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Effect of Geometrical Proportionality on Losartan Potassium Sustained Release Matrix Tablets: A Comparative Evaluation of Wet Granulation and Direct Compression

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ABSTRACT

The objective of the present study was investigation of effect of geometrical proportionality and comparative evaluation of wet granulation and direct compression on Losartan potassium sustained release matrix tablets 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 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, best formulations are compared with direct compression method and it is subjected for In-vitro drug release studies and evaluated the geometrical proportionality (oval and concave round). Mathematical analysis of the release kinetics indicated a coupling of first order mechanism. Thus formulations were subjected to comparative study of In-vitro drug release with the marketed formulation. The drug release form 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, direct compression and Geometrical proportionality.

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INTRODUCTION

Oral sustained release dosage form has greater flexibility in dosage form design than the parenteral route. Patient compliance is more for the oral route when compared to other dosage forms except psychosis and unconscious patients. It is very safe route of drug administration compared to parenteral route [1-2]. From the past three decades, sustained and controlled release drug delivery systems are the familiar dosage forms which have importance in current drug delivery systems. There are several reasons in designing sustained and control release formulations as they reduce the frequency of dosing and drug activity with chronic use. This type of single dosage drug delivery is most useful in treatment of chronic diseases (diabetes and hypertensive patients) and seasonal diseases (like asthma) to deliver drug for 1-3 days at the site of action, thereby minimizing or eliminating first pass metabolism and local or systemic side effects [3-4]. The matrix system is commonly used for manufacturing sustained release dosage forms especially tablets because it makes such manufacturing easy [5]. Hypertension is the most common cardiovascular disease. Currently using antihypertensive drugs are angiotensin receptor blockers. Losartan potassium is well tolerated drug but all ACE inhibitors can cause hypotension and hyperkalemia, but not Losartan potassium (angiotensin II receptor antagonist).It is readily absorbed from the gastrointestinal track with oral bioavailability of about 33% and a plasma elimination half-life ranging from 1.5 to 2 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 [6-9].

Developing a sustained release drug delivery system like matrix tablet for ACE inhibitor Losartan potassium is desirable for an effective treatment of hypertension because can be promptly terminated in case of toxicity by removing other dosage form of sustained release. 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 [10-11].

MATERIALS AND METHODS

Materials

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.

METHODS

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Preparation of Losartan potassium sustained release matrix tablets

Preparation of granules

Losartan potassium granules were prepared by wet granulation method using 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 fine powder was mixed with water to obtained wet mass. The wet mass was passed through sieve no. 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. Compaction force of 26 kN 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).

Preparation of Losartan potassium by direct compression

Form the above wet granulation method shown four best formulations (WF1, WF6, WF7 and WF9) those releasing profile upto 24 hrs, those formulations are compared with direct compression method. Losartan potassium and all ingredients were accurately weighed (**Table 2**), milled and sieved through sieve no. 100/120 and then blended. The powder blended containing 50mg of Losartan potassium was compressed into tablets by direct compression technology, using multi station rotatory tablet punching machine (Riddhi 10 stn mini tablet press RDB4-10, Rimek, Ahmedabad, India) using 10mm rounded concave punches at pressure 26kN. In each formulation 50 tablets were prepared.

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 found out using the fennel 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 by using Monsanto hardness tester (Lab tech, India). The friability test was performed using Roche friabilator (Ketan instruments, India). 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. 10 mL from this stock solution 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 [12-19].

Table 2: Preparation of direct compression of Losartan potassium sustained release matrix tablets

Compositions	DF1	DF6	DF7	DF9
Losartan potassium (mg)	50	50	50	50
HPMC K100M (mg)	200	125	125	-
Eudragit RLPO (mg)	-	75	75	200
Eudragit S100 (mg)	30	30	-	15
Eudragit L100 (mg)	-	-	30	15
Micro crystalline cellulose (mg)	20	20	20	20
Magnesium stearate (mg)	2	2	2	2
Talc (mg)	8	8	8	8
di-calcium phosphate (mg)	40	40	40	40
Total (mg)	350	350	350	350

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 % weight gain by the tablet was calculated by formula [20-21]

$$\text{swelling index} = \frac{M_t - M_o}{M_t} \times 100$$

Where,

M_t – weight of tablets at time‘t’

M_0 – weight of tablets at time‘0’

In-vitro dissolution profile

The dissolution profile were studied by using USP type-II apparatus (USP XXIII dissolution test apparatus - II paddle model, TDL 084, Elctrolab, India) using 900 mL 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. Aliquot 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 [22].

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, WF9, DF1, DF6, DF7 and DF9 [23-25].

Geometric proportionality of sustained release matrix tablets

This evaluation is carried out to study the effect of tablet shape on its dissolution profile. In this process, tablets are manufactured in different geometrical shapes using the same blend of the materials and dissolution profile studied. This study is of consequence for matrix tablets since it follows both diffusion and erosion. Diffusion and erosion intern is affected by surface area, hence this is study offers some important information regarding the influence of shape of the tablets on its dissolution profile [26].

Accelerated 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 25 ± 2 ^{o}C / 60 ± 5% RH and 40 ± 2 ^{o}C / 75 ± 5% RH for a period of 3 months. Samples from each formulation which kept for examination were withdrawn at definite intervals. The withdrawn samples were assayed for drug content at 254 nm [27-29].

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 10.2 ± 1.29 to13.96 ± 1.09. The angle of repose of the powders were in the range of 24.67 ± 1.02 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 5.97 ± 0.0.012 mm. The hardness of all formulations, were found to be between 5.62 ± 0.09 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 0.63 ± 0.15 %. 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 to 99.96 %.

In-vitro dissolution study formulations WF1, to and WF9 showed 74.56 ± 0.68, to 101.75 ± 1.23. 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.

These selected formulations are compared with the direct compression formulations these are DF1, DF6, DF7and DF9 showed dissolution profile was 98.51 ± 1.27, 99.42 ± 1.35, 86.35 ± 0.99, 95.42 ± 0.98 respectively. This showed that the drug release from the tablet was sustained for 24 hrs. DF1, DF7 and DF9 showed release upto 24 hrs. Whereas in formulation DF6 showed release up to18hrs. For the direct compression formulations were compared with geometrical proportionality (round concave) those formulations dissolution profile were 99.16 ±1.62, 100.07 ± 1.69, 99.73 ± 1.47 and 96.75 ± 1.84 respectively and then all formulations are compared with marketed product (Losacar). The marketed product showed the drug release upto 16 hrs only.

Table 3: Pre-compression parameters

WET GRANULATION METHOD					
Formulations Code	**Bulk density***	**Tapped density***	**Carr,s index***	**Husners 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
DIRECT COMPRESSION METHOD					
DF1	0.246 ± 0.007	0.265 ±0.006	7.20 ± 0.819	1.07 ± 0.009	28.94 ± 0.495
DF6	0.292 ± 0.010	0.313 ± 0.009	6.86 ± 0.545	1.07 ± 0.006	26.70 ± 1.40
DF7	0.286 ± 0.003	0.305 ± 0.003	6.270 ± 0.074	1.06 ± 0.001	28.28 ± 1.16
DF9	0.340 ± 0.010	0.368 ± 0.012	7.608 ± 1.388	1.08 ± 0.016	23.79 ± 0.475

Mean ± SD *n=3

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 was indicates 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.

Table 4: 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
DIRECT COMPRESSION METHOD					
DF1	5.70 ± 0.141	5.95 ± 0.028	99.08 ± 1.145	350.12 ± 0.794	0.63 ± 0.15
DF6	5.72 ± 0.125	5.95 ± 0.017	99.30 ± 1.756	350.15 ± 0.988	0.53 ± 0.17
DF7	5.82 ± 0.095	5.97 ± 0.012	97.78 ± 1.256	350.05 ± 0.887	0.54 ± 0.13
DF9	5.62 ± 0.09	5.96 ± 0.012	99.44 ± 1.853	349.8 ± 0.951	0.56 ± 0.15

Mean ± SD, *n=3, ** n=10, ***n=20.

Table 5: In-vitro drug dissolution profile for all formulations

Formulation code	Time (hrs)	Cumulative percentage drug release (%)
WF1	24	96.67 ± 1.23
WF2	20	95.61 ± 1.29
WF3	20	101.75 ± 1.23
WF4	18	100.11 ± 1.37
WF5	18	99.85 ± 1.42
WF6	24	83.15 ± 0.72
WF7	24	95.63 ± 0.47
WF8	18	96.97 ± 0.46
WF9	24	74.56 ± 0.68
DF1	24	98.51 ± 1.27
DF6	18	99.42 ± 1.35
DF7	24	86.35 ± 0.99
DF9	24	95.42 ± 0.98
Marketed (Losacar)	16	94.21 ± 1.96

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Table 6: In-vitro drug release studies for geometrical all direct compressed tablets

Formulation code	Shape of tablets	Time in hrs	Cumulative percentage drug release (%)
DF1	Oval	24	98.51 ± 1.27
DF6		18	99.42 ± 1.35
DF7		24	86.35 ± 0.99
DF9		24	95.42± 0.98
DF1	Concave round	24	99.16 ± 1.62
DF6		18	100.07 ± 1.69
DF7		24	99.73± 1.47
DF9		24	96.75± 1.84

Table 7: 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
DF1	4.423	10.186	0.916	-0.0605	0.1393	0.935	25.548	0.962	1.038	0.958
DF6	6.472	14.905	0.952	-0.0935	0.2153	0.86	22.406	0.928	1.107	0.934
DF7	4.105	9.454	0.948	-0.0364	0.0838	0.98	31.077	0.95	1.101	0.636
DF9	4.616	10.631	0.949	-0.0537	0.1236	0.978	25.169	0.977	1.052	0.964

Table 8: Stability studies at 25 ± 2 °C / 60 ± 5% RH 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 9: Stability studies at 40 ± 2 °C / 75 ± 5% RH 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.

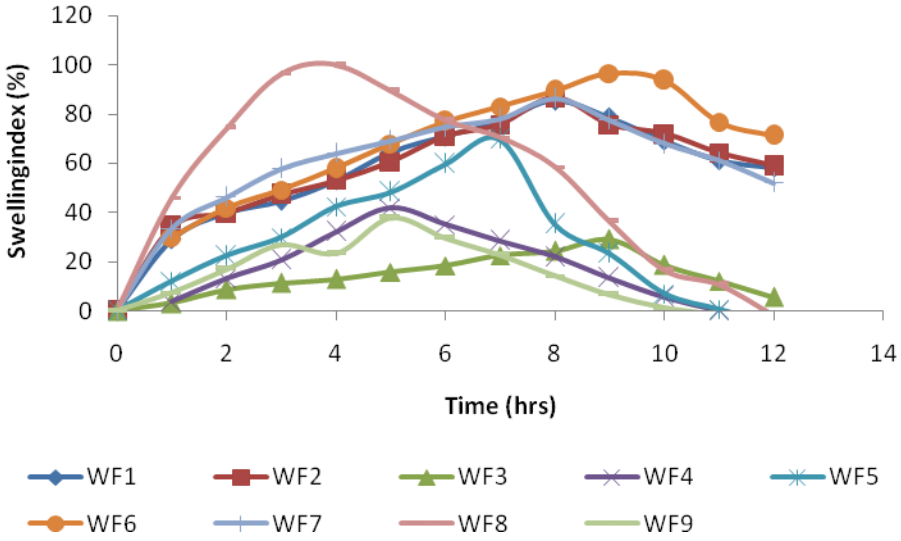

Figure 1: Swelling index of formulation WF1-WF9

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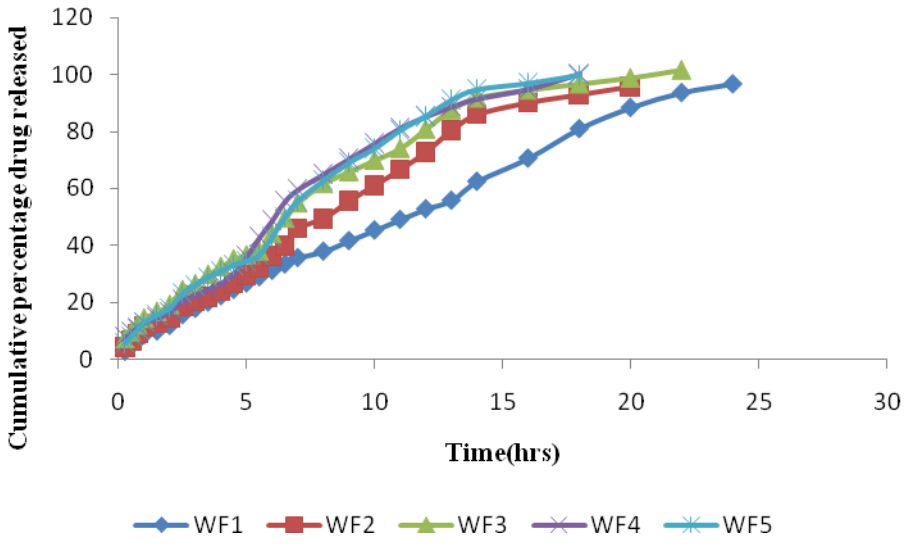

Figure 2: In-vitro release profile of Losartan potassium from WF1 – WF5

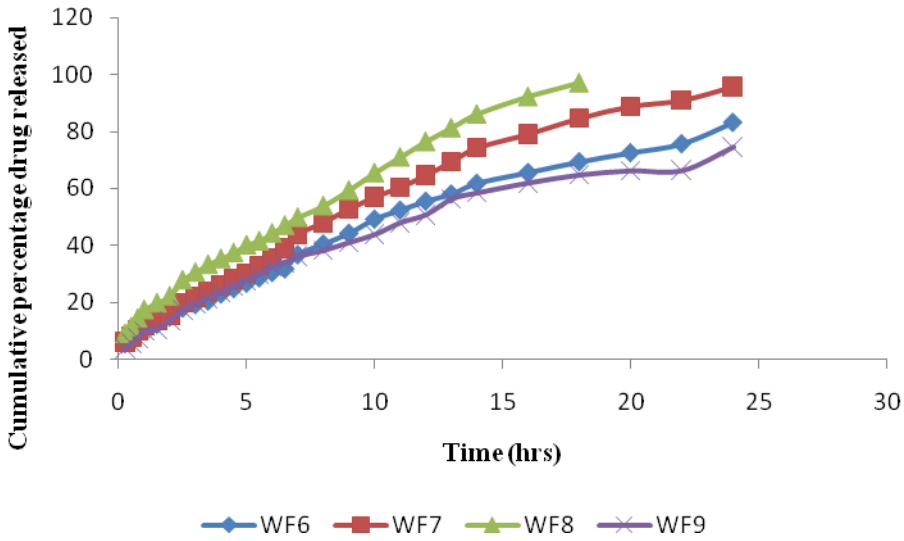

Figure 3: In-vitro release profile of Losartan potassium from WF6 – WF9

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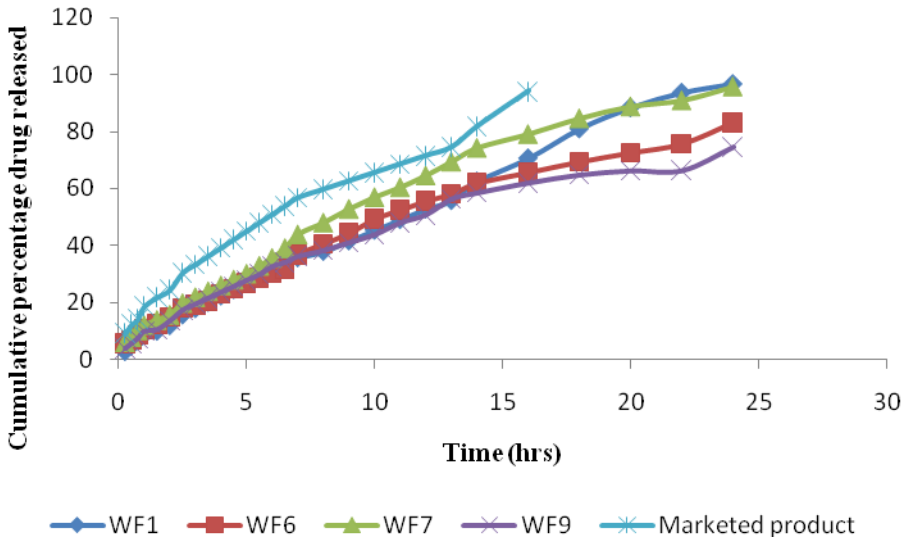

Figure 4: In-vitro drug releasing profile compared with marketed product

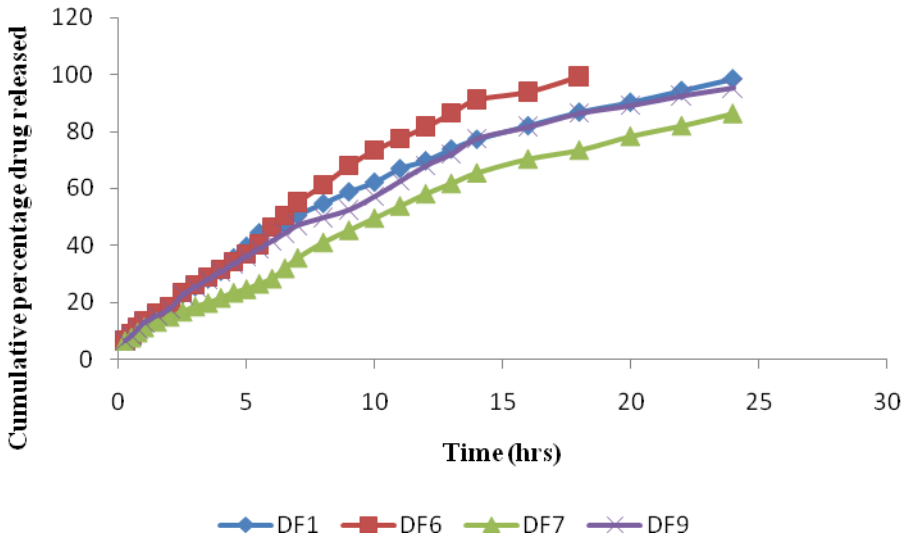

Figure 5: In-vitro release profile of Losartan potassium from DF1, DF6, DF7 and DF9

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. In comparison to other formulation. These best formulations were compared with direct compression method. The In-vitro dissolution profile was indicated that formulations DF1, DF6, DF7 and DF9 were produced

sustained effect upto 24 hrs. But compared to wet granulation the releasing time was very less. Direct compressed tablet Geometrical proportionality showed uniform result as compared between oval and concave shape. 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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