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Formulation and *In-Vitro* Evaluation of Sustained Release Matrix Tablets Of Losartan Potassium

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ABSTRACT

The objective of the present research work was to develop sustained release matrix tablets of Losartan potassium, an angiotensin-II antagonist for the treatment of hypertension. Eight sustained release formulations were prepared by wet granulation and formulated using different drug: polymer ratios. Hydroxypropyl methylcellulose (HPMC) with release modulators Ethyl Cellulose (EC) and Eudragit RS100 were used to develop the sustained release matrix tablets. The prepared sustained release matrix tablets were evaluated for various parameters like hardness, friability, uniformity of weight, uniformity of drug content, *invitro* drug release. The USP apparatus type II was used to perform the dissolution studies, the dissolution medium was 0.1 N HCl for first 2h and followed by phosphate buffer pH 6.8 for remaining period of study. Optimized formulation (F4) showed 90.98% release at the end of 12h. The release kinetics was analyzed using several kinetics models. The n value of peppas equation for the optimized formulation was 0.837, which indicates that the drug release follows anomalous transport, limited by diffusion and erosion of the polymer matrix.

Keywords: Losartan potassium, HPMC K15M, Ethyl cellulose, Eudragit RS100, Sustained release, Matrix tablets.

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INTRODUCTION

Among the different approaches for oral sustained-release dosage forms, matrix tablets are of major interest to the pharmaceutical industry because of their highly efficient manufacturing technology. Polymers (natural, synthetic and semi-synthetic) are the basic ingredients-carriers of these systems and their nature and characteristics may play an essential role and significantly influence the behaviour of these devices (Sandra Furlanetto et al.,2006).

Sustained release (SR) dosage forms are designed to complement the pharmaceutical activity of the medicament in order to achieve selectivity and longer duration of action. Sustained release preparations help to reduce the dosage frequency, side effects of drugs and improve patient's convenience (Ramya et al., 2011). In SR formulations, the drug dissolves into the matrix, matrix physically swells to form a gel, allowing the drug to exit through the gel's outer surface (Dusane et al., 2011).

Hydrophilic matrix tablet is one of the least complicated approaches for developing modified release dosage form. Sustained release dosage form can be formulated by incorporation of the drug into a matrix containing release retarding hydrophilic polymer (Muhammad et al., 2010). Selection of release retarding polymers is very crucial for freely soluble drugs among 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 method.

In formulation of SR Matrix tablets hydrophilic polymers are widely used because of their low cost, desired drug release profile and broad regulatory acceptance. It's a non-toxic nature and ease of handling makes it an excellent release retardant material (Prabakaran and Vishalini, 2010).

Variables of HPMC such as the particle size, viscosity and proportion of HPMC modify the characteristics of porosity and tortuosity of the swollen matrix and therefore, modify the release rate of drugs. Increasing proportions of HPMC in the matrix decreases the release rate. An increasing particle size of HPMC produces increasing release rates from the tablets and decreasing release rates occur often with an increasing viscosity grade (Leopoldo et al., 2000). For such drugs it is essential to include an additional hydrophobic polymer for retardation. In the present study, Ethyl cellulose is used, which is a non toxic, inert hydrophobic polymer (Rajesh et al., 2011).

Losartan potassium is a potent, highly specific angiotensin II type 1 (AT1) receptor antagonist with antihypertensive activity (Prajapati and Patel, 2010). It is freely soluble in water, slightly soluble in acetonitrile, and soluble in isopropyl alcohol. It is readily absorbed from the GI tract with oral bioavailability of about 33% and plasma half-life is about 1.5 to 2.5 h (Manish et al., 2012). To increase therapeutic efficacy, reduce frequency of administration and for better patient compliance sustained release losartan potassium matrix tablets were developed and reported by using hydrophilic and hydrophobic polymers (Shahid and

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Mohammad, 2012). The aim of the present study was to optimize a SR matrix tablet of losartan potassium using HPMC K15M, Ethyl cellulose and Eudragit RS100 as release modulators.

MATERIALS AND METHODS

Materials

Losartan potassium was obtained from Fourrts India Pvt Ltd., Chennai. Eudragit RS100 was received as gift samples from Evonik laboratories Pvt Ltd., Mumbai, HPMC K15M, Ethyl cellulose, Poly vinyl pyrrolidine, Micro crystalline cellulose, Magnesium stearate, Aerosol, all the ingredients used were of analytical grade.

Method of preparation

Tablets containing 50mg Losartan potassium were prepared by wet granulation technique with composition detailed in Table 1. Drug and polymer were mixed thoroughly with granulating agent and the wet mass passed through sieve no 12. The granules were dried at 60^{o}C for 5min and passed through sieve no 16 to get uniform size granules. Magnesium stearate was used as lubricant. Finally tablets were compressed by Cadmach 16 station rotary tablet punching machine.

Table 1: Formulation chart

Contents	Quantities (mg)							
	F1	F2	F3	F4	F5	F6	F7	F8
Losartan potassium	50	50	50	50	50	50	50	50
HPMC K15M	150	120	100	75	140	120	100	75
Ethyl cellulose	-	30	50	75	-	-	-	-
Eudrgit RS 100	-	-	-	-	10	30	50	75
Micro crystalline cellulose	37	37	37	37	37	37	37	37
Poly vinyl pyrrolidine	10	10	10	10	10	10	10	10
Aerosol	1	1	1	1	1	1	1	1
Magnesium stearate	2	2	2	2	2	2	2	2
Total weight	250	250	250	250	250	250	250	250

Fourier transforms infrared spectroscopy (FT-IR)

FT-IR spectra for pure drug and drug-excipient mixtures were done by means of FT-IR spectrophotometer (Shimadzu 4300, Japan) using the KBr pellet method.

Pre-compression characters

The powder blend was evaluated for bulk density, tapped density, angle of repose, compressibility index, and Hausner ratio (Lachman, 1991).

Physicochemical evaluation

Hardness of the tablets was evaluated using a Monsanto hardness tester. The friability of tablets for each batch was determined using an automated USP Roche friabilator. Thickness of the tablets was evaluated using digital vernier calipers. The tablets were also subjected to tests for uniformity of drug content and weight variation.

***In vitro* dissolution studies**

The prepared matrix tablets were subjected to *in vitro* dissolution studies using USP type II dissolution apparatus. The dissolution studies were carried out in 0.1NHCl for 2 h & in pH 6.8 phosphate buffer for next 10 h at 37± 0.5^0C and a basket rotating speed of 50 rpm. At regular time interval, 5 ml of sample was withdrawn from the dissolution medium and replaced with equal volume of fresh medium. After filtration and appropriate dilution, the samples were analyzed at 234 nm for losartan potassium against blank using UV-Visible spectrophotometer. (Shahid and Mohammad, 2012).

Drug release kinetics

To analyze the mechanism of drug release from the matrix tablets, the release data were fitted to the following equations.

Zero-order equation: (Cooper and Gunn, 1986).

$$Q = k_0 t$$

Where, Q is the amount of drug released at time t, and k_0 is the release rate.

First-order equation: (Hadjiioannou, et al., 1993).

$$\text{Log } Q = \text{Log } Q_0 - k_1 t/ 2.303$$

Where, Q is the amount of drug un-dissolved at t time, Q_0 is drug concentration at t = 0 and k_1 is the release rate constant.

Higuchi's equation: (Higuchi, 1963).

$$Q = k_2 t^{1/2}$$

Where, Q is the percent of drug release at time t, and k_2 is the diffusion rate constant.

Hixson-Crowell equation:

$$Q_o^{1/3} - Q_t^{1/3} = K_3 t$$

Where, Qt is the initial amount of drug, Q_o is cumulative amount of drug release at time t, K_3 is Hixson-Crowell release constant and t is time in hours.

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Korsmeyer-Peppas equation: (Korsmeyer et al., 1983).

$$\text{Log } (M_t / M_f) = \text{Log } k + n \text{ Log } t$$

Where, M_t is the amount of drug release at time t, M_f is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the tablet and n is the diffusion exponent indicative of the mechanism of drug release.

To clarify the diffusion exponent (n) for different batches of matrix tablet, the log value of percentage drug released was plotted against log time for each batch. A value of $n \leq 0.45$ indicates Fickian (case I) release; > 0.45 but < 0.89 for Non-Fickian (anomalous) release; and > 0.89 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain, and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion-controlled drug release.

Mean dissolution time (MDT):

MDT is a measure of the dissolution rate, the higher the MDT, the slower the release rate and it was calculated from the following equation. (Afrasim Moin and Shivakumar, 2010).

$$MDT = \frac{\sum_{t=0}^{t=\infty} t_{mid} \times \Delta M}{\sum_{t=0}^{t=\infty} \Delta M}$$

Where, t is the dissolution sample time, t_{mid}, is the time at the midpoint between t and t-1, and ΔM is the amount of drug dissolved between t and t-l.

RESULTS AND DISCUSSION

Characterization of granules blend

Table 2: Micrometrics properties of different formulations

Formulation Code	Angle of Repose(^{0})	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Hausner's Ratio (H_R)	Carrs Index
F1	25.31±0.02	0.5±0.04	0.6±0.02	1.20±0.03	16.67±0.02
F2	26.82±0.04	0.62±0.02	0.72±0.03	1.16±0.02	13.89±0.05
F3	27.61±0.05	0.54±0.04	0.65±0.04	1.20±0.05	16.92±0.03
F4	26.57±0.01	0.58±0.01	0.68±0.02	1.17±0.01	14.71±0.01
F5	25.67±0.03	0.67±0.02	0.9±0.01	1.34±0.01	25.56±0.04
F6	25.94±0.06	0.54±0.03	0.64±0.03	1.19±0.03	15.63±0.06
F7	27.58±0.02	0.67±0.01	0.78±0.02	1.16±0.02	14.10±0.02
F8	26.34±0.03	0.68±0.02	0.82±0.04	1.21±0.05	17.07±0.01

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The blend prepared for compression of matrix tablets were evaluated for their flow properties like angle of repose, bulk density, tapped density, Hausner ratio and compressibility index. The values of pre-compression parameters evaluated were within prescribed limits and indicated good free flowing property. The results were shown in Table 2.

Compatibility testing of drug with polymer

Fourier transforms infra-red (FTIR) spectroscopy

FTIR spectrum show characteristic peaks for major functional groups present in Losartan potassium A combined spectrum for drug and drug with ethyl cellulose, eudragit RS 100 and hydroxyl propyl methyl cellulose was observed as shown in Figure 1. The major peaks are identical to functional group of Losartan potassium. Hence, it was confirmed that there was no incompatibility between drug and the polymers.

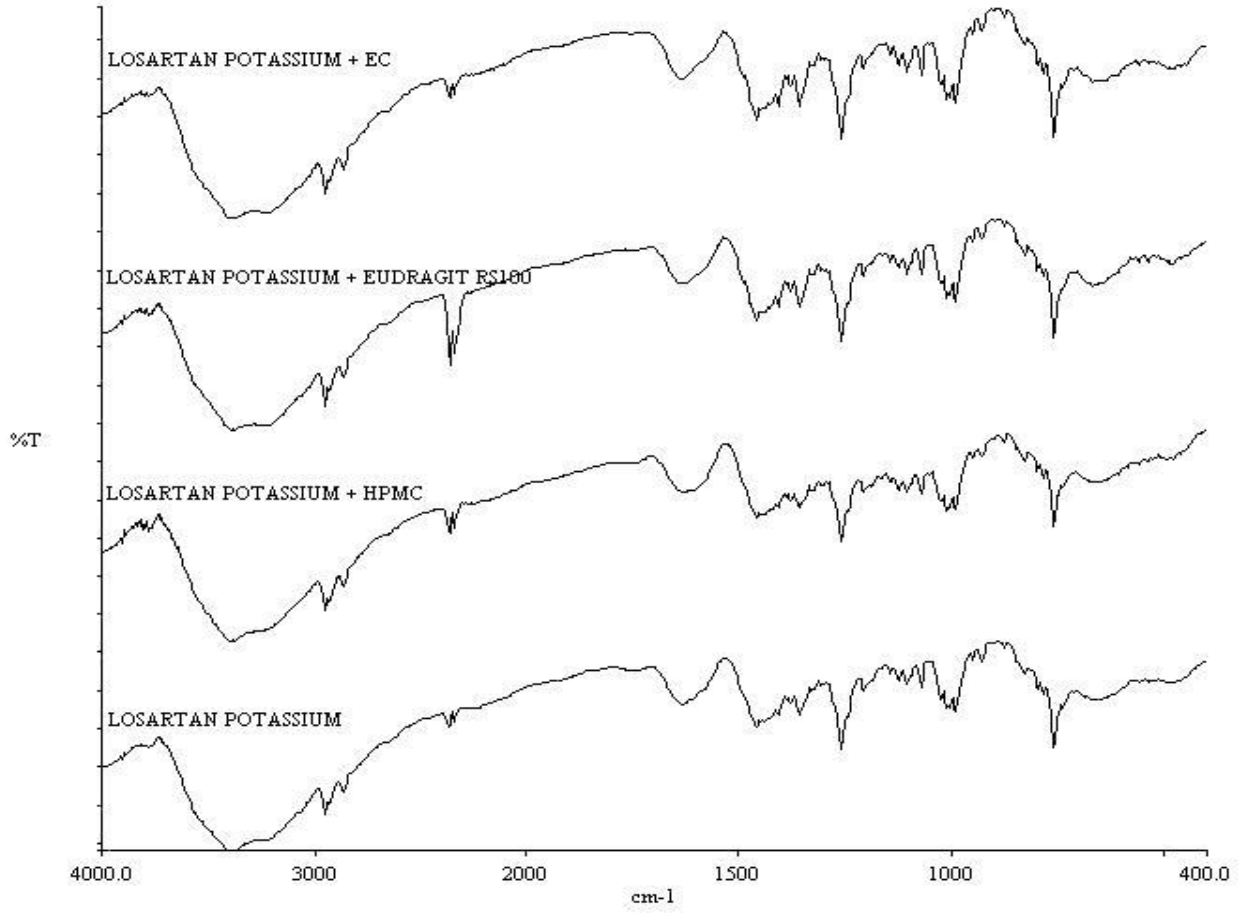

Figure 1 Fourier transform infrared spectra of losartan and complex of losartan, HPMC K15M, Ethyl cellulose, Eudragit RS100

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Evaluation of Losartan potassium sustained release tablets

The mechanical properties of the Losartan Potassium tablets were evaluated like hardness, friability, thickness, diameter, weight variation and drug content. All the formulations showed satisfactory results as per Indian Pharmacopoeia (IP) limits. The results were shown in Table 3.

Table 3: Physical properties and drug content of different formulations

Formulation Code	Hardness ($kg/cm^{2)}$	Friability (%)	Dimension		Weight variation (%)	Drug content (%w/w)
			Thickness (mm)	Diameter (mm)		
F1	5.77±0.54	0.86±0.02	5.14±0.13	9.1±0.0	0.21±0.08	99.9±0.55
F2	5.58±0.41	0.43±0.09	5.11±0.11	9.1±0.0	0.34±0.12	98.8±1.01
F3	5.62±0.32	0.32±0.01	5.12±0.11	9.1±0.0	0.25±0.08	98.7±0.25
F4	5.94±0.13	0.27±0.00	5.61±0.10	9.1±0.0	0.20±0.02	100.2±0.59
F5	6.16±0.68	0.59±0.08	5.69±0.15	9.1±0.0	0.38±0.06	99.7±0.72
F6	5.52±0.37	0.67±0.02	5.67±0.11	9.1±0.0	0.35±0.04	98.9±0.87
F7	5.49±0.40	0.31±0.06	5.62±0.14	9.1±0.0	0.25±0.11	99.8±0.55
F8	5.86±0.37	0.25±0.04	5.96±0.12	9.1±0.0	0.42±0.06	98.8±0.82

In Vitro dissolution studies

In vitro dissolution studies of all the formulations of sustained release tablets of Losartan potassium were carried out in 0.1N HCl for first 2 hours and pH 6.8 phosphate buffers for next 10 hours respectively. The study was performed for 12 hours, and percentage drug release was calculated at 1 hours time intervals. The dissolution profiles of all the formulations are shown in Fig.ure 2. The *in vitro* dissolution profiles were compared with the theoretical values using f2 and MDT values as shown in Table 4. Among the three drug polymer ratios studied, the formulation F4 containing drug-polymer ratio 1:1 released approximately 90.98% of the drug in 12 hours.

Table 4: Comparison of dissolution data with theoretical release

F code	MDT values (h)	f_2 values
F1	7.24	39
F2	7.33	40
F3	7.35	76
F4	7.37	81
F5	7.34	45
F6	6.5	46
F7	6.65	44
F8	7.30	44
Theoretical Release	7.50	-

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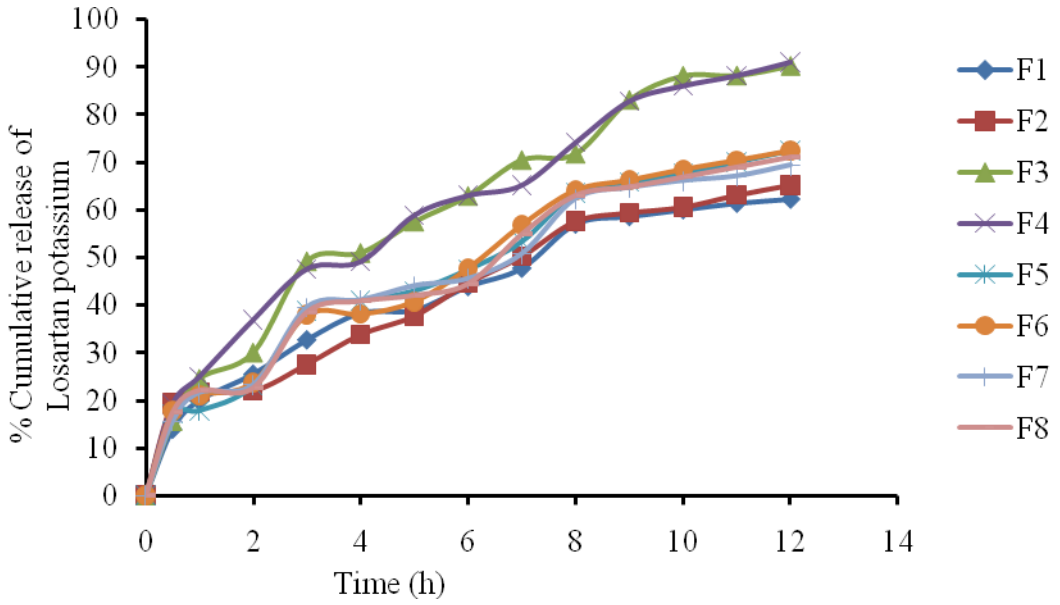

Figure 2: Cumulative drug release of losartan potassium

Kinetics of Drug Release

The *in vitro* drug release data was subjected to goodness of fit test by linear regression analysis according to zero order, first order, kinetic equations, Higuchi and Peppas models in order to determine the mechanism of drug release. The results of linear regression analysis of data including regression coefficients are summarized in Table 5. The release of drug from the formulations containing micro crystalline cellulose was found to be governed by diffusion controlled process. When the data was treated according to Peppas equation, the release exponents (n values) for most of the formulations was found to be in between 0.45 and 0.89 indicating non-Fickian release mechanism.

Table 5: *In Vitro* drug release kinetics for formulations of losartan potassium sustained release matrix tablets.

F code	Zero order		First order		Higuchi		Peppas			Release type
	R^2	K_0	R^2	K_1	R^2	K_2	R^2	n	K	
F1	0.960	4.691	0.984	0.078	0.995	18.55	0.993	0.786	10.256	Higuchi
F2	0.970	4.868	0.987	0.082	0.984	18.87	0.954	0.748	10.889	First order
F3	0.967	6.997	0.986	0.188	0.994	27.47	0.993	0.883	11.912	Higuchi
F4	0.969	6.784	0.987	0.186	0.996	26.68	0.994	0.837	13.001	Higuchi
F5	0.969	5.526	0.990	0.103	0.991	21.57	0.979	0.82	10.631	First order
F6	0.970	5.531	0.989	0.105	0.988	21.53	0.977	0.799	11.084	First order
F7	0.960	5.201	0.984	0.094	0.99	20.48	0.983	0.799	10.861	First order
F8	0.965	5.322	0.986	0.099	0.988	20.81	0.976	0.789	11.137	First order

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CONCLUSION

The results of experimental studies of losartan potassium matrix tablets proved that the granules of losartan potassium showed good flow properties, tablet's quality control such as hardness, friability and uniformity of content tests are within the acceptable limits. The drug-polymer ratio was found to influence the release of drug from the formulations. As the polymer level is increased, the drug release rates were found to be decreased. The present study clearly manifests the necessity of judicial combination of different class of polymers to get an acceptable drug release profile. Optimized formulation F4 showed a desired drug release over a period of 12 h. The mean dissolution time and similarity factor value of F4 suggest that their dissolution profiles were similar with theoretical release. From the Korsmeyer-Peppas study, the n value of the formulation show that the release profile obeys non-Fickian diffusion which shows that drug is released via, swelling, diffusion and erosion mechanism.

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