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Formulation and Evaluation of Losartan Potassium Sustained Release Matrix Tablets

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ABSTRACT

The objective of the present study was to formulate once daily sustained release matrix tablet of Losartan potassium to increase therapeutic efficacy, reduce frequency of administration and improve patient compliance. The sustained release matrix tablet was prepared by wet granulation method by varying concentration and ratios of hydrophilic and hydrophobic polymers to release the drug in sustained manner for a period of 24 hrs. The preformulation studies were carried out for the drug, polymers and physical mixtures. The prepared granules were compressed into tablets. The prepared formulations were evaluated for the pre-compression and post-compression parameters. In-vitro release profile were studied in both simulated gastric and intestinal fluid for 24 hrs, from the in-vitro dissolution profile, the best formulations were compared with marketed product (Losacar) Mathematical analysis of the release kinetics indicated a coupling of first order mechanism. The drug release from the optimized formulation showed more than marketed product. Further the accelerated stability studies were carried out as per ICH guidelines.

Keywords: Losartan potassium, Sustained release, Wet granulation and Compared with Marketed product.

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INTRODUCTION

The word new or novel in the relation to drug delivery system is a search for something out of necessity. An appropriately designed sustained or controlled release drug delivery system can be major advance towards solving the problem associated with the existing drug delivery systems [1].

The oral route is the most common route of drug administration because of its advantages in terms of convenient administration, thus leading to increased patient compliance. Extended release formulations in many cases provide further significant advantages, including improved therapeutic effect, increased patient compliance by reducing dosing frequency and decrease in incidence and or intensity of adverse effect by a constant blood concentration [2].

The simplest way to retard drug release is to disperse it in a solid matrix. The matrix system is commonly used for manufacturing sustained release dosage forms especially tablets because it makes such manufacturing easy [3].

Losartan potassium (LP) is a potent, highly specific angiotensin II type 1 (AT_1) receptor antagonist with antihypertensive activity. 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 hr. Administration of Losartan potassium in a sustained release dosage would be more desirable for antihypertensive effects by maintaining the plasma concentrations of the drug well above the therapeutic concentration. To reduce the frequency of administration and to improve patient compliance, a once-daily sustained-release formulation of Losartan potassium is desirable [4].

Sustained release drug delivery offers safe and easy method of drug utilization, since the medication can be promptly terminated in case of toxicity.

When given in adequate doses, the AT_1 receptor antagonists appear to be as effective as ACE inhibitors in the treatment of hypertension. As with ACE inhibitors, these drugs may be less effective in African-American and low-rennin patients.

Developing a sustained release drug delivery system like matrix tablet for ACE inhibitor Losartan potassium is desirable for an effective treatment of hypertension [5].

MATERIAL AND METHODS

Losartan potassium was generous gift sample from M/s Madras Pharmaceutical Company, Chennai, India. Hydroxy propyl methyl cellulose (Methocel K100M), Eudragit-L100,

Eudragit-S100, Eudragit-RLPO was obtained as gift samples from M/s Dr. Reddy's laboratories, Hyderabad, India. All other reagents and solvents used were of analytical grade.

Formulation of Losartan potassium sustained release matrix tablets

Losartan potassium granules were prepared by wet granulation method. Specified quantity of Losartan potassium, HPMC K100M, Eudragit RLPO, Eudragit L-100, Eudragit S-100, micro crystalline cellulose, di-calcium phosphate were weighed according to the formulation (Table 1) and mixed uniformly. The powder mass was passed through sieve # 60 and then the fine powder was mixed with water to obtained wet mass. The wet mass was passed through sieve # 22 / 44 and stored for further studies. Sufficient quantity of magnesium stearate and talc were finally added to the prepared granules and compressed into tablets.

Quantity sufficient for a batch of 50 tablets was mixed thoroughly to ensure complete mixing. Tablet containing 50 mg equivalent to Losartan potassium were compressed into tablets using compaction force of 26kN and using 13 x 6 mm oval shape punches on multi station rotatory tablet punching machine (Riddhi 10 stn mini tablet press RDB4-10, Rimek, Ahmedabad, India).

Table 1: Preparation of wet granules of Losartan potassium sustained release matrix tablets

Compositions (mg)	**WF1**	**WF2**	**WF3**	**WF4**	**WF5**	**WF6**	**WF7**	**WF8**	**WF9**
Losartan potassium	50	50	50	50	50	50	50	50	50
HPMC K100M	200	200	-	-	150	125	125	200	-
Eudragit RLPO	-	-	200	200	80	75	75	-	200
Eudragit S100	30	-	30	-	-	30	-	15	15
Eudragit L100	-	30	-	30	-	-	30	15	15
MCC	20	20	20	20	20	20	20	20	20
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	8	8	8	8	8	8	8	8	8
di-calcium phosphate	40	40	40	40	40	40	40	40	40
Total	350	350	350	350	350	350	350	350	350

EVALUATION

Pre and post compression parameters of the formulation tablets

Bulk density and tapped density was found out using measuring cylinder method. Angle of repose was measured by funnel method. The dimensional specifications (thickness and diameter) were measured using vernier calipers (Mitutoyo, Japan). Weight variation study was carried for 20 tablets from each formulation using electronic weighing balance (Citizen, Japan). Hardness test was performed using Monsanto hardness tester (Lab tech, India). The friability test was performed using Roche friabilator (Ketan instruments, India).

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The assay was performed for the average weight of five tablets and triturating the tablets and taking triturate was equivalent to 100 mg of drug transferred in 100 mL phosphate buffer pH 6.8 solution to the conc. of 1000 µg / mL. From this stock solution10 mL was taken and diluted to 100 mL with phosphate buffer pH 6.8 solution. Then 20 µg / mL solutions were prepared by taking 2 mL from the above stock solution and diluting to 10 mL. The Absorbance was measured by UV Spectrophotometric method at 254 nm (shown in Table 2 and 3) [6-11].

Table 2: Pre-compression parameters

Formulations Code	Bulk density*	Tapped density*	Carr,s index*	Hausner's ratio*	Angle of repose*
WF1	0.330 ± 0.004	0.384 ± 0.008	13.96 ± 1.09	1.16 ± 0.010	28.68 ± 0.651
WF2	0.373 ± 0.003	0.413 ± 0.01	11.19 ± 0.385	1.10 ± 0.035	28.25 ± 0.645
WF3	0.295 ± 0.023	0.329 ± 0.024	10.40 ± 0.770	1.11 ± 0.010	25.55 ± 0.719
WF4	0.318 ±0.010	0.355 ± 0.009	10.48 ± 1.15	1.11 ±0.014	28.40 ± 0.681
WF5	0.339 ± 0.01	0.392 ± 0.013	13.55 ± 0.322	1.15 ± 0.005	28.83 ± 1.04
WF6	0.347 ± 0.005	0.387 ± 0.014	10.20 ± 1.29	1.11 ± 0.016	25.56 ± 1.22
WF7	0.300 ± 0.004	0.323 ± 0.002	7.080 ± 1.21	1.07 ± 0.014	24.67 ± 1.02
WF8	0.369 ± 0.006	0.408 ± 0.007	9.600 ± 0.151	1.10 ± 0.002	29.64 ± 1.05
WF9	0.375 ± 0.005	0.413 ± 0.006	9.161 ± 0.740	1.10 ± 0.010	24.83 ± 1.30

Mean ± SD *n=3.

Table 3: Post compression parameters of tablets

Formulations code	Hardness* (kg/cm^2)	Thickness* (mm)	Drug content* (mg)	Weight variation***	Friability** (%)
WF1	6.15 ± 0.191	5.19 ± 0.037	90.24 ± 1.235	349.05 ± 4.904	0.23 ± 0.12
WF2	7.17 ± 0.221	5.18 ± 0.054	97.60 ± 1.560	350.84 ± 5.871	0.20 ± 0.09
WF3	7.07 ± 0.150	5.28 ± 0.071	98.52 ± 1.485	351.7 ± 5.939	0.22 ± 0.14
WF4	5.85 ± 0.251	5.88 ± 0.030	99.96 ± 1.864	351.35 ± 3.910	0.31 ± 0.08
WF5	6.52 ± 0.150	5.85 ± 0.068	94.84 ± 1.356	352.35 ± 4.568	0.51 ± 0.08
WF6	6.52 ± 0.125	5.88 ± 0.020	95.08 ± 1.894	350.65 ± 2.033	0.50 ± 0.05
WF7	6.70 ± 0.081	5.88 ± 0.025	97.72 ± 1.756	350.6 ± 2.087	0.51 ± 0.09
WF8	6.27 ± 0.095	5.90 ± 0.012	98.36± 1.764	350.25 ± 1.802	0.49 ± 0.11
WF9	6.50 ± 0.081	5.93 ± 0.018	96.52 ± 1.523	350.65 ± 1.899	0.54 ± 0.12

Mean ± SD, *n=3, ** n=10, ***n=20.

Swelling index studies

The extent of swelling was measured in terms of % weight gain by the tablet. One tablet from each formulation was weighed and kept in Petri dish containing 20 mL of phosphate buffer of pH 6.8. At the end of specified time intervals tablets were withdrawn from Petri dish and excess buffer blotted with tissue paper and weighed. The results were as mentioned in Figure 1**.** The % weight gain by the tablet was calculated by formula [12, 13]

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$$swelling\ index = \frac{\text{Mt-Mo}}{\text{Mt}} \times 100$$

Where,

M_t – weight of tablets at time't'

M_0 – weight of tablets at time'0'

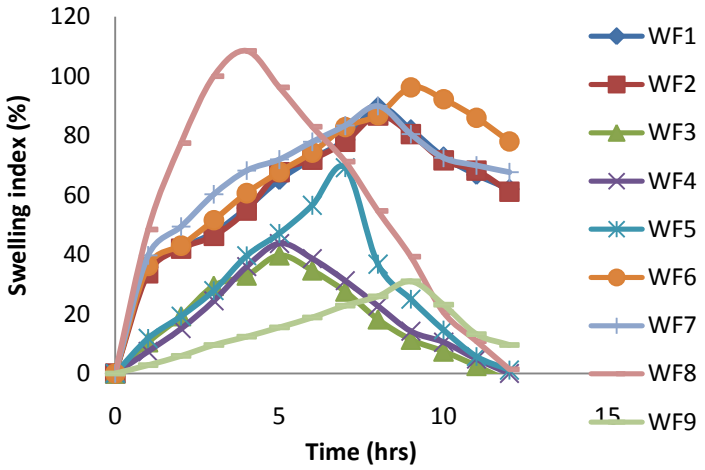

Figure 1: Swelling index of formulation WF1-WF9

In-vitro dissolution Studies

Dissolution rate was studied by using USP type-II apparatus (USP XXIII dissolution test apparatus - II paddle model, TDL 084, Electrolab, India) using 200mL of 0.1N HCl for 2 hrs and 900 mL of phosphate buffer pH 6.8 for 22 hrs as dissolution medium. Temperature of the dissolution medium was maintained at 37 ^{o} ± 0.5 ^{o}C. Aliquots of dissolution medium (1 mL) was withdrawn at every 15, 30 min and 1 and 2 hrs interval and replaced with equal volume of fresh medium. The absorbance of filtered solution was measured by UV Spectrophotometric method at 254 nm and concentration of the drug was determined from standard calibration curve (shown in Table 4 and figure 2-4).

Table 4: In-vitro drug dissolution profile for all formulations

Formulation code	Time (hrs)	Cumulative percentage drug release (%)
WF1	24	96.65 ± 2.23
WF2	20	96.15 ± 2.79
WF3	20	98.27 ± 2.063
WF4	18	98.27 ± 2.537
WF5	18	99.92 ± 1.402
WF6	24	83.15 ± 0.702
WF7	24	95.67 ± 0.407
WF8	18	97.02 ± 0.426
WF9	24	74.45 ± 0.681
Marketed (Losacar)	16	89.69 ± 1.926

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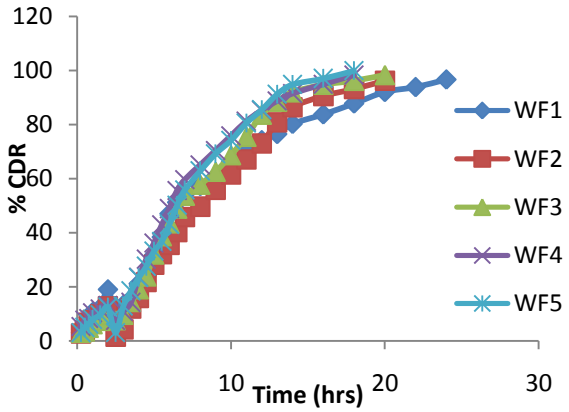

Figure 2: In-vitro release profile of Losartan potassium from WF1 – WF5

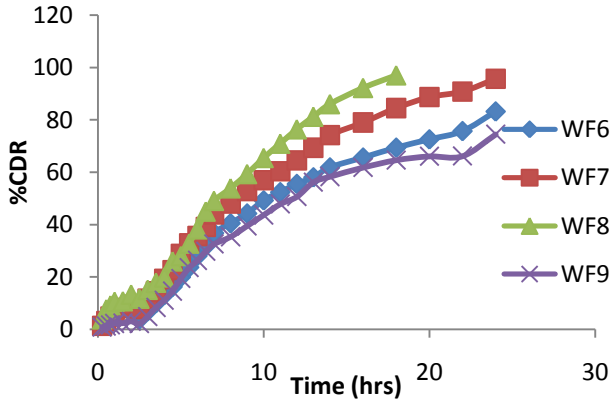

Figure 3: In-vitro release profile of Losartan potassium from WF6 – WF9

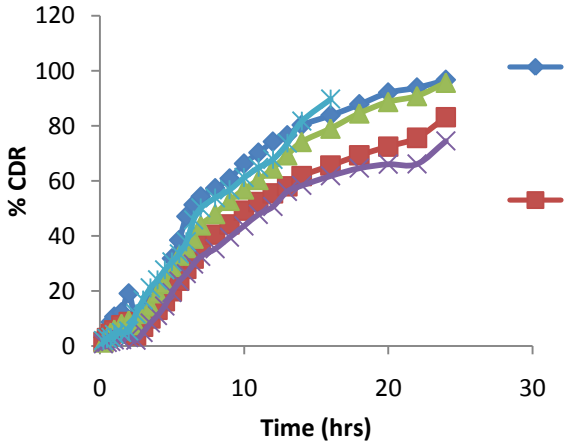

Figure 4: In-vitro drug releasing profile compared with marketed product

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CURVE FITTING ANALYSIS

The curve fitting analysis was carried out for the selected formulations, WF1, WF6, WF7 and WF9. The following results were classified using the software, graphpad, prism 5.0. It can be guess from the above table that the selected formulation WF1, WF6, WF7 and WF9 follows first order as well as non Fickian drug release. The results were shown in Table 5 [14, 15].

Table 5: Curve fitting analysis values for all Formulations

Formulation code	Zero order			First order			Higuchi		Peppas	
	n	K	r^2	n	K	r^2	n	r^2	n	r^2
WF1	4.785	11.019	0.926	-0.0579	0.1333	0.976	24.94	0.952	0.808	0.942
WF2	5.564	12.813	0.961	-0.0661	0.1522	0.946	27.66	0.933	0.935	0.992
WF3	5.511	12.691	0.927	-0.0894	0.2058	0.933	29.31	0.935	0.967	0.931
WF4	6.339	14.598	0.941	-0.0875	0.2015	0.942	30.23	0.934	0.817	0.876
WF5	6.562	15.112	0.958	-0.089	0.2049	0.932	31.25	0.940	0.946	0.876
WF6	3.775	8.694	0.954	-0.0313	0.0720	0.981	20.75	0.957	0.960	0.945
WF7	4.425	10.191	0.957	-0.051	0.1174	0.969	24.44	0.969	0.969	0.977
WF8	5.862	13.500	0.981	-0.0711	0.1637	0.934	27.52	0.941	0.790	0.944
WF9	3.511	8.0858	0.937	-0.0258	0.0594	0.979	19.54	0.957	1.186	0.937

STABILITY STUDIES

Stability studies were performed as per ICH guidelines. Selected formulations of Losartan potassium SR matrix tablets were sealed in self-sealing cover and stored at refrigeration temperature (2-8^{o}C) and room temperature (25^{o} ± 2^{o}C / 60 ± 5% R.H) for a period of 3 months. Samples from each formulation kept for examination were withdrawn at definite intervals. The withdrawn samples were assayed for drug content at 254 nm (shown in table 6 and 7) [4, 16].

Table 6: Stability studies at 2-8 ^{o}C for formulation WF1, WF6, WF7 and WF9.

Formulation code	Tested Period (months)	Hardness	Friability	Percentage drug content
WF1	1	6.11 ± 0.203	0.25 ± 0.15	90.04 ± 1.356
	2	6.10 ± 0.215	0.27 ± 0.17	89.12 ± 1.547
	3	6.10 ± 0.232	0.26 ± 0.19	88.02 ± 1.489
WF6	1	6.45 ± 0.151	0.57 ± 0.11	94.04 ± 1.861
	2	6.31 ± 0.142	0.59 ± 0.12	92.84 ± 1.745
	3	6.11 ± 0.134	0.61 ± 0.15	91.56 ± 1.678
WF7	1	6.61 ± 0.132	0.59 ± 0.14	96.48 ± 1.851
	2	6.52 ± 0.125	0.63 ± 0.16	95.24 ± 1.856
	3	6.45 ± 0.165	0.62 ± 0.12	93.78 ± 1.963
WF9	1	6.35 ± 0.189	0.59 ± 0.17	95.92 ± 1.745
	2	6.24 ± 0.175	0.65 ± 0.19	93.74 ± 1.752
	3	6.02 ± 0.165	0.71 ± 0.15	91.88 ± 1.874

Mean ± SD, n=3.

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Table 7: Stability studies at 25 ± 2 °C / 60 ± 5% R.H for formulation WF1, WF6, WF7 and WF9.

Formulation code	Tested period(months)	Hardness	Friability	Percentage drug content
WF1	1	6.09 ± 0.413	0.29 ± 0.16	89.84 ± 1.563
	2	6.07 ± 0.397	0.31 ± 0.19	87.92 ± 1.475
	3	6.07 ± 0.397	0.38 ± 0.21	88.02 ± 1.894
WF6	1	6.25 ± 0.325	0.59 ± 0.23	92.64 ± 1.618
	2	6.15 ± 0.354	0.57 ± 0.15	91.92 ± 1.457
	3	6.08 ± 0.354	0.66 ± 0.18	89.94 ± 1.786
WF7	1	6.45 ± 0.532	0.68 ± 0.19	95.04 ± 1.518
	2	6.31 ± 0.452	0.64 ± 0.12	93.52 ± 1.568
	3	6.31 ± 0.566	0.69 ± 0.13	91.58 ± 1.639
WF9	1	6.12 ± 0.659	0.75 ± 0.10	95.12 ± 1.457
	2	6.01 ± 0.625	0.79 ± 0.11	93.34 ± 1.527
	3	5.94 ± 0.565	0.82 ± 0.14	91.08 ± 1.748

Mean ± SD, n=3.

RESULTS AND DISCUSSION

The present investigation was to formulate once daily sustained release matrix tablet of Losartan potassium to increase therapeutic efficacy, reduce frequency of administration and improve patient compliance. The sustained release matrix tablet was prepared by wet granulation method by varying concentration and ratios of hydrophilic and hydrophobic polymers to release the drug in sustained manner for a period of 24 hrs. The Carr's Index (Compressibility) of the powders was in the range of 7.08 ± 1.21 to13.96 ± 1.09. The angle of repose of the powders were in the range of 24.83 ± 1.30 to 29.64 ± 1.05, which indicate a good flow property of the powders. The thickness of all the formulations was found to be between 5.18 ± 0.054 mm to 5.93 ± 0.018 mm. The hardness of all formulations, were found to be between 5.85 ± 0.251 to 7.17 ± 0.221 kg / cm^2. The % Friability values of all the formulations were found to be between 0.20 ± 0.09 to 0.51 ± 0.09 %. Drug content for each of the formulations were estimated. The drug content for all the batches was found to be in the range of 90.24 ± 1.235 to 99.96 ± 1.864 %.

In-vitro dissolution study formulations WF1, to and WF9 showed 95.67 ± 0.407, to 98.27 ± 2.537. This showed that the drug release from the tablet was sustained for 24 hrs. WF1, WF6, WF7 and WF9 showed release upto 24 hr. whereas formulation WF2 and WF3 showed release up to 20hr. Then all formulations are compared with marketed product (Losacar). The marketed product showed the drug release upto 16 hrs only.

Selected formulations were fitted into different mathematical models like Zero order, First order, Higuchi, and Peppas plots. The results are given in table 7. From the regression values it was observed that the optimized formulationsWF1, WF6, WF7 and WF9 follows first order kinetics since the regression coefficient is found to be linear. Slope (n) value of optimized formulations WF1, WF6, WF7 and WF9 were found to be 1.186 to 0.808 which in

turn indicates that diffusion was non Fickian and WF9 shows super case –II transport in nature. The regression coefficient (r^2) values of first order in the optimized formulation WF5 and WF8 were less than the r^2 values of zero order. Thus, the drug release followed first order kinetics.

CONCLUSION

Sustained release matrix tablets of Losartan potassium were prepared by wet granulation. The preformulation studies were carried out which ruled out the interaction between the drug and polymers. The granulations were punched into tablets and tablets were evaluated. The results of dissolution studies indicated that formulation WF1, WF6, WF7 and WF9 produced sustained drug release over a period of 24 hrs. It can be concluded that the polymers plays major role in the design of sustained release matrix tablet. The study reveals that the release of drug is low when the matrix tablet contained hydrophilic and hydrophobic polymers as a combination than the other matrices and also shows first order kinetics. Hence it clearly manifest the necessity of combining different classes of polymers is to get an acceptable pharmacokinetic profile.

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