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Formulation, Evaluation and Comparison of Sustained Release Matrix Tablet of Losartan Potassium Using Natural Polymers

Avinash V. Dhobale[1]*, M. Siddaiah[2], M. Shaileh[3], A. Madhu Babu[3]

1.Research Scholar, Departments of Pharmaceutics, Bhagwant University Ajmer, Rajasthan, India.

2.Departments of Pharmaceutics, Bhagwant University Ajmer, Rajasthan, India.

3.Department of Medical Science, All India Institute Medical Science Bhopal, Madhyapradesh, India.

ABSTRACT

The aim of this research work was to Evaluation of Some Natural Polymer used as Sustained Release Matrix Tablet, any pharmaceutical formulation contains two ingredients one is the active ingredient and other is an excipients. An excipients help in the manufacturing of dosage form and it also improves physicochemical parameters of the dosage form. Polymers play an important role as excipients in any dosage form. They influence drug release and should be compatible, non-toxic, stable, economic etc. 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. Okara and Tramarind Gum Mucilage were investigated as the model hydrophilic retardant polymers. Wet granulation method was and 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.

Keywords: Okara, Drug, Polymer, Tablet, Sustained, Excipient.

*Corresponding Author Email: avd.lsdp@gmail.com

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INTRODUCTION

Active ingredient and excipients are two main ingredients of any Pharmaceutical formulation. Excipients help in the manufacturing of Dosage form as well as improve physicochemical parameters of the Dosage form. Polymers play a vital role in any dosage form as Excipients. The influencing capacity of polymers towards the drug Release and should be compatible, non-toxic, and stable and economic Etc. They are broadly classified in three categories viz. natural Polymers, semi-synthetic and synthetic polymers. Natural polymers are generally used as rate controlling agents, taste masking agents, Protective and stabilizing agents in the oral drug delivery system. Oral drug delivery, the fastest and more preferred route for drug administration is also the largest & oldest segment of the total drug delivery market. Natural polymers or gums have been used in the preparation of release and controlled release drug dosage forms, because of their great properties, such as biodegradability, non-toxicity, biocompatibility in Nature and swelling when they come in contact with aqueous media. Tamarind (Tamarind indica L.) belongs to the Leguminosae family The oil extracted from its seeds is rich in eicosanoic fatty acids such as palmitic, oleic and linoleic, the highest concentrations corresponding to linoleic acid and palmitic acid, present in 36%–49% and 14%–20%, respectively Tamarind seed polysaccharide (TSP), is a natural branched polysaccharide polymer. TSP constitutes about 65% of the tamarind seed composition. Okra (Abelmoschus esculentus) is the only vegetable crop of significance in the Malvaceae family and is very popular in the Indo-Pak subcontinent. It is an oligo purpose crop, but it is usually consumed for its green tender fruits as a vegetable in a variety of ways. These fruits are rich in vitamins, calcium, potassium, and other mineral matters. The mature okra seed is a good source of oil and protein has been known to have superior nutritional quality. Okra seed oil is rich in unsaturated fatty acids such as linoleic acid which is essential for human nutrition. They are also known as ladies finger. It is used as a binder and produces tablet formulations with good and optimum physicochemical properties. It also retards the release of drug, increasing the half-life of a successfully used in controlled/sustained release tablet formulations and is also a hydrophilic polymer. It is also used as retardant, disintegrant, suspending agent, and matrix forming material. 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 AND METHOD

Chemicals:

Losartan potassium was obtained as a gift sample from Concept Pharma Aurangabad and other ingredients like okra gum & Tramarind Gum Mucilage were isolated & extracted was carried out at LSDP college laboratory (Pharmaceutics Research lab) Pune ,and other Excipients magnesium stearate, MCC PVP K-30 IPA, Talc. Purchased from Grail Pharma Pvt.Ltd, Aurangabad.

Method of isolation and extraction of Okra gum:

About 2kg of fresh immature fruit of Abelmosch-usesculentus were obtained from a local market. After removal of the seeds, the fresh immature fruits were sliced, homogenized and extracted with cold water containing 1% (w/v) sodium Meta bisulphate. The crude mucilage was centrifuged at 4000 rpm for 5 min and the gum was precipitated from the supernatant with acetone. The precipitated gum was washed several times with acetone; the obtained cream colored product was dried under vacuum in a desiccators. A light brown colored powder was obtained after complete removal of moisture. The dried gum was pulverized using end runner mill and screened through a 0.25 mm stainless steel sieve. This was stored in a well closed amber colored specimen bottle till ready for us.

Method of isolation and extraction TSP Extraction:

Cold distilled water (200 mL) was added to TSP powder (20 g) to prepare slurry. The slurry obtained was poured into boiling distilled water (800 mL) and then boiled for 20 min on a hot plate to give a clear solution that was stored overnight. The thin clear solution was further centrifuged at 6000 rpm for 20 min to separate all the foreign matter. The supernatant was separated and poured into excess 95% ethanol with continuous stirring. The obtained precipitate was collected using a stainless sieve, and dried in an oven at a temperature 50 °C for 4 h. The dried polymer was stored in a desiccator. In the same way, tamarind seed powder, waste from the export tamarind juice

industry and were extracted using the procedure mentioned above. Only tamarind seeds taken from paddy farmland , were extracted by Accelerated Solvent Extraction (ASE) using methanol as a solvent, following by ethanol, at a temperature of 100 °C for 30 min to give methanol extract (7.51%) and ethanol extract (3.31%).

Preparing the matrix tablets:

For preparing the matrix tablets, Losartan potassium and various concentrations of Okara and Tramarind Gum Mucilage were used as a polymer. The other excipient used was MCC for its diluents 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 e composition of each matrix formulation. The formulation of each Losartan potassium sustained release matrix tablets is composed of two selected polymers i.e. Okara, and Tramarind Gum Mucilage 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. The concentration of other ingredients used for formulations of Losartan Potassium tablets batched (F1-F9) having value mentioned in the table 1.

Table 1: 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
Okara gum	50	75	100	-	-	-	25	37.5	50
Tramarind 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

RESULTS AND DISCUSSION:

Loss on drying of losartan potassium

The pharmacopoeia 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. Compatibility studies (IR studies) are shown in figure 1, 2, 3 and figure 4 respectively. Evaluation parameter of prepared losartan potassium powder blend having results present in the table 2.

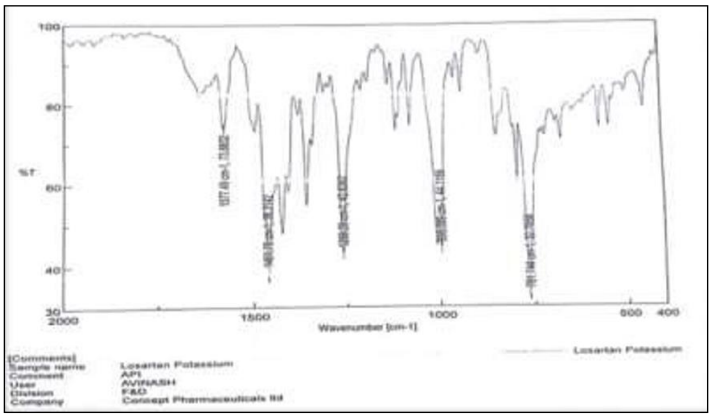

Figure 1: IR Spectrum of Losartan Potassium

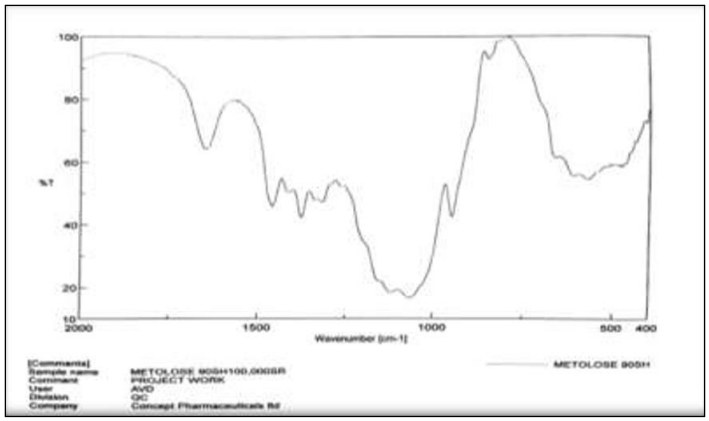

Figure 2: IR Spectra of Okara gum

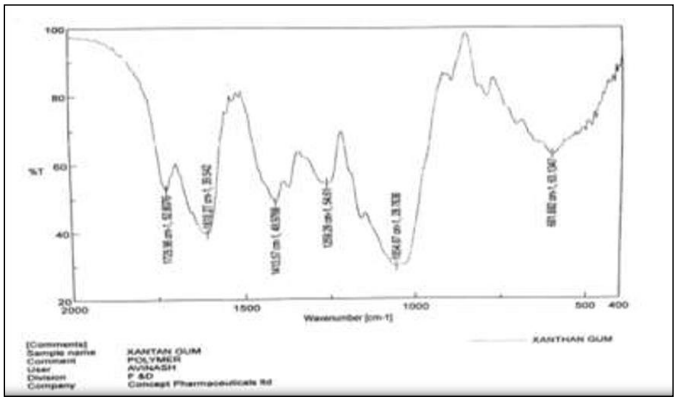

Figure 3: IR spectra of Tramarind Gum Mucilage

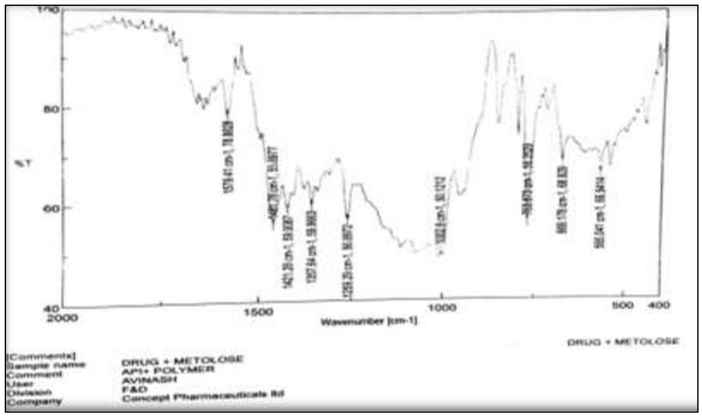

Figure 4: IR Spectra of Drug with Okara

Table 2: Evaluation of prepared Losartan potassium powder blend

Formulation	Loose Bulk Density(g/cm)	Tapped bulk density(g/cm^2)	Carr's index (%)	Hausner ratio	Angle of 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)**

Evaluation of sustained release Losartan Potassium matrix:

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 3 and In-vitro dissolution profile of batch from F1, to F9 formulation have been shown in figure 5, 6 and 7. Evaluation parameter of sustained release losartan potassium matrix tablets results present in the table no 3. In-Vitro Release – Dissolution Studies data has been represented in table 4, 5 and 6 for all batches (F1 - F9).

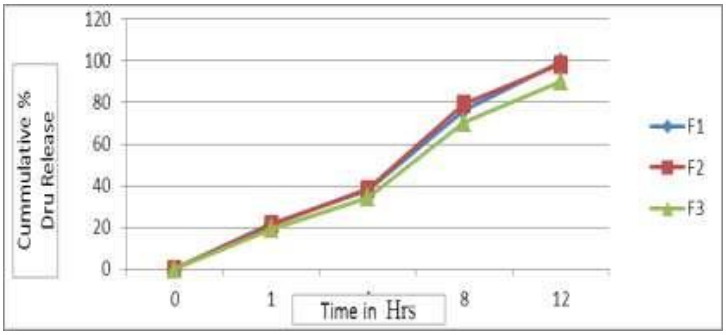

Figure 5: In-vitro dissolution profile of F1, F2 and F3 Formulation

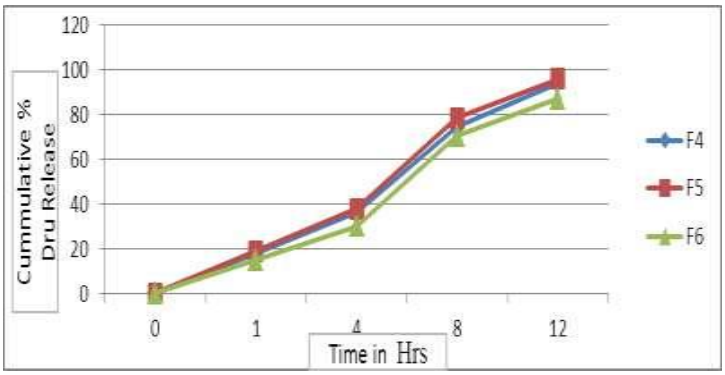

Figure 6: In-vitro dissolution profile of F4, F5 and F6 Formulation

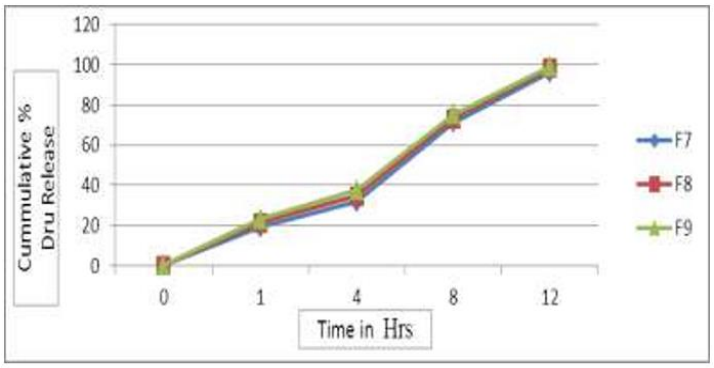

Figure 7: In-vitro dissolution profile of F7, F8 and F9 Formulation

Evaluation of sustained release Losartan Potassium matrix:

Table 3: Standard physical test for matrix tablets.

Formulation	Hardness ($kg/cm^{2)}$	Percent Friability (%)	Thickness (mm)	Content Uniformity (%)	Weight variation
F1	5.10.1	0.57±0.03	3.50.2	101.20%	2520.55
F2	5.00.1	0.69±0.03	3.70.2	99.63%	2500.47
F3	5.20.2	0.49±0.04	3.50.1	98.93%	2480.57
F4	5.20.1	0.65±0.02	3.50.2	98.28%	2510.20
F5	5.00.2	0.51±0.06	3.80.4	96.60%	2480.43
F6	5.20.1	0.62±0.04	3.70.3	89.94%	2500.52
F7	5.10.2	0.67±0.06	3.80.4	97.23%	2510.20
F8	5.30.1	0.68±0.01	3.50.2	98.16%	2490.81
F9	5.00.2	0.55±0.05	3.70.3	99.11%	2500.51

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

Release kinetics:

As observed from table 7, the values of correlation coefficients (R2) 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 (R2) as calculated are shown in table 8 and table 9.

Table 4: 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

Table 5: 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

Table 6: 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

Table 7: 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

Table 8: 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 9: 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:

Swelling index parameter was performed of all batched at different time points moreover the data analysed time vs swilling index (%) which are presented in table 10, 11, 12 & 14 figure 8, 9 & 10.

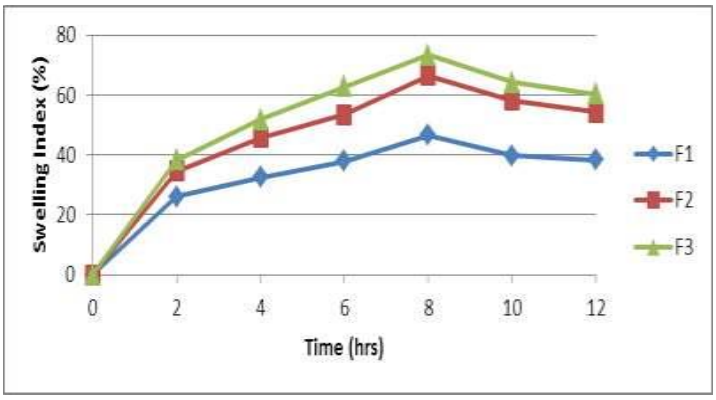

Figure 8: Swelling index of formulation of F1-F3 Formulation

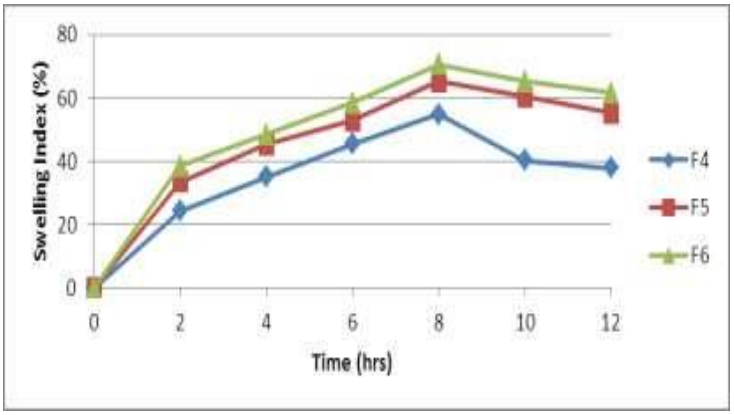

Figure 9: Swelling index of formulation of F4 to F6

Table 10: Swelling index of formulation F1 to F3

Time in (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

Table 11: Swelling index: Swelling 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

Table 12: 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

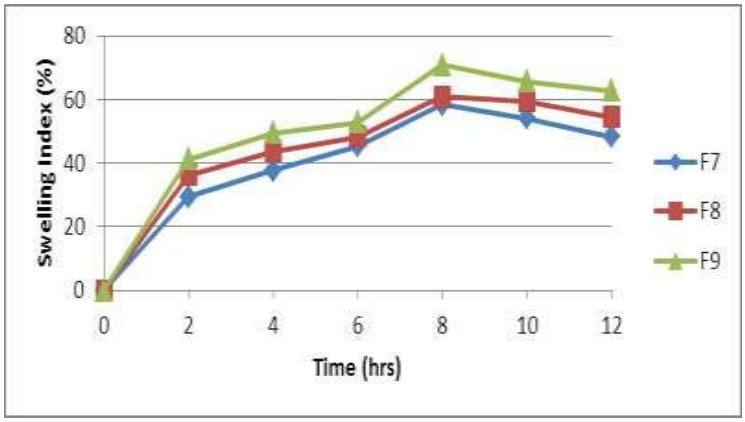

Figure 10: Swelling index of formulation of F7 to F9 Accelerated stability study

Before and after stability study was performed for formulation F2, F4 and F8 having performed thickness, hardness and drug content studies and the result shown in table 13.

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 Okara 90 sh, drug with Tramarind Gum Mucilage 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 0-10□g/ml at 250nm against 1.2 PH Phosphate buffer and 6.8 PH 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/cm2 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 0.4140.09 g/cm3 to 0.539 0.011g/cm3 and 0.462 0.012 g/cm3 0.5320.014 g/cm3 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 range of 7.890.019% to 12.690.042% indicates acceptable flow property. Hausner ratio was found to be 1.0690.014 to 1.1480.009 which shows acceptable flow properties and good packing ability. Tablet 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 Friabilator 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 Pharmacopoeias 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 calliper. 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 pharmacopoeias 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 Okara (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 Okara in the concentration of 30%, formulation F8 containing Okara (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 20C/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.

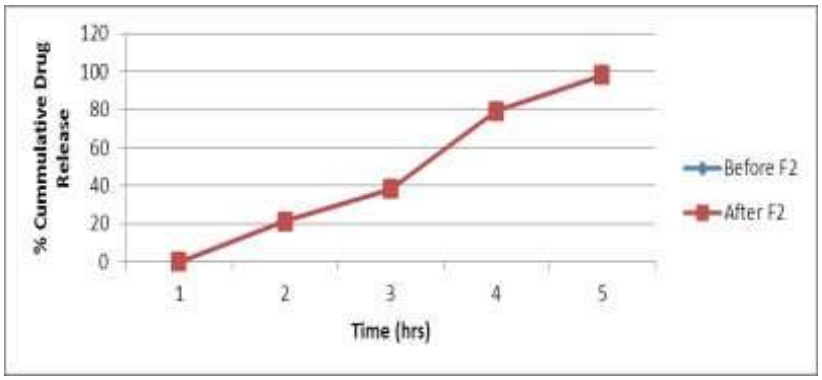

Figure 11: In- vitro Dissolution profile of formulation F2 before and after stability study

Table 13: Parameters studied on F2, F4 and F8 formulations before and after

Parameter	Before stability study			After stability study		
	F2	F4	F8	F2	F4	F8
Thickness	3.70.02	3.50.02	3.50.02	3.70.02	3.50.2	3.60.1
Hardness	5.00.1	5.20.1	5.30.2	5.00.1	5.10.1	5.30.2
Drug content	99.63%	98.28%	98.16%	98.02%	94.13%	97.89%

Table 14: Cumulative percent drug release of optimized Formulation F2, before and after stability study.

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

CONCLUSION:

In the present works on natural polysaccharides were studied in terms of their use as excipients in various formulations. Gums and mucilage's are widely used natural materials for conventional and novel dosage forms. All the prepared formulation containing different concentrations of Okara and

Tramarind Gum Mucilage. The prepared formulations satisfy all pharmacopoeia standards. The concentration of Okara and Tramarind Gum Mucilage 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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