RESEARCH ARTICLE

FORMULATION AND *IN-VITRO* EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF LOSARTAN POTASSIUM USING NATURAL GUMS

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ABSTRACT

The objective of the present study was to prepare and evaluate sustain release matrix tablets of Losartan potassium using natural polymers. Tablets were prepared by wet granulation method using different drug: polymer concentrations. Natural gums like karaya gum, Tara gum and locust bean gum were used as release retardant polymers. Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC) study revealed no chemical interaction between drug and polymers used. Pre compression and post compression parameters complied with the Indian Pharmacopoeial limit for the tablets. The effect of diluents type, polymer type used and its increase in concentration on the drug release was studied in this work. *In-vitro* dissolution studies were carried out in 0.1 N HCl for 2h and pH 6.8 buffer for next 10 h. In all the formulations as the concentration of the polymer was increased, drug release was retarded accordingly. The mechanism of drug release for all the formulations was found to be by anomalous transport i.e. by swelling coupled with diffusion from the polymer. Most of the formulations followed zero order kinetics with n value > 0.5. Formulation FV was selected as the best formulation with about 95.11% drug release within 12 h.

Keywords
Losartan potassium, Karaya gum, Tara gum, Locust bean gum, Sustained release Matrix tablets

INTRODUCTION

Sustained release formulations describe the slow release of a drug substance from a dosage form to maintain therapeutic response for extended period (8-12 h) of time[1]. In long term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages[2]. Sustained release formulations are preferred for such therapy because they maintain uniform drug levels; reduce dose and side effects, show better patient compliance, and increase the safety margin for high potency drugs[3]. Introduction of matrix tablets as sustained release has

given a new breakthrough for Novel Drug Delivery System (NDDS) in the field of pharmaceutical technology. The hydrophilic polymer matrix is widely used for formulating a sustained release dosage form[4-8]. Drug release retardant materials are the key performers in the matrix systems. Natural polymers are economical, readily available, non-toxic and capable of chemical modifications, potentially biodegradable and biocompatible[9].

Losartan Potassium (LP) is a potent, highly specific Angiotensin II Type 1 (AT1) receptor antagonist with antihypertensive activity[10]. 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 h. Administration of LP in a sustained release dosage form with an extended release over 8 h, would be more desirable as these characteristics would allow a rapid onset followed by protracted anti-hypertensive effects by maintaining the plasma concentrations of the drug well above the therapeutic concentration, thus minimizing the need for frequent administration and dose related side effects[11-12].

MATERIALS AND METHODS

LP was obtained as a gift sample from Aurobindo Pharma Pvt ltd., Hyderabad. Karaya gum and Tara gum were purchased from Exandal Corporation (California, U.S.A). Locust bean gum purchased from Silia natural gums (Italy). Micro Cystalline Cellulose (MCC) was received as gift sample from JRS Pharma pvt. Ltd., (Newyork). Di-calcium Phosphate (DCP), Lactose, Magnesium stearate, Talc, Poly Vinyl Pyrrolidone (PVP) were procured from Finar chemicals (Mumbai, India).

Preparation of Losartan Potassium (LP) sustained release matrix tablets

Accurately weighed quantities of the drug, polymer and DCP/MCC/Lactose were mixed in a polybag and then taken into a glass mortar and then wetted with isopropyl alcohol (IPA) as granulating fluid. The cohesive mass was then passed through mesh no. #40. The granules obtained were dried in a hot air oven at temperature not more than $50^{o}C$ for about 45min. The granules were then passed through sieve no. # 20 to separate fines. Based on the drug content, granules were weighed and required quantities of talc and magnesium stearate were added and compressed on single punch tablet press (Cadmech, India) using 10mm round punches to the hardness of 6-8 kg/cm^2. The formulations were shown in Table 1.

Preformulation studies of LP

Fourier Transform Infrared Spectrophotometry (FTIR)

The compatibility between drug and polymers was detected by FTIR spectra obtained on Shimadzu 8400 (Japan). The pellets were prepared on KBr press (Startech lab, India). The spectra were recorded over the wave number range of 4000 to 500 cm^{-1}.

Differential Scanning Calorimetry (DSC)

DSC was performed to characterize thermal changes in melting behavior of LP with other excipients present in different formulations. Thermograms were obtained by using a differential scanning calorimeter (METTLER, STAR^e SW 8.10) at a heating rate $10^{o}C/min$ over a temperature range of $50\text{-}450^{o}C$. DSC was calibrated with indium, before running the samples. The sample (3 mg) was hermetically sealed in an aluminum crucible. Nitrogen gas was purged at the rate of 10 mL/ min for maintaining inert atmosphere.

Drug content of LP

Content uniformity was determined by accurately weighing 20 tablets and crushing them in a mortar, an accurately weighed quantity of powder equivalent to 20 mg of

drug was transferred to a 100 mL volumetric flask[13]. Few mL of water was added and shaken for 15 min. Volume was made up to 100 mL with distilled water. The solution was filtered through Whatmann filter paper (No.41). 5 mL of the filtrate was diluted to 100 mL with 0.1N HCl, and then absorbance of the resulting 10 µg/ml solution was recorded at 235 nm using UV-VIS spectrophotometer (ELICO SL 150).

Pre-compression parameters

The flow properties of the drug and the granules prepared by the wet granulation method and were evaluated for their bulk density, tapped density, compressibility index, and angle of repose and Hausner's ratio[14]. The tapping method was used to determine the bulk density, tapped density, percent compressibility index and Hausner's ratio.

$$Compressibility\ index = \left[\frac{\rho t - \rho b}{\rho t}\right] \times 100$$

$$Hausner's\ ratio = \frac{\rho t}{\rho b}$$

Where, ρ_t is tapped density and ρ_b is initial bulk density of tablet blend. Angle of repose (θ) of the tablet blend measures the resistance to particle flow and was determined by fixed funnel method by using the formula

$$Tan\theta = \frac{h}{r}$$

Where, θ is angle of repose, h is height of powder and r is radius. The pre-compressional parameters were given in Table 3.

Post compressional studies of the prepared matrix tablet

The prepared sustained release tablets were evaluated for uniformity of weight using 20 tablets (Shimadzu BL-220H analytical balance), hardness using 6 tablets (Monsanto hardness tester) and friability using 20 tablets (Roche type friabilator). The post compression parameters[15-16] were given in Table 4.

Solubility determination

Excess of LP was added to 5mL of each fluid in a 25mL stoppered conical flasks and the mixtures were shaken for 24h at room temperature on a rotary flask shaker. After 24 h of shaking, 1mL aliquots were withdrawn and filtered immediately. The filtered samples were diluted suitably and assayed for drug by measuring absorbance at 235nm. Shaking was continued until 3 consecutive estimations were same. The solubility experiments were run in triplicate. The results were given in Figure 1 and Table 2.

In-vitro dissolution studies

The tablets were subjected to *in-vitro* dissolution studies using USP Type II dissolution apparatus (LAB INDIA DS 8000) at 37±2°C and 50 rpm speed. To mimic the gastro intestinal conditions, 900 ml of 0.1N HCl was used as dissolution medium for initial 2h and 6.8 pH buffer for next 10 h. Aliquot equal to 5 mL was withdrawn at specific time intervals and replaced with fresh buffer. The aliquots were diluted and drug release was determined spectrophotometrically at a wavelength of 235 nm by comparing with the standard calibration curve. The dissolution parameters are given in Table 5.

Release kinetics

To study the mechanism of drug release, the dissolution data were fitted into different kinetic models such as Zero order, First order, Higuchi and Korsmeyer-peppas equations[17-20]. The most appropriate model was chosen on the basis of goodness of fit test. The data were processed for regression analysis using suitable statistical functions. The regression values and rate constants for all the formulations are given in Table 5.

Stability studies

The accelerated stability studies were carried out as per ICH guidelines for the formulated sustained release LP tablets. Stability studies were carried out at

40°C/75% RH for the optimized formulation (FV) for 3 months. The matrix tablets were stored at 40°C/75% RH in closed high density polyethylene bottles for 3 months. The samples were withdrawn after periods of 1 month, 2 month and 3 months. The samples were analyzed for its hardness, drug content and *in-vitro* drug release[21].

Results and discussion

The prepared sustained release tablets were evaluated for thickness, weight variation, hardness, friability, drug content, *in-vitro* drug dissolution studies and stability studies. All the studies were performed in triplicate and results are expressed as mean ±SD.

Drug excipient compatibility testing
FTIR spectroscopy

Major functional groups present in LP show characteristic peaks in IR spectrum. Figure 2a shows peaks observed at different wave numbers and the functional group associated with these peaks for drug and Figures 2b-2g shows drug with different polymer. The major peaks are identical to functional group of LP. Hence, it was confirmed that there was no incompatibility between drug and various polymers.

DSC

The prominent and sharp endothermic peak at 270.29 ^{o}C in the thermogram of pure LP Figure 3a-3d represents the melting point of LP. In all the DSC spectrums, the characteristic drug melting point peak was observed with slight changes in terms of broadening or shifting towards lower temperature. This could be due to the mixing of drug and excipient, which lowers the purity of each component in the mixture and may not necessarily indicate potential incompatibility. From these results there was no drug excipient interaction. This indicates the choice of excipients used in the formulation of matrix tablets were suitable.

Evaluation of tablets for pre-compressional parameters

The flow properties of drug alone were poor. The flow of granules was found to be excellent in wet granulation method and the flow properties of formulation blend was found to be good. 5 gm of formulation blend was taken and their pre-compression parameters like tapped densities, bulk density, angle of repose, compressibility index, Hausner's ratio were calculated for the formulation blend and the results were shown in Table 3.

Evaluation of tablets for post compressional parameters

The prepared tablets were subjected to various quality control tests like drug content, weight variation, hardness, friability and the results were given in Table 4.

In-vitro dissolution studies

The formulations FI, FII, FIII were formulated by wet granulation method using locust bean gum at a concentration of 16, 20, and 25% respectively with MCC 101 as diluent. In FI the locust bean gum could not prolong the drug release until 12 h, instead the tablet dispersed completely at the end of 10 h with about 98.93% of drug release. So, FII was formulated by increasing the conc. of locust bean gum and the release was less when compared to FI i.e. 95.11, but FII tablet also dispersed at the end of 10 h. Thus in order to prolong the drug release until 12 h the concentration of the Locust bean gum was increased up to 25% in FIII. The formulation FIII prolonged the drug release until 12 h with a release of 89.16%. As the concentration of the Locust bean gum was increased among FI, FII, and FIII the drug release was prolonged until 12 h. FIV,FV,FVI are the formulations with Tara gum as the release retardant at the conc.of 16, 20, 25% respectively with MCC 101 as the diluent.Formulation FIV showed 98.47% release at the end of 12 h. FV,FVI showed

95.11% and 88.24% drug release respectively at the end of 12 h. Thus it was observed that as the conc.of tara gum was increased the drug release was less due to the formation of more visous gel layer around the tablet at high conc.of the gum. The formulations FIV, FV gave good sustained release within the 12 h. Formulations FVII, FVIII, FIX were prepared with Karaya gum at a conc. of 16, 20, and 25 % respectively with MCC 101 as diluent. The percent drug release at the end of 12 h for the formulations FVII, FVIII, FIX was 90.07, 84.27, and 78.62 % respectively. From this it was clear that as the conc. of the Karaya gum increased the amount of drug release from the tablets was less. Thus the effect of Karaya gum in acting as a release retardant was more pronounced than the other two gums at the same conc. used. Thus Karaya gum was more potent release retardant among the three polymers used. Formulation FX, FXI, FXII were prepared with 20% Karaya gum, 20% Tara gum, 20 % locust bean gum respectively. In all these three formulations lactose was the diluent. The formulations FX, FXI gave 96.33, 98.47% drug release at the end of 10 h and the tablets dispersed completely at the end of 10 h. Formulation FXII gave 98.61% drug release at the end of 8 h only. At the end of 8 h the tablet dissolved completely in the dissolution medium. From these results it was known that lactose is a freely soluble diluent and absorbs more dissolution fluid into the tablet causing rapid release of the drug. Further in FXII locust bean gum was used which at 20% conc. and lactose as diluent could not prolong the release more than 8 h. Formulations FXIII, FXIV, FXV were prepared with 20% of Karaya, Tara, Locust bean gums respectively. In all these 3 formulations dicalcium phosphate dihydrate was the diluent. The percent drug released at the end of 12 h for FXIII, FXIV, and FXV was 80.45, 90.07, and 90.05% respectively. The dissolution profiles of all the formulations is clearly depicted in the Figure 4.From the obtained results it was evident that the percent drug release with formulations having DCP as diluent was much less when compared to the formulations having MCC and Lactose as diluents.

Release kinetics

The dissolution data was fitted into release kinetic profiles to assess the mechanism of drug release. The r^2 value for all the models was compared and the best fit was determined. From the 'n' value the mechanism of drug release for all the formulations was found to be by anomalous transport i.e. by swelling coupled with diffusion from the polymer.

Stability studies

The stability study results obtained were shown in Table 6. The LP sustained release tablets did not show any significant change in physicochemical parameters and other tests. Thus, it was found that the sustained release tablets of LP formulation (FV) were stable under these storage conditions for at least 3 months.

Table 1 Formulations prepared by wet granulation method

Formulation Ingredients	FI (mg)	FII (mg)	FIII (mg)	FIV (mg)	FV (mg)	FVI (mg)	FVII (mg)	FVII (mg)	FIX (mg)	FX (mg)	FXI (mg)	FXII (mg)	FXII (mg)	FIV (mg)	FXV (mg)
LP	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
Locust Bean gum	50	62.5	75	_	_	_	_	_	_	_	_	62.5	_	_	62.5
Tara gum	_	_	_	50	62.5	75	_	_	_	_	62.5	_	_	62.5	_
Karaya gum	_	_	_	_	_	_	50	62.5	75	62.5	_	_	62.5	_	_
MCC 101	170	157.5	145	170	157.5	145	170	157.5	145	_	_	_	_	_	_
DCP	_	_	_	_	_	_	_	_	_	_	_	_	157.5	157.5	157.5
Lactose	_	_	_	_	_	_	_	_	_	157.5	157.5	157.5	_	_	_
PVP	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
IPA	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Talc	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

Table 2 Solubility data for LP in different media

Medium	Solubility (mg/mL)
Water	3.3±0.603
1.2 pH	1.73±0.502
6.8 pH	1.28±0.345
7.4 pH	1.23±0.421

Table 3 Pre-compression powder flow properties for all the formulations

Powder Blend	Angle of Repose (θ)	Bulk density(ρ_b) (g/mL)	Tapped density(ρ_t) (g/mL)	Compressibility index (%)	Hausner's ratio
Pure drug	41.22	0.816	1.11	26.4	1.36
FI	17.66	0.781	0.819	4.6	1.05
FII	18.41	0.841	0.862	2.44	1.02
FIII	19.33	0.667	0.735	9.25	1.10
FIV	21.32	0.689	0.769	10.4	1.11
FV	23.31	0.698	0.811	13.9	1.16
FVI	24.56	0.574	0.654	12.2	1.14
FVII	26.10	0.722	0.821	12.05	1.14
FVIII	27.14	0.748	0.884	15.38	1.18
FIX	29.31	0.691	0.832	16.9	1.20
FX	24.5	0.760	0.851	10.69	1.12
FXI	23.8	0.712	0.832	14.4	1.17
FXII	24	0.678	0.795	14.7	1.17
FXIII	23.2	0.752	0.851	11.63	1.13
FXIV	25	0.669	0.769	13.00	1.15
FXV	25.5	0.657	0.765	13.08	1.07

Table 4 Post compressional properties of all formulations

Parameters Formulations	Hardness (kg/cm^2) ± S D	Percent Friability	Weight Variation ± SD	Drug content (mg/tab) ± SD
FI	6.47±0.15	0.6	300±0.15	50±1.25
FII	6.40±0.10	0.8	300±0.10	49±1.98
FIII	6.57±0.15	0.6	300±0.18	47±1.67
FIV	6.51±0.10	0.6	300±0.12	48±1.25
FV	6.50±0.10	0.9	300±0.04	50±0.98
FVI	6.32±0.12	0.7	300±0.06	50±0.65
FVII	6.21±0.08	0.9	300±0.08	50±0.54
FVIII	6.53±0.06	1.1	300±0.04	49±0.78
FIX	6.63±0.15	0.8	300±0.01	50±0.85
FX	6.71±0.12	0.8	300±0.02	50±0.97
FXI	6.52±0.11	0.6	300±0.05	50±0.36
FXII	6.50±0.10	1.2	300±0.05	50±0.84
FXIII	6.37±0.10	0.9	300±0.03	50±0.97
FXIV	6.77± 0.15	0.7	300±0.02	48±0.68
FXV	6.77± 0.20	0.8	300±0.03	49±0.68

Table 5 The rate constant and regression values for all the formulations

Formulations	Zero order		First order		Higuchi	Peppas	
	K	r^2	K	r^2	r^2	n	r^2
FI	8.76	0.975	0.331	0.724	0.946	0.516	0.996
FII	8.41	0.972	0.237	0.803	0.943	0.531	0.976
FIII	6.52	0.975	0.145	0.852	0.93	0.544	0.946
FIV	6.96	0.962	0.244	0.686	0.940	0.481	0.982
FV	6.82	0.964	0.184	0.764	0.925	0.480	0.997
FVI	6.50	0.977	0.143	0.863	0.939	0.571	0.975
FVII	6.90	0.950	0.165	0.953	0.989	0.525	0.994
FVIII	6.29	0.972	0.128	0.922	0.959	0.529	0.982
FIX	6.11	0.973	0.112	0.975	0.980	0.6142	0.994
FX	8.72	0.979	0.264	0.821	0.954	0.542	0.957
FXI	8.93	0.980	0.320	0.737	0.942	0.519	0.996
FXII	10.51	0.941	0.412	0.692	0.897	0.453	0.991
FXIII	5.97	0.944	0.115	0.947	0.975	0.500	0.993
FXIV	6.59	0.971	0.151	0.852	0.939	0.486	0.995
FXV	6.73	0.973	0.156	0.886	0.968	0.518	0.997

Table 6 Stability studies of optimized formulation (FV) of LP sustained release tablet

Characteristic	Initial	1 Month	2 Month	3 Month
Hardness (kg/cm^2)*	6.50±0.447	6.16±0.288	6.00±00	6.3±0.29
Drug content (mg/Tablet)*	100.72±1.5	100.6±1.68	99.45±1.3	99.39±1.5
In-vitro drug release at 12th h	95.45±0.97	94.73±0.77	93.45±0.77	94.00±0.62
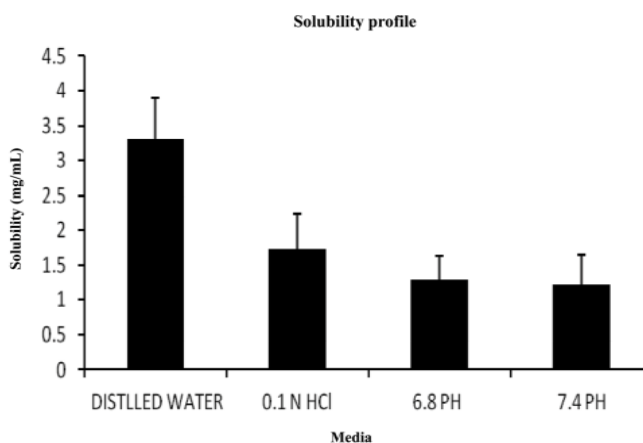
Figure 1 Solubility studies of Losartan potassium in different media.
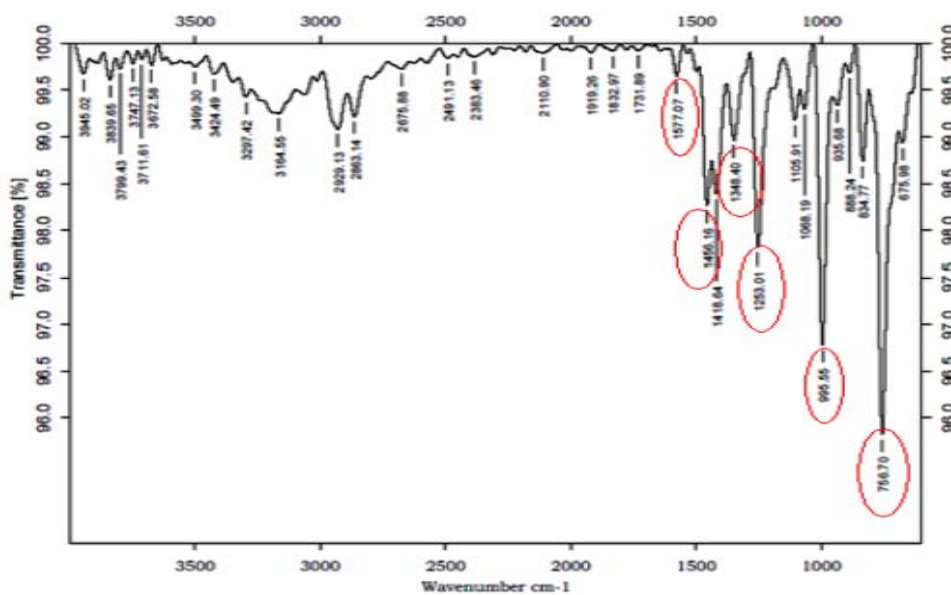
Figure 2a FTIR Spectra of Pure drug Losartan Potassium
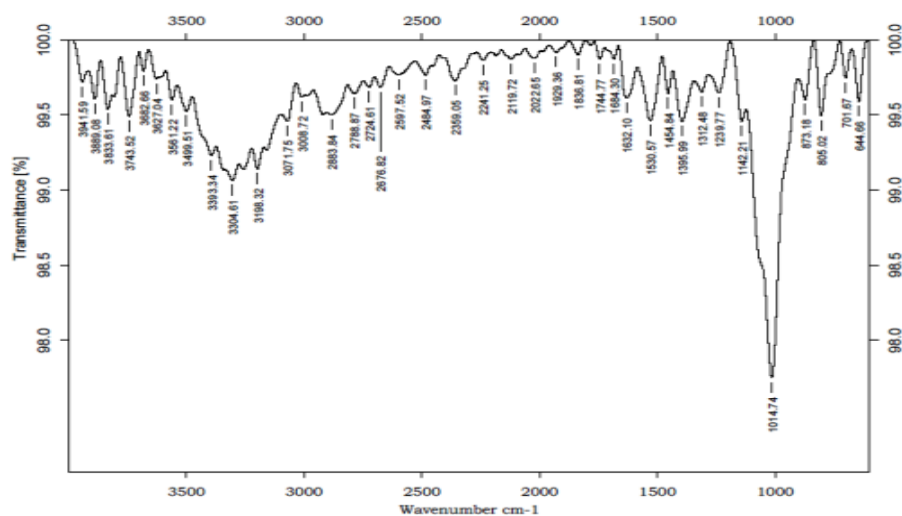
Figure 2b FTIR Spectrum of Locust bean Gum
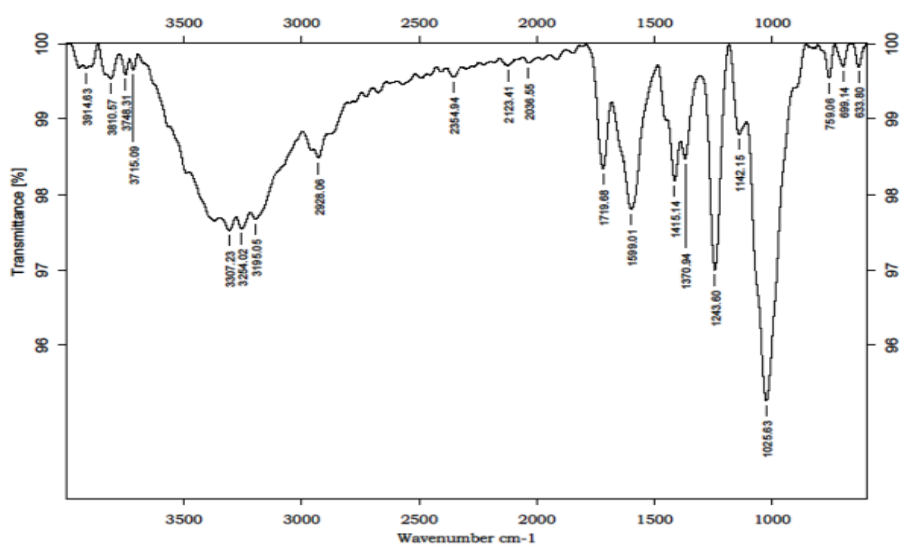
Figure 2c FTIR Spectrum of karaya gum
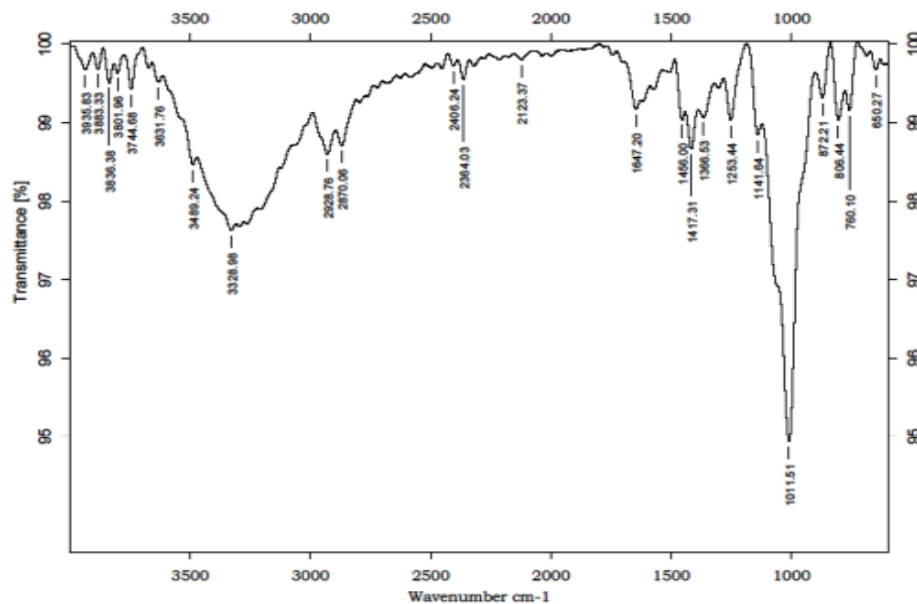
Figure 2d FTIR Spectrum of Tara Gum
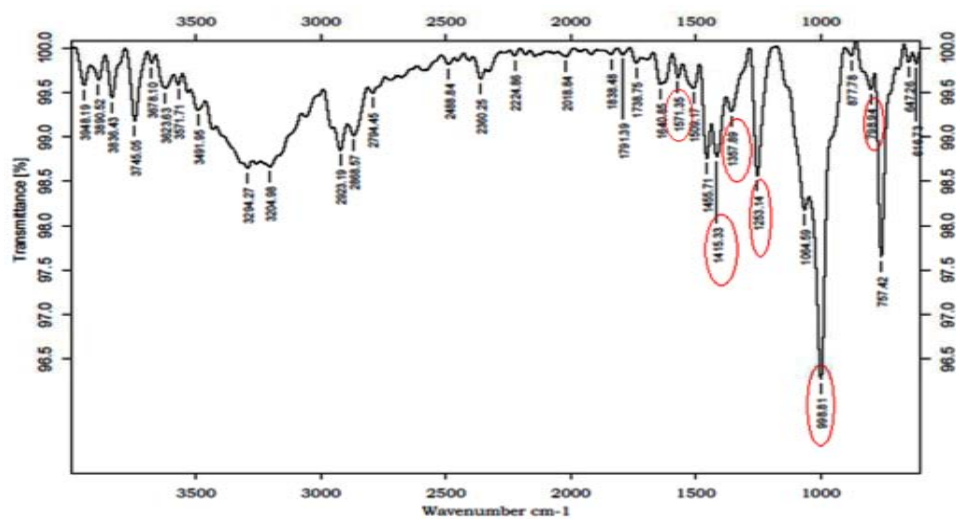
Figure 2e FTIR Spectrum of Losartan Potassium with Locust Bean Gum
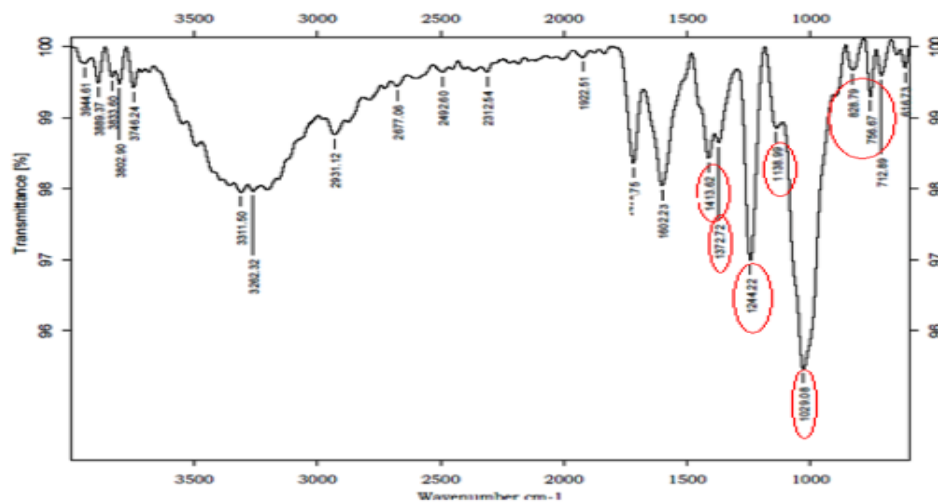
Figure 2f FTIR Spectrum of Losartan Potassium with Karaya Gum
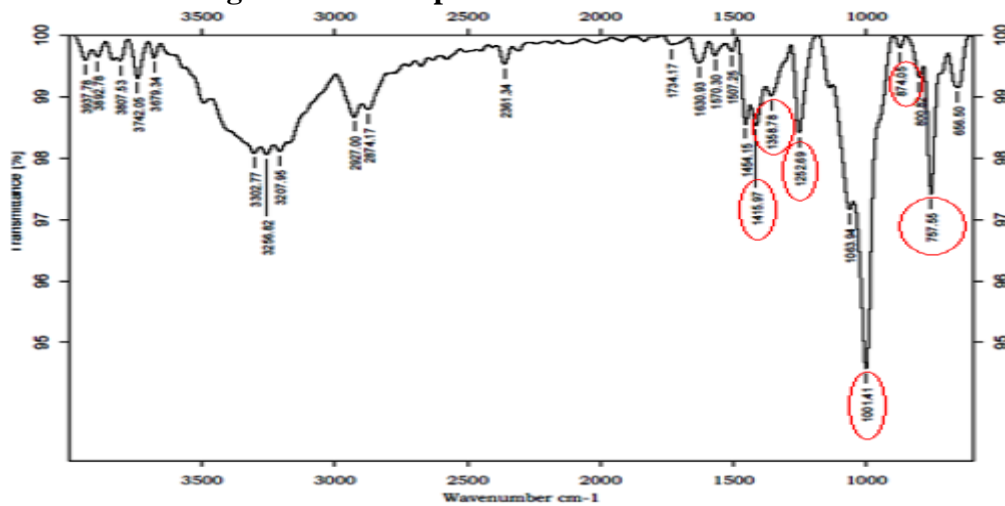
Figure 2g FTIR Spectrum of Losartan Potassium with Tara Gum
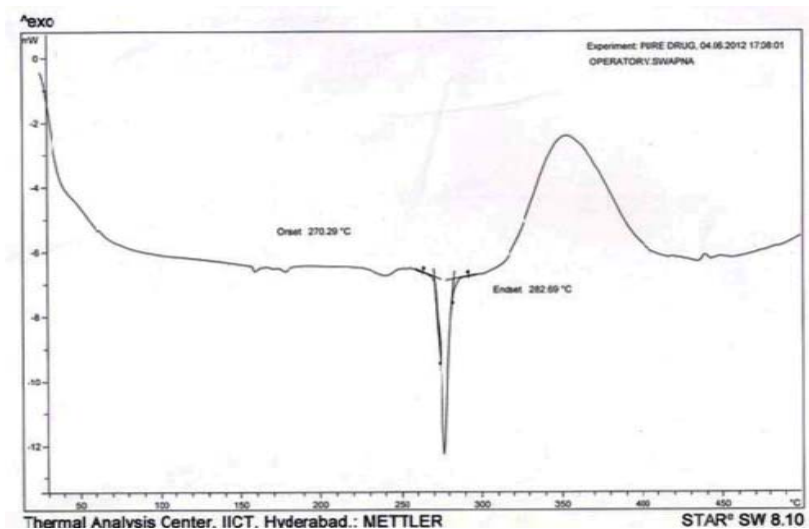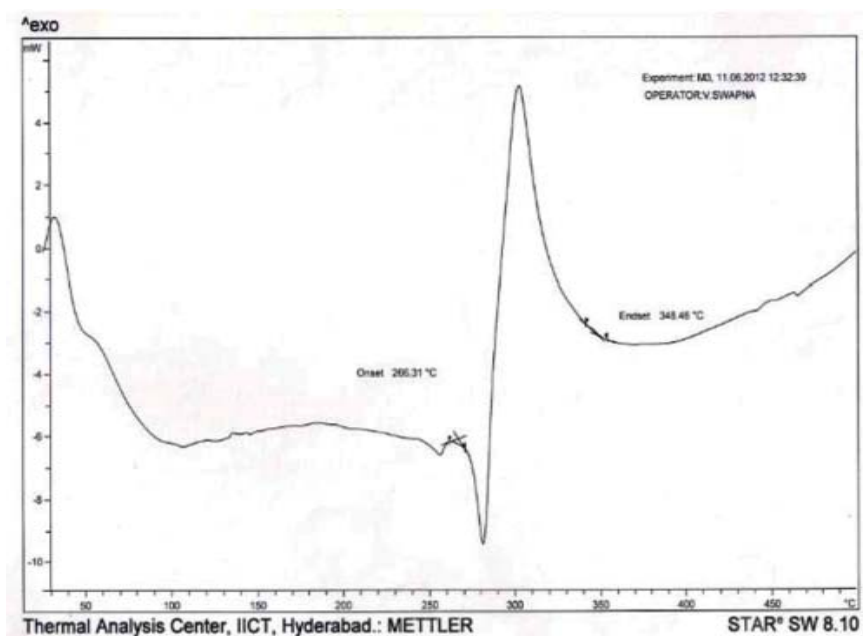

Figure 3a DSC Thermogram of Losartan Potassium
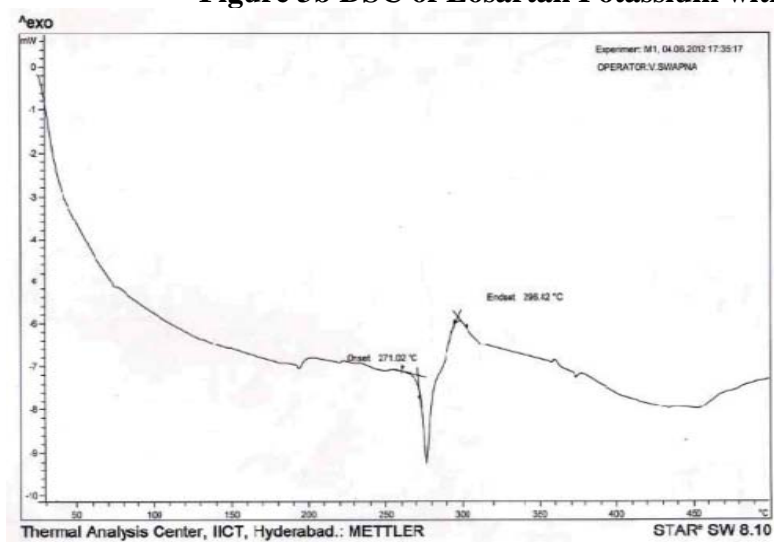
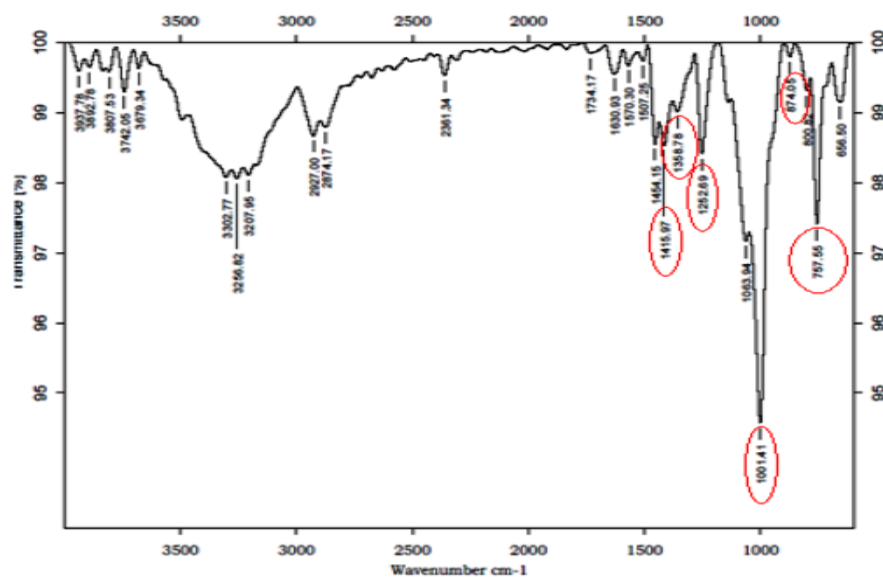**Figure 3b DSC of Losartan Potassium with Locust Bean Gum**

Figure 3c DSC of Losartan Potassium with Karaya Gum
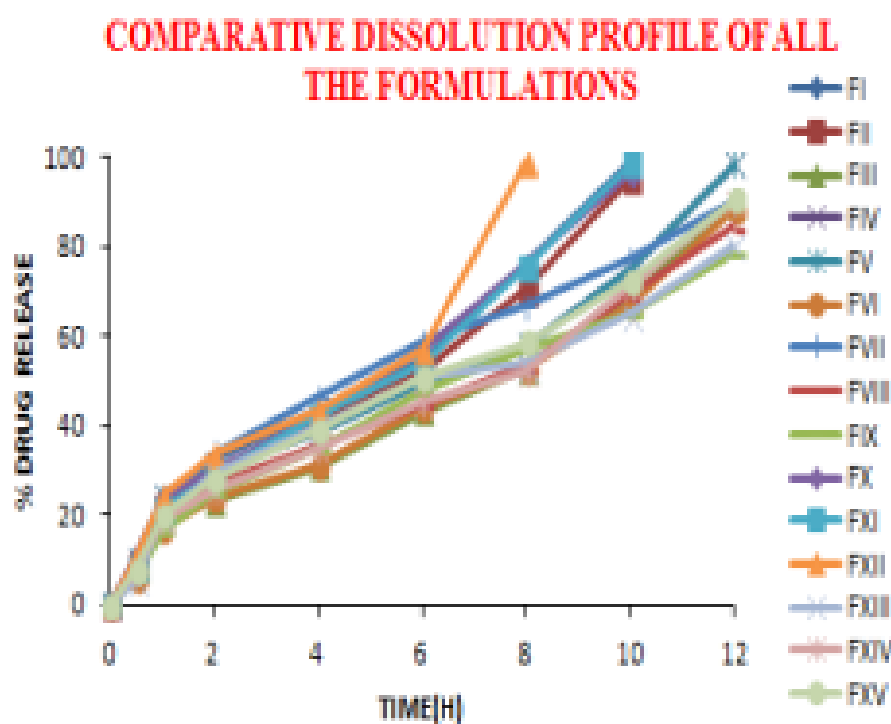
Figure 3d DSC of Losartan Potassium with Tara Gum

Figure 4 Dissolution Profile of all the formulations FI to FXV

CONCLUSION

The effect of type of polymer used and its increase in concentration on the drug release was studied in this work. Also the effect of type of diluent used on the drug release from the matrix tablets was studied. Among the three polymers used, Karaya gum showed maximum retardation effect than Tara and locust bean gums because of its more swelling and gelling tendency. The release retardation effect was in the order

Karaya gum > Tara gum > Locust bean gum

Among the three diluents used i.e. MCC 101, DCP and lactose the drug release was controlled more by DCP. The order of release retardation was

DCP > MCC101 > Lactose

This was because lactose is freely soluble in water so when used as diluent in matrix tablets absorbs more water quickly and dissolves the drug rapidly.MCC 101 is partially soluble diluent thus it doesn't release the drug as quickly as lactose. DCP is insoluble diluent so it releases the drug slowly when compared to the other two. Formulation FV was selected to be the best formulation with about only 26.18 % drug release at the end of 2 h and 95.11% drug release within 12 h. The kinetics of drug release was best explained by zero order equation. The drug release from the tablets was sufficiently sustained and non-Fickian transport of the drug from tablets was confirmed. The LP sustained release tablets were stable at 40°C/75% RH up to 3 months. Thus, the sustained release matrix tablets of LP were successfully prepared using natural polymers in an economical way and are much preferable when compared to immediate release tablets for better therapy and patient compliance.

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