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Research Article

FORMULATION AND INVITRO EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF LOSARTAN POTASSIUM

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ABSTRACT

The ultimate aim of the present study was to prepare twice daily sustained release matrix tablets of losartan potassium using Eudragit RLPO, RSPO and Ethyl cellulose individually and in combination of above polymers. Sustained release matrix tablets were developed using different drug polymer ratios and prepared by direct compression method. The influence different concentrations and nature of polymer was studied. Matrix tablets assessed for their physicochemical properties and invitro drug release studies. Drug-excipient interaction was evaluated by Differential scanning calorimetry and FTIR. There was no drug excipient interaction. The prepared matrix tablets are with in house specifications for all the physicochemical properties. In vitro release data shows individual low polymer concentration of RLPO, RSPO sustain the drug release up to 10hrs but combinations with EC sustain the drug release more than 12hrs.Eudragits in higher polymer proportion drug release was extend up to 12hrs. Ethyl cellulose has more retardation than Eudragits. Based on in vitro drug release data and f2 factor formulations F2, F6 are optimized. Mathematical analysis of the release kinetics indicated that drug release mechanism was fickian diffusion.

Key words: Eudragit RLPO, Eudragit RSPO, losartan potassium, ethyl cellulose.

INTRODUCTION

An ideal drug delivery system should be able to deliver an adequate amount of drug for an extended period of time for its optimum therapeutic activity. Most drugs are inherently not long lasting in the body and require multiple daily dosing to achieve the desired blood concentration to produce therapeutic activity. To overcome such problems greater attention has been focused on sustained release drug delivery system[1].

Losartan potassium is an orally active non-peptide angiotensin -II receptor antagonist used in treatment of hypertension due to mainly blockade of AT1 receptors [2]. The main limitation of low therapeutic effectiveness is due to narrow therapeutic index, poor bioavailability (25-35%), and short biological half life (1.5-2h). Conventional tablets should be administered 3-4 times to maintain plasma drug concentration. To increase therapeutic efficacy, reduce frequency of administration and for better patient compliance twice daily-sustained release losartan potassium matrix tablets are prepared by using hydrophilic eudragits and hydrophobic ethyl cellulose.

Losartan potassium is belongs to the class II of BCS (Biopharmaceutics classification of system), exhibits high solubility and low permeability. Selection of release retarding polymers is very crucial for freely soluble drugs for maintaining constant in vivo release. In all the SR dosage forms matrix tablets are easy to prepare on a commercial scale.

Matrix tablets are formulated by direct compression or wet granulation In formulation of sustained release hydrophilic polymers are widely using because of their low cost, desired drug release profile broad regulatory acceptance. Hydrophilic polymers of HPMC Sodium alginate, methyl cellulose, sodium CMC and carbopols [3] are widely using in matrix formulations. Hydrophilic Eudragit RLPO, RSPO polymers were selected for present study. Eudragits are neutral copolymers of poly (ethacrylate, methyl methacrylate) and trimethyl aminoethyl methacrylate chloride] Eudragit polymers show pH independent drug release. For highly water soluble drugs the use of hydrophilic polymers are restricted in preparation of matrix tablets due to rapid release of drug through hydrophilic gel network. For such drugs it is essential to include hydrophobic polymers for retardation [4].

Ethyl cellulose is non toxic, inert hydrophobic polymer used in preparation of sustained release formulations, film coated tablets [5],microspheres [6, 7] and microcapsules [8, 9]. Consequently, present work is developing to sustained-release losartan potassium, using hydrophilic (Eudragits) and hydrophobic (EC) polymers either alone or as blend.

MATERIALS AND METHODS

Materials

Losartan potassium was a gift sample from Aurabindo Pharmaceuticals, Hyderabad. Eudragit RLPO, Eudragit RSPO, ethyl cellulose were gift samples from Oxford laboratory, Mumbai. All other chemicals or ingredients used in this study are either analytical or pharmaceutical grade.

Methods

Matrix embedded sustained release tablets of losartan potassium were prepared by direct compression technique using various concentrations of ethyl cellulose, Eudragit RLPO and RSPO, along or in combination with ethyl cellulose (Table-1). All the excepients except magnesium stearate were thoroughly blended in a mortar uniformly. After sufficient mixing of the drug with other components, finally magnesium state was added and mixed for 2 more minutes. Finally tablets were compressed by 16 station rotary tablet punching machine (Cadmach machinery co, Ahemdabad) equipped with round concave faced punches of 9mm diameter.

Table 1: Composition of losartan Potassium (50mg) matrix tablets

Formulation	Eudragit RLPO	Eudragit RLPO	Ethyl cellulose	MCC (200)	Aerosil
F1	87.5	-	-	148.5	5
F2	100	-	-	136	5
F3	125	-	-	111	5
F4	50		50	136	5
F5	-	87.5	-	148.5	5
F6	-	100	-	136	5
F7	-	125	-	111	5
F8	-	50	50	136	5
F9	-		75	161	5
F10	-		87.5	148.5	5
F11	-		100	136	5
F12	25	25	50	136	5

All the Tablets contain talc 2% as glidant, magnesium stearate 1% as a lubricant. Total weight of tablet is 300 mg. MCC-Microcrystalline cellulose

Table 2: Physical Properties of Compressed Tablets

F.Code	Hardness kg/cm^2) *	Thickness (mm) *	Weight variation (%) **	Friability (%)	Drug content
F1	5.37± 0.47	4.58 ± 0.09	0.568±0.08	0.44 ± 0.08	99.9+ +0.55
F2	5.37± 0.48	4.30 ± 0.07	0.835±0.02	0.25 ± 0.12	98.9+ +0.55
F3	5.25± 0.25	4.31 ± 0.07	0.563±0.08	0.24 ± 0.08	99.5+ +0.55
F4	5.25±0.28	4.30 ± 0.07	0.927±0.05	0.27 ± 0.08	98.6+ +0.55
F5	4.75±0.28	4.8 2 ± .23	0.746±0.02	0.38 ± 0.04	99.4+0.25
F6	4.5 ±0.41	4.12 ± 0.41	1.027±0.08	0.43 ± 0.08	98.6+0.89
F7	4.5 ±0.41	4.96 ± 0.13	1.169±0.02	0.33 ± 0.04	99.6+0.78
F8	4.72 ±0.61	5.16 ± 0.01	1.357±0.04	0.26 ± 0.06	100.2+0.59
F9	4.72 ±0.61	4.69 ± 0.04	0.545 ±0.06	0.62 ± 0.14	98.9+0.67
F10	4.86 ±0.41	4.72 ± 0.08	0.759 ±0.22	0.78 ± 0.11	99.8+0.87
F11	4.96 ±0.41	4.64 ± 0.35	1.012 ±0.05	0.79 ± 0.11	98.2 + 1.01
F12	5.25 ±0.28	4.58 ± 0.09	1.023 ±0.15	0.41 ± 0.04	98.4 + 0.72

* All values represent mean ± SD, n = 20, * All values represent mean ± SD, n = 6

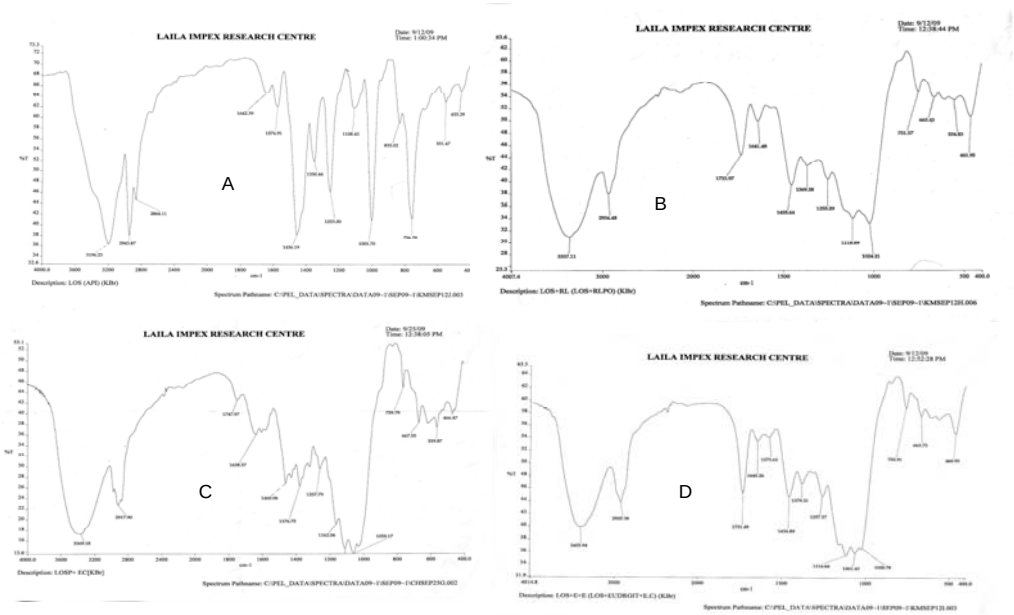

Fig. 1: FTIR spectrums of Losartan potassium (A), LP+Eudragit RLPO (B), LP+Eudragit RSPO(C), LP+ Ethylcellulose (D)

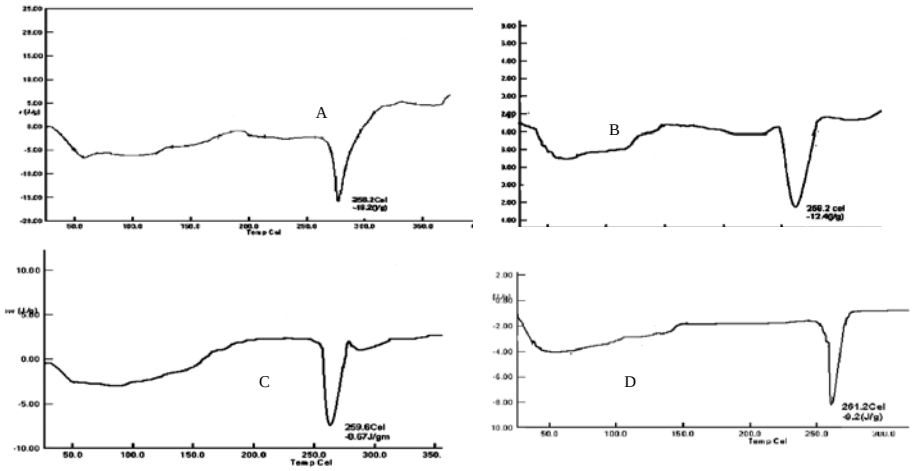

Fig. 2: DSC Thermograms of Losartan potassium (A), LP+Eudragit RLPO (B), LP+Eudragit RSPO(C),LP+Ethylcellulose(D)

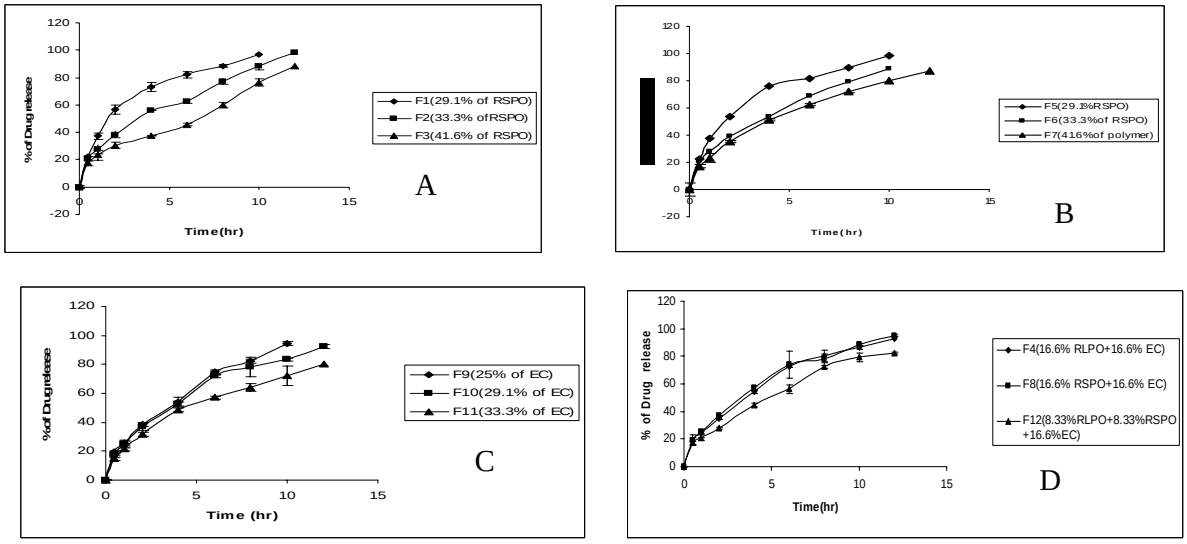

Fig. 3: Drug release profiles of Losartan potassium matrix tablets prepared with varying percentages of: A) Eudragit RLPO; B) Eudragit RSPO;C) EC; D)Combination of eudragits with EC ;(mean ±SD, n=3)

Table 3: Correlation coefficient (R^2) and release exponent (n) values for different kinetic models, f2 factor and theoretical release

F.Code	Zero order	First Order	Higuchi's	Korsmeyer	Peppas'n'	f2 values	Time in hrs to be released	% release
F1	0.8502	0.9621	0.9812	0.9730	0.58	52.95	0	0
F2	0.9192	0.9710	0.9935	0.9951	0.48	77.02	1	26.52
F3	0.8502	0.9105	0.9105	0.9658	0.52	65.04	2	33.2
F4	0.9118	0.9506	0.9915	0.9924	0.54	62..23	4	46.56
F5	0.8073	0.8862	0.9579	0.9614	0.44	68.42	6	59.92
F6	0.9334	0.9671	0.9989	0.9979	0.48	76.82	8	73.28
F7	0.9226	0.9928	0.9986	0.9985	0.57	64.08	10	86.64
F8	0.8502	0.9621	0.9835	0.973	0.47	61.12	12	100
F9	0.9294	0.9901	0.998	0.9975	0.53	72.25		
F10	0.9214	0.9841	0.994	0.9959	0.54	72.25		
F11	0.9237	0.9925	0.9919	0.9926	0.54	69.41		
F12	0.9222	0.9605	0.9912	0.9939	0.52	64.2		

EVALUATION OF MATRIX TABLETS

Dimensions

The dimensions (diameter and thickness) were determined to within ± 0.01 mm by using digital vernier calipers [10].

Hardness

The hardness of the tablets was determined by using Monsanto type hardness tester. For adequate mechanical stability 4-5 kgs/tablet hardness is required. Determinations are made in triplicate [11].

Uniformity of weight

In one batch all tablets should be in uniform weight and weight variation should be with in the limits [11]. The weights were determined by using digital weigh balance (Shimadzu) within ±1mg. weight control is based on a sample of 20 tablets.

Friability

The friability of the tablets was measured by Roche friabilator (Campbell Electronics, Mumbai, India). Tablets of known weight (Wo) of sample are rotated for fixed revolutions (100 revolutions) and weighed again (W) and reweighed to determine the loss in weight. Loss in weight of tablet is the measure of friability and % friability was calculated by using the equation. The weight loss should not be more than 1%.[11]

$$F(\%) = [1-Wo/W] X100 \ldots\ldots\ldots (1)$$

Determination of drug content

Three tablets were powdered and powder equivalent to weight of one tablet (300mg) was transferred to 100ml volumetric flask containing distilled water. For ensuring complete solubility sonication was done for 30 mins. Solution was suitably diluted and the absorbance was determined by UV-Visible spectrophotometer at 250nm.

Drug Excipient Compatibility Studies

To study the losartan potassium compatibility with different formulation excipients Fourier transform infrared spectroscopy (FTIR) and Differential scanning calorimetry (DSC) was done. FTIR, DSC studies are performed on samples of losartan potassium (LP)pure drug(A), solid admixture of LP+Eudragit RLPO(B), LP+Eudragit RSPO(C), LP+Ethyl cellulose(D) .

The IR Spectra of the test samples were obtained using KBR disk method. About 2-3 mg of samples were mixed with dried IR grade potassium bromide powder and the spectra were obtained using FTIR spectrophotometer in between the wave number range of 4000-400cm^{-1}.DSC studies were performed using a DSC(diamod, Mettler star) with thermal analysis data system, computer, and a plotter interface. Indium/zinc standards were used to calibrate the temperature and enthalpy scale. Accurately weighed 5-6 mg samples

were hermetically sealed in aluminum pans and heated at constant rate of 10°C/min over a temperature range of 40 to 300 °C and inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50ml/min.

In vitro drug release studies

In vitro drug release studies of matrix tablets were done in eight-station USP XXII type1 dissolution test apparatus(Electro lab TDT-08, India) at 37°C (± 0.5°C) and 100 rpm speed in 900mL of distilled water as a dissolution medium. Five millitre (5ml) samples were taken by filtration at predetermined time intervals and after each sampling the volume of dissolution medium was replaced with 5ml of distilled water. The absorbances of samples were measured at 250nm using UV-Visible double beam spectrophotometer (Elico SL 164 India) and cumulative percentage drug release was calculated.

Determination of Theoretical Release profile& Similarity factor

Theoretical release profile of a drug is constructed to check whether the formulations are releasing the drug similar to the predicted profile. Theoretical release profile of a drug is plotted on basis of the loading dose and the drug availability rate [12].

$$D_t = \text{Dose}\ [1+0.693 \times t / t_{½}] \ldots\ldots\ldots\ldots\ldots (2)$$

D_t = Total dose of drug; Dose = dose of the immediate release part. (13.26),t = time (hrs) during which the sustained release desired (12hrs), t ½ = half – life of the drug (3 hrs).

The dissolution similarity was assessed by f2 similarity factor[13].

$$f_2 = 50 \times \log \{[(1+1/n) \sum (R_t - T_t)^2]^{-0.5} \times 100 \} \ldots\ldots\ldots\ldots (3)$$

Where n = number of sample points, R_t=Percent of marketed product (or) theoretical release profile, T_t=Percent of test formulations release observed.

Accelerated stability studies

Optimized formulations were packed in blister and stored in ICH certified stability chambers maintained at 40°C and 75% RH for three months. The tablets were withdrawn periodically and evaluated for friability, hardness, drug content and in vitro release studies.

Mechanism of drug release

To know the mechanism of drug release from these formulations the data were treated according to first order [14] (log cumulative percentage of drug remaining vs time) higuchi's[15] (cumulative % drug release vs square root of time) and korsmeyer et al's[16] (log cumulative % drug release vs log time) equations along with zero order[17] (cumulative amount drug release vs. time).Korsmeyer and Peppas model was fitted into the following equation[17].

$$M_t / M_\infty = K.t^n \quad \ldots\ldots (4)$$

M_t / M_∞ is the fraction of drug released= the release constant, t= release time, n=diffusion exponent If n =0.89, the release is zero order. If n = 0.45, the release is Fickian diffusion. If 0.45 < n < 0.89, the release is anomalous diffusion or non fickian diffusion (Swellable & Cylindrical Matrix).

RESULT AND DISCUSSION

Physicochemical Properties of Compressed Tablets

Table-2 indicates the results of physicochemical properties (hardness, thickness, weight variation, friability and assay) of compressed matrix tablets. Tablet thickness was in the range of 4.12 to 5.16mm; and hardness, 4.5-5.25Kg/cm^2. Tablet friability and weight variation of all the tablet batches were in the range of 0.24 to 0.79% and 0.56 to 1.16% respectively. The formulated tablets of all batches showed low weight variations and uniform drug content (>99%) and satisfactory. All the tablet formulations showed acceptable pharmacotechnical properties and complied with the in house specifications for weight variation, drug content, hardness and friability.

Drug-excipient compatibility studies

Fig.1 (A, B, C, D) shows the FTIR spectra of pure losartan potassium, LP**+** Eudragit RLPO, LP+Eudragit RSPO, LP+Ethyl cellulose, respectively. The spectrum of pure losartan potassium shows some characteristic peaks at 764 cm^{-1} due to C-Cl bond, 1574 due to a N=N stretching,1456,1574 due to C=C bond, 3196 due to stretching vibration of O-H bond. The physical mixtures of drug with polymers also showed similar peaks at the above wave numbers.

DSC was performed to characterize thermal changes in the melting behaviour of losartan potassium with other excipients present in different formulations. Fig. 2 (A, B, C, D) depicts the thermograms of heat verses temperature for pure losartan potassium, LP**+** Eudragit RLPO, LP+Eudragit RSPO, LP+Ethyl cellulose respectively. The prominent and sharp endothermic peak at 258.2 °C (ΔH is –16.2 J/g) in the thermogram of pure losartan potassium representing the melting point of losartan. In all the DSC spectrums the characteristic drug melting point peak was observed. From these results there was no drug excipient interaction. This indicates the choice of excipients used in the formulation of the matrix tablets was suitable

In Vitro drug release studies

The dissolution profiles of losartan potassium tablets containing varying percentages of eudragit RLPO (F1, F2, and F3) are shown in Fig 3A. With in 1 hr 37% of drug release occurs due to burst release and total amount of drug released with in 10hrs from F1(29.1% of polymer) .Formulations F2, F3(33.3,41.6% of polymer) releases 94.35%, 88.6% for 12 hrs respectively. The results of dissolution studies of formulations F5 to F7 composed of varying percentages of eudragit RSPO are shown in Fig.3B. From F5 (29.1% of polymer) 98% of drug release occurred in 10hrs and also shows burst release. F6, F7 (33.3, 41.6% of polymer) release 97%, 87% of losartan potassium respectively after 12hrs.

The initial drug release of either of eudragit RLPO(F1) or RSPO (F5) containing 29.1% of polymer varied in between 30-40% in first hour. This initial burst release may be due to surface erosion or initial disaggregation of the matrix tablet prior to gel layer formation around the tablet core and also total amount of drug released with in 10hrs. Hence the release pattern was not desirable limit. However when polymer concentration increases (33.34% and 41.66%) either of eudragit polymer no burst release was observed (less than 25% of drug release in 1 hour)[18] and release was sustained upto12hrs.Increasing polymer concentration the rate of drug release was decreased. The release of drug from matrix tablets depends not only on the nature of the polymer but also drug polymer ratio. The slower drug release in higher polymer content is due to structural reorganization of hydrophilic polymer and increases the tortuosity (or) gel strength of polymer and forms viscous gelatinous layer. Failure to generate a uniform and coherent gel may cause rapid drug release [19]

The dissolution profiles of losartan potassium tablets containing varying percentages of ethyl cellulose (F9 to F11) are shown in Fig.3C. From F9 (25% of polymer) 98.4% of losartan potassium release was observed after 10hrs. F10, F11 (29.1%, 33.3% of polymer) released 92.2%, 80% of losartan potassium after 12hrs from matrix tablets. Ethyl cellulose containing 29.1% of polymer (F10) showed the drug release up to 12hrs but same concentration of either of eudragit polymer complete drug release occurs in 10hrs.This is due to decreased penetration of the solvent molecules in the presence of hydrophobic polymer, leading to reduced diffusion of the drug from matrix tablets. The pore network in hydrophobic polymers becomes more tortuous resulting in slower drug release [20].

The dissolution profiles of losartan potassium tablet containing blends of eudrgits with EC (F4, F8 and F12) are shown in Fig.3D. F4 (16.6 %of RLPO+16.6% EC), F5 (16.6 %of RSPO+16.6% EC) and F6 (8.33 %of RLPO+8.33 %of RSPO+ 16.6% EC) releases 92.8%, 94.9% and 82.35 of losartan potassium after 12 hrs from matrix tablets. In combination showed a significant difference in the drug release as compared with 33.31% of either of eudragit polymer. Nearly 20 % of

the drug releases from the above formulations in first hour which reflects no burst release occurred.

The results of kinetic analysis of the dissolution data, dissolution efficiency (DE_{12}) theoretical release and similarity factor values of all the formulations are shown in Table-3. DE_{12} at the end of 12h was 80.1-98.4%. The drug release data of all tablet formulations did not fit satisfactorily with zero order, first order and higuchi models and showed good fit to the korsmeyer-peppas mode and some degree with Higuchi model. From the regression coefficients the plots shows highest linearity with Higuchi model followed by first order followed by zero order. The value of the release exponent 'n' for the various matrices ranged from 0.44-0.57. Indicating that the release mechanism was Fickian release and totally based on diffusion Diffusion is related to transport of drug from the dosage matrix into the in vitro dissolution medium. As gradient varies, the distance for diffusion increases. The similarity factor values of F2, F6 are 77.8, 76.8 suggesting that their dissolution profiles were similar with theoretical release.

Accelerated stability studies

The results obtained from accelerated stability studies indicate that F2 and F6 tablets did not show any physical changes such as appearance, friability and hardness after 3 months**.** Drug content (mean ± SD, n=3) was100.6± 0. 12% at 0 month; 100.3±0.22% at 1st month; 99.5±0.35% at month 3; no change was observed in the drug content. Further more there was no change the drug release profile of the formulations over the period of accelerated stability studies.

CONCLUSION

Sustained release matrix tablets of losartan potassium with eudragit RLPO, RSPO & EC were developed could improve patient compliance and increase therapeutic efficacy.

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