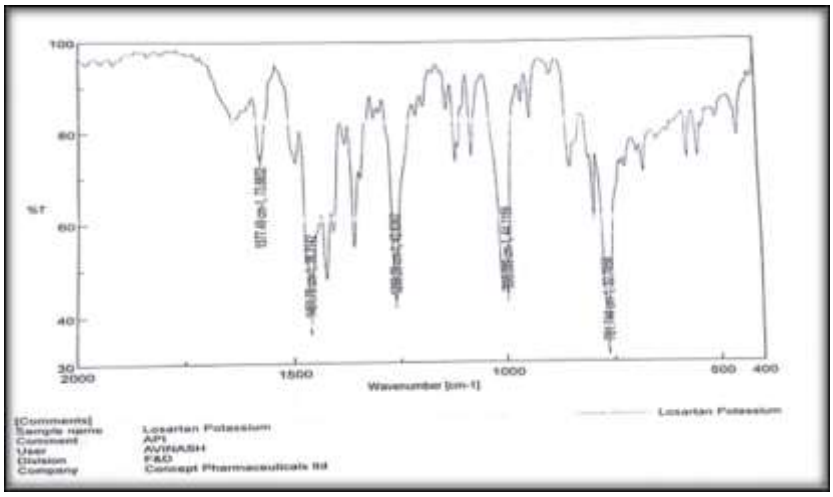

Figure 1. IR Spectrum of Losartan Potassium.

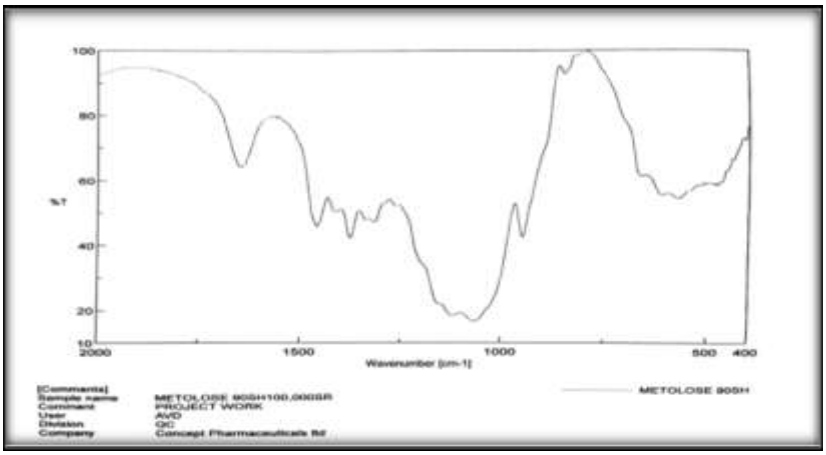

Figure 2. IR Spectra of Metolose 90 Sh 100000SR.

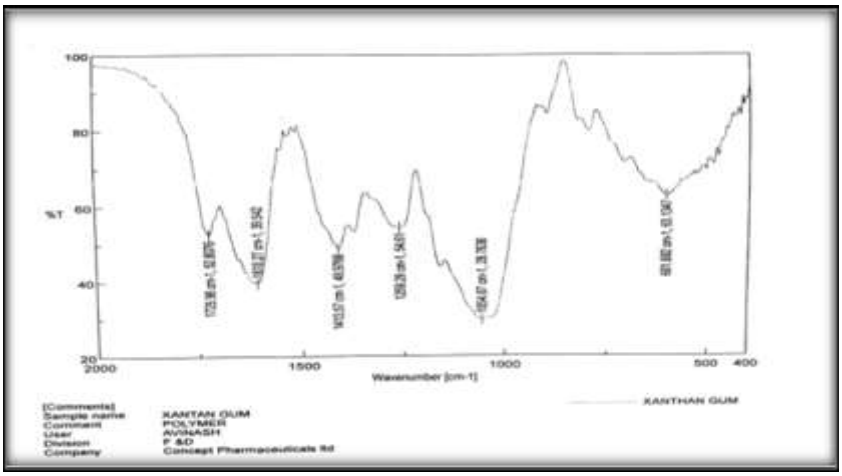

Figure3. IR spectra of Xanthan gum.

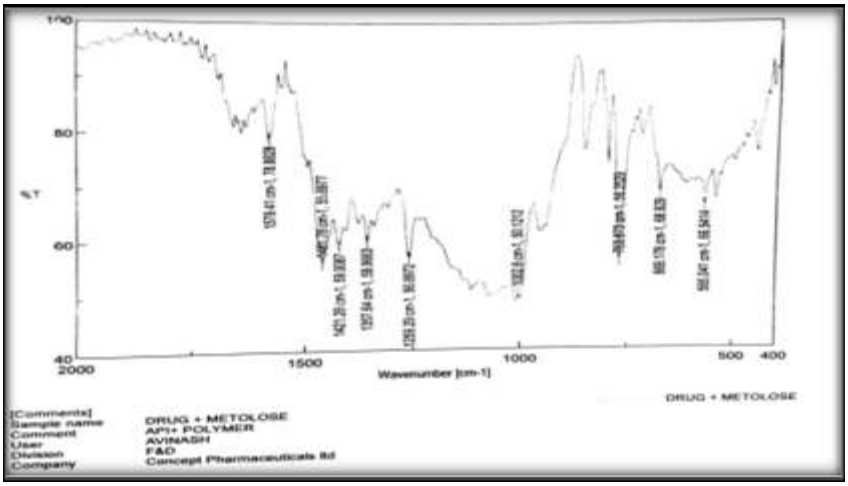

Figure 4.IR Spectra of Drug with Metolose 90 Sh.

Evaluation of sustained release Losartan Potassium matrix tablets.

Table No.2: Standard physical test for matrix tablets.

Formulation	Hardness ($kg/cm^{2)}$	Percent friability (%)	Thickness (mm)	Content uniformity (%)	Weight variation
F1	5.1±0.1	0.57±0.03	3.5±0.2	101.20%	252±0.55
F2	5.0±0.1	0.69±0.03	3.7±0.2	99.63%	250±0.47
F3	5.2±0.2	0.49±0.04	3.5±0.1	98.93%	248±0.57
F4	5.2±0.1	0.65±0.02	3.5±0.2	98.28%	251±0.20
F5	5.0±0.2	0.51±0.06	3.8±0.4	96.60%	248±0.43
F6	5.2±0.1	0.62±0.04	3.7±0.3	89.94%	250±0.52
F7	5.1±0.2	0.67±0.06	3.8±0.4	97.23%	251±0.20
F8	5.3±0.1	0.68±0.01	3.5±0.2	98.16%	249±0.81
F9	5.0±0.2	0.55±0.05	3.7±0.3	99.11%	250±0.51

*** All the values represent mean ± standard (n=3).**

Tablets of all formulations (F1 to F9) were evaluated for different parameters such as thickness, hardness, weight variation, drug content and friability and results shown in table.

In-Vitro Release Studies

Table No. 03: In Vitro Dissolution data of F1, F2, and F3 Formulation.

Times in (Hrs)	Cumulative Percent drug release		
	F1	F2	F3
0	0	0	0
1	21.52	21.38	19.14
4	37.74	38.27	34.46
8	76.18	79.24	70.49
12	99.20	98.07	89.93

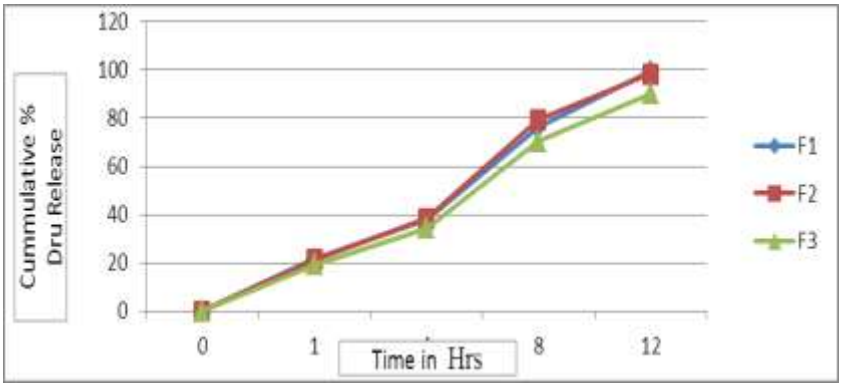

Figure 5: In-vitro dissolution profile of F1, F2 and F3 Formulation.

Table No.04: In Vitro Dissolution data of F4, F5, and F6 Formulation.

Times in (Hrs)	Cumulative Percent drug release		
	F4	F5	F6
0	0	0	0
1	17.93	19.14	14.94
4	36.10	37.77	30.23
8	74.56	78.60	70.48
12	94.28	95.79	86.94

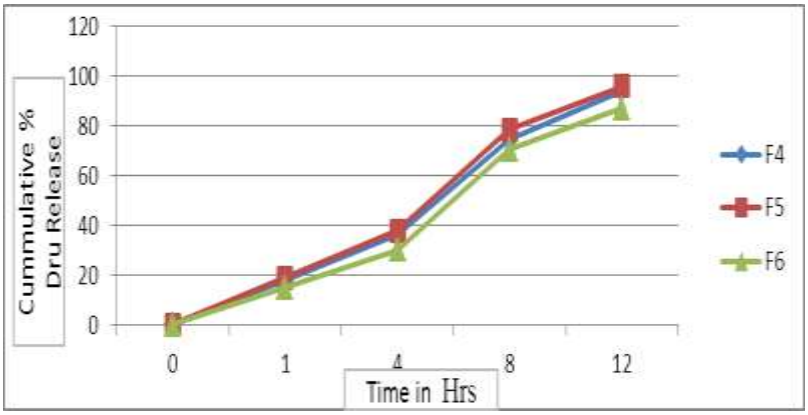

Figure6: In-vitro dissolution profile of F4, F5 and F6 Formulation.

Table No. 5: In-Vitro Dissolution data of F7, F8 And F9 Formulation.

Times in (Hrs)	Cumulative Percent drug release		
	F7	F8	F9
0	0	0	0
1	19.24	21.28	23.15
4	31.64	34.52	37.49
8	71.21	73.14	75.32
12	96.23	97.16	99.11

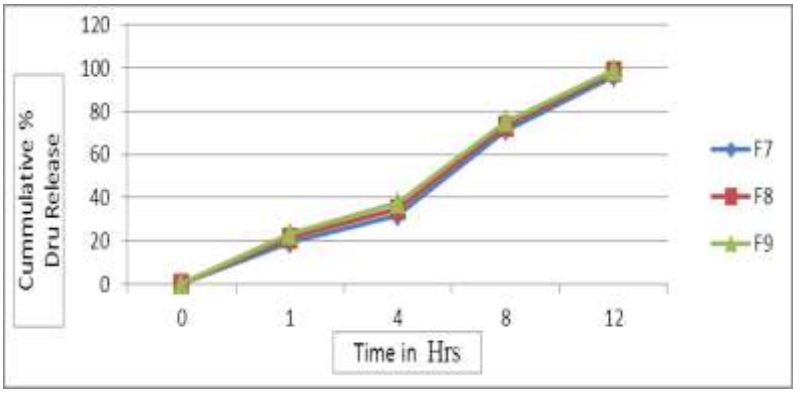

Figure 7: In-vitro dissolution profile of F7, F8 and F9 Formulation.

Release kinetics

Table No.6: Kinetic data of sustained release matrix tablet of losartan potassium.

Formulation Code	Zero Order(R^2)	First order(R^2)	Matrix Model(R^2)	Korsemeyer-peppas model (R^2)
F1	0.9217	0.9835	0.9867	0.9767
F2	0.9524	0.9247	0.9854	0.9925
F3	0.9257	0.9372	0.9688	0.9879
F4	0.9653	0.9428	0.9842	0.9462
F5	0.9565	0.9851	0.9467	0.9904
F6	0.9629	0.9124	0.9871	0.9796
F7	0.9821	0.9457	0.9291	0.9863
F8	0.9685	0.9611	0.9894	0.9638
F9	0.9806	0.9629	0.9728	0.9890

As observed from table no.23, the values of correlation coefficients (R^2) for all formulations were high enough to evaluate the drug dissolution behavior. The values of release of exponent (n) were found to be a function of retardant polymer used and physico-chemical nature of drug. The values of release exponent (n), kinetic rate constant (k) and correlation coefficient (R^2) as calculated are shown.

Table No.7: Estimated values of n and k by regression of log (M_t / M_∞) on log (t).

Batch No.	N	K	r^2	Model Fitting
F1	0.8361	12.5117	0.9867	Matrix
F2	0.7859	10.8169	0.9894	Matrix
F3	0.8277	13.6834	0.9879	Peppas
F4	0.7945	11.3376	0.9842	Matrix
F5	0.8446	11.6545	0.9904	Peppas
F6	0.8285	13.5947	0.9871	Matrix
F7	0.8126	12.4831	0.9863	Peppas
F8	0.8079	12.3165	0.9925	Matrix
F9	0.8332	11.3089	0.9890	Peppas

Table No.8: N value and release for Korsmeyer-Peppas model.

N	Mechanism
0.5	Fickian diffusion (Higuchi matrix)
0.5 < n < 1	Non-Fickian diffusion
1	Case II transport
>1	Super Case II transport

Swelling Index

Table No.9: Swelliing index of formulation F1 to F3.

Timein (Hrs)	Swelling index		
	Formulation code		
	F1	F2	F3
2	26.16	34.52	38.31
4	32.42	45.75	51.76
6	37.85	53.43	62.71
8	46.61	66.54	73.32
10	39.74	58.21	64.24
12	38.22	54.25	60.22

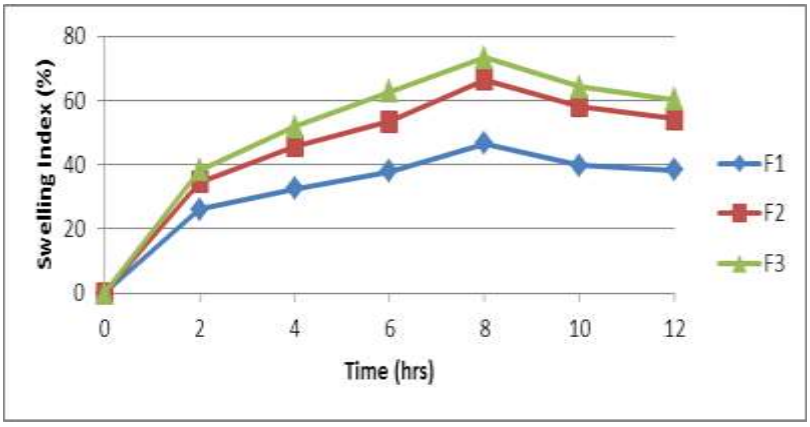

Figure 8. Swelling index of formulation of F1-F3 Formulation.

Table No.10: Swelling index: Swelliing index of formulation F4 to F6.

Time in (Hrs)	Swelling index		
	Formulation code		
	F4	F5	F6
2	24.45	33.54	38.51
4	35.21	45.24	48.47
6	45.52	52.84	58.38
8	54.87	65.12	70.67
10	40.26	60.48	65.19
12	37.84	55.21	61.54

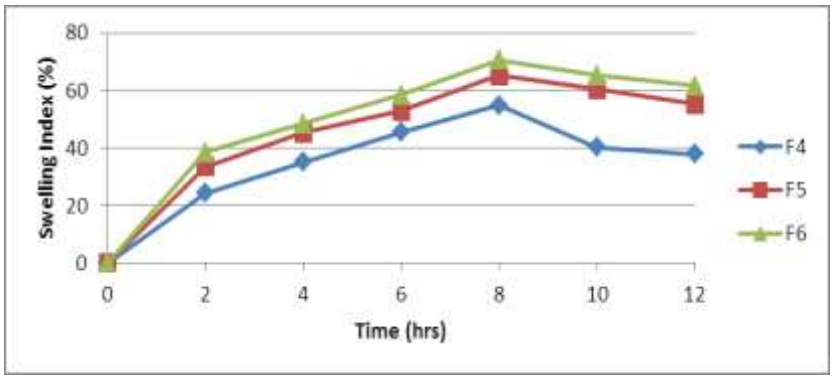

Figure 9. Swelling index of formulation of F4 to F6.

Table No.11: Swelling index of formulation of F7 to F9 At different time.

Time in (Hrs)	Swelling index		
	Formulation code		
	F7	F8	F9
2	29.28	36.13	41.24
4	37.72	43.61	49.52
6	45.25	48.32	52.81
8	58.41	60.82	70.89
10	54.02	59.45	65.58
12	48.15	54.39	62.78

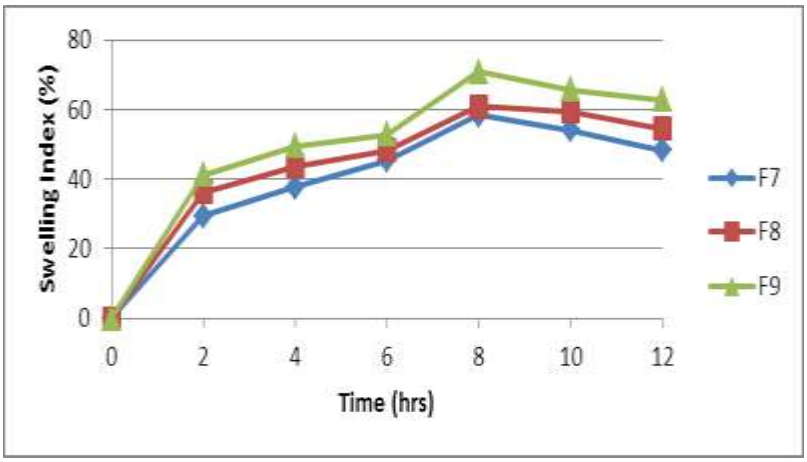

Figure 10.Swelling index of formulation of F7 to F9 Accelerated stability study.

Table No. 12: Parameters studied on F2, F4 and F8 formulations before and after.

Parameter	Before stability study		
	F2	F4	F8
Thickness	3.7±0.02	3.5±0.02	3.5±0.02
Hardness	5.0±0.1	5.2±0.1	5.3±0.2
Drug content	99.63%	98.28%	98.16%

Parameter	After stability study		
	F2	F4	F8
Thickness	3.7±0.02	3.5±0.2	3.6±0.1
Hardness	**5.0±0.1**	5.1±0.1	5.3±0.2
Drug content	98.02%	94.13%	97.89%

Table No. 13: Cumulative percent drug release of optimized Formulation F2, before and after stability study.

Times in (Hrs)	Cummulative percent drug release	
	Before stability study	After stability study
	F2	F2
0	0	0
1	21.38	21.37
4	38.27	38.12
8	79.24	79.20
12	98.07	98.02

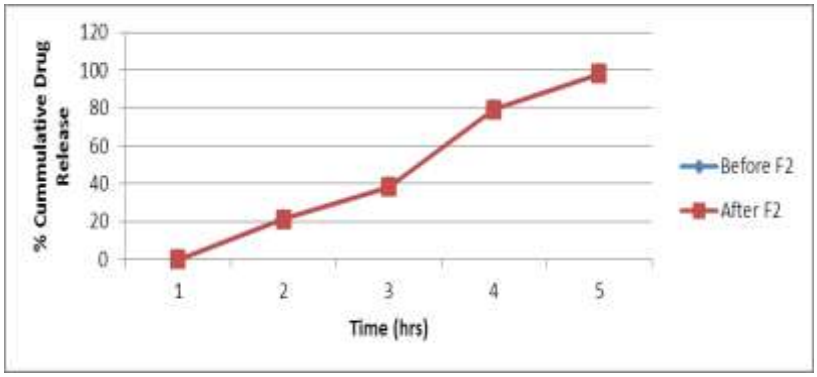

Fig 11: in- vitro Dissolution profile of formulation F2 before and after stability study.

The UV spectrum of losartan potassium in 0.1 N HCl showed maximum absorption at 250 nm. hence, drug used in the formulation was found to be pure according to I.P. specification. The UV spectrum of the losartan potassium in 0.1N HCL. FTIR spectrum of pure losartan potassium, drug with metolose 90 sh, drug with Xanthan gum shows all characteristics peaks for pure losartan potassium, which suggest lack of sufficient interaction between drug and polymers for formulation of sustain released matrix tablets. Losartan potassium was found to be beer's and lambart's law. In the concentration range of 0-10µg/ml at 250nm against 1.2 P^H Phosphate buffer and 6.8 P^H phosphate buffer. The result of angle of repose of all the formulation were found to be in range of indicating excellent flow property and this was further supported by lower compressibility index values. Thus it can be concluded that the powder for all batches possessed good flow characteristics. It has been stated that the bulk density values less than 1.2g/cm^2 indicate good packing and values greater than 1.5g/cm^2

indicate poor packing. The loose density and tapped bulk density values for all the formulation varied in range of 0.414±0.09 g/cm^3 to 0.539± 0.011g/cm^3 and 0.462± 0.012 g/cm^3 0.532±0.014 g/cm^3 respectively. The values obtained lies within the acceptable range. The percent compressibility of granules was determined by carr's compressibility index, the result shown in table. The percent compressibility for all formulation lies within the ange of 7.89±0.019% to 12.69±0.042% indicates acceptable flow property. Hausner ratio was ound to be 1.069±0.014 to 1.148±0.009 which shows acceptable flow properties and good packing ability. Taablets of all formulation (F1to F9) Were evaluated for different parameters such as thickness, hardness, weight variation, drug contain and friability and results ae shown in table.

Tablet hardness was determined by Roche fraibilator and weight loss was calculated and represented in the terms of percent friability. Friability values of all the formulation were less than 1%, indicating good strength of tablet and with stand the sufficient pressure drying the handling and transportation. In weight variation test, the Pharmacopoeial limit for percent of deviation for tablets weighing 80mg to 250mg is 7.5%. The average percent deviation of all tablets was found to be within the limit and hence all formulation passes the weight variation test. Examination of tablets from each batch showed flat circular shape with no cracks having white colour. The thickness of tablets was determined using vernier caliper. The thickness of tablet ranged from All formulation showed uniform thickness. The drug content was found to be uniform among all formulation and ranged from 86.94 % to 99.20 % as per pharmacopoeial standard. All the formulations were subjected to *in-vitro* dissolution studies and results are shown in table no. and fig no. The results revealed that release profiles of matrix tablets of losartan potassium containing varying proportion of metolose 90 sh (20%, 30%, 40% of total weight of tablet) i.e. batch F1,F2,F3 showed drug release as 99.20%, 98.07%, 89.93% for 12hrs, respectively.

In-vitro release studies of all the formulation (F1-F9) were also compared and evaluate. The results showed that the drug profile of formulation F2, F8 resembles formulation. Hence formulation F2 containing metolose 90sh in the concentration of 30%, formulation F8 containing metolose 90 sh (of the total weight of the tablets) was considered as optimized formulation and used for further study.

As time increase, the swelling index was increased, because weight gain by tablet was proportional to rate of hydration up to 8 hrs. Later on it decreases gradually due to dissolution of outermost galled layer of tablet into dissolution medium. The direct relationship was observed between swelling index and gum concentration increases swelling index increased. with increase in time there is decrease in swelling index may be due to erosion of the galled layer from the tablets. The stability studies were carried out on optimized formulation F2.The formulation was stored at 40 ± 2^0C/75 ± 5% RH for Three month (90 days). After 90 days, samples were withdrawn and evaluated for Thickness, Hardness, Drug content and *In-vitro* drug release studies.

There were no considerable changes in physical parameter of tablet such as Thickness, Hardness, and Drug content of formulation F2, F4, F6 after accelerated stability study.

CONCLUSION

All the prepared formulation containing different concentrations of metolose 90 Sh and Xanthan gum. The prepared formulations satisfy all pharmacopoeia stanrdard. The concentration of metolose 90sh and Xanthan gum increases an increase in the viscosity of the gel as well as the formation of gel layer with a longer diffusion path.

Based on the satisfactory results of validation parameters for the assay method such as Precision, Specificity, Linearity & Range, Accuracy (Recovery), Ruggedness it is concluded that the method of testing assay for SR Losartan Potassium -50 Tablet stands validated.

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