



Research Article

Development and *In Vitro* Evaluation of Sustained Release Matrix Tablets of Losartan PotassiumRAVI KUMAR NAYAK*¹, NARAYANA SWAMY VB², SENTHIL A¹, MAHALAXMI R³¹Department of Pharmaceutics, Karavali College of Pharmacy, Mangalore-575028, Karnataka, INDIA,²Department of Pharmacognosy, Karavali College of Pharmacy, Mangalore-575028, Karnataka, INDIA,³Department of Pharmaceutics, Manipal College of Pharmaceutical Sciences, Manipal -576104, Karnataka, INDIA.**ARTICLE DETAILS***Article history:*

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ABSTRACT

In the present investigation an attempt has been made to increase therapeutic efficacy, reduced frequency of administration and improved patient compliance by developing controlled release matrix tablets of Losartan Potassium. 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. The tablets were evaluated for preformulation studies like angle of repose, bulk density, compressibility index and physical characteristics like hardness, weight variation, friability and drug content. In-vitro release of drug was performed in PBS pH 6.8 for 24 hours. All the physical characters of the fabricated tablet were within acceptable limits. Drug-excipient interaction was evaluated by Differential scanning calorimetry and FTIR. There was no drug excipient interaction. The tablet with xanthan gum (F4) in the ration of drug: polymer (1:2) exhibited greater swelling index and better dissolution profile than those with pectin, xanthan gum, sodium alginate and pectin. Optimized tablet formulation (F4) containing xanthan gum showed no change in physical appearance and dissolution profile upon storage at 40°C/75% relative humidity for three months. The drug release of optimized formulation follows the Higuchi kinetic model, and the mechanism is found to be non-Fickian/anomalous according to Korsmeyer-Peppas equation. Compared to conventional tablets, release of losartan potassium from these matrix tablets was prolonged, leading to achieve an effective therapy with low dosage of the drug, to reduce the frequency of medication.

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INTRODUCTION

Drug products designed to reduce the frequency of dosing by modifying the rate of drug absorption have been available for many years [1]. Regular research is going on in field of use of natural occurring biocompatible polymeric material in designing of dosage form for oral controlled release administration [2-4]. Natural gums are biodegradable and nontoxic, which hydrate and swell on contact with aqueous media, and these have been used for the preparation of dosage form [5]. Guar gum a polysaccharide derivative with glycoside linkage has been used as matrix former for controlled release of isoniazide [6] and diltiazem [7].

Pectins, including high and low ester and amidated, are used in food all over the world. It is an edible plant polysaccharide, has been shown to be useful for the construction of drug delivery systems for specific drug delivery [8]. Xanthan gum is a high molecular weight extracellular polysaccharide, produced on commercial scale by the viscous fermentation of gram negative bacterium *Xanthomonas campestris*. The molecule consists of a backbone identical to that of cellulose, with side chains attached to alternate glucose residues. It is a hydrophilic polymer, which until recently had been limited for use in thickening, suspending and emulsifying water based systems [9].

The oral route is the route most often used for administration of drugs. Tablets are the most popular oral formulations available in the market and are preferred by patients and physicians

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alike. 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 [10]. Sustained release formulations are preferred for such therapy because they maintain uniform drug levels, reduce dose and side effects, better patient compliance, and increase safety margin for high potency drugs [11].

Losartan is a competitive antagonist of angiotensin II and 10,000 times more selective for ATI and ATII receptor, does not block any other receptor or ion channel. Losartan is soluble in aqueous buccal fluids and used in treatment of hypertension; nephropathy in type 2 diabetic patients; reduce risk of stroke in patients with hypertension and left ventricular hypertrophy. Oral absorption of losartan is not affected by food, but bioavailability is only 33% due to first pass metabolism. It partially carboxylase in liver to an active metabolite (E3174) which is a 10- 30 times more potent non competitive AT1 antagonist [12]. The plasma half life of losartan is 2 h, but that of E3174 is 6-9 h. Both the components are 98% plasma protein bound, do not enter the brain and excreted by the kidney. It has been suggested that drugs with biological half life in the range of 2-8 h are good candidates for sustained release formulation [13]. To reduce the frequency of administration and to improve patient compliance, a once-daily sustained-release formulation of Losartan potassium is desirable.

The objective of the present study was to formulate Losartan potassium sustained release matrix tablet using sodium alginate, Xanthan gum, pectin gum, rosin gum and guar gum polymer and to elucidate the effect of type of polymers and its concentration on release pattern of drug from sustained release matrix tablets.

MATERIALS AND METHODS

Materials

Losartan potassium is procured from Dr. Reddy's Laboratories, Ltd, Hyderabad, India. Xanthan gum, pectin gum, rosin gum, sodium alginate and guar gum polymer were procured from Rajesh Chemicals, Mumbai. Microcrystalline Cellulose pH 101 (Avicel PH 101) was gift sample from Emcure labs Ltd. Pune. Talc and Magnesium stearate were procured from Apex Chemicals (Ahmedabad, India). All other reagents and chemicals used were of analytical grade.

Methods

Characterization of drug and excipients

Fourier transforms infra red spectroscopy (FTIR)

FTIR spectra of pure Losartan potassium and physical mixture of drug and excipients were recorded on Shimadzu Corporation, (Tokyo, Japan) Model-1601 PC. Potassium bromide pellet method was employed and background spectrum was collected under identical situation. Each spectrum was derived from single average scans collected in the region 650- 4000 cm⁻¹ at spectral resolution of 2cm⁻² and ratio against background interferogram. Spectra were analyzed by software supplied by Shimadzu.

Differential Scanning Calorimetry (DSC)

Thermal properties of the pure Losartan potassium and the physical mixture of drug and excipients were analyzed by Shimadzu DSC-60, Shimadzu Limited Japan. The samples were heated in a hermetically sealed aluminum pans. Heat runs for each sample were set from 30 to 3500C at a heating rate of 100C/ min, using nitrogen as blanket gas.

Preparation of sustained release matrix tablets of Losartan potassium

Sustained release matrix tablet containing 50 mg of Losartan potassium were prepared by direct compression technique using various polymers viz; Guar gum, Xanthan gum, Rosin gum, Pectin and Sodium alginate. The composition of each batch is shown in table 1. All the components were screened through a #100 sieve and then thoroughly mixed in a bottle using tumbling method for a period of 15 min. The resultant powder mixture was lubricated with magnesium stearate by further blending for 3 min and finally talc was added to the blend. The resulting powder mixture was subjected to various precompression parameters.

Pre Compression Parameters [14]

Angle of repose

Angle of repose was determined by using funnel method. Powder was poured from a funnel that can be raised vertically until a maximum cone height, h, was obtained. Diameter of heap, D, was measured. The angle of repose, θ , was calculated by formula

$$\tan \theta = h / r$$
$$\theta = \tan^{-1} (h / r)$$

Where, θ is the angle of repose, h is the height in cm and r is the radius.

Table 1: Formulation of Losartan potassium Sustained Release Matrix Tablet

INGREDIENTS*	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Losartan potassium	50	50	50	50	50	50	50	50	50	50
Sodium alginate	50	100	--	--	--	--	--	--	--	--
Xanthan Gum	--	--	50	100	--	--	--	--	--	--
Rosin Gum	---	--	--	--	50	100	--	--	--	--
Pectin	--	--	--	--	--	--	50	100	--	--
Guar Gum	--	--	--	--	--	--	--	--	50	100
Avicel pH101	94	44	94	44	94	44	94	44	94	44
Magnesium stearate	2	2	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4	4	4
Total weight of tablet	200	200	200	200	200	200	200	200	200	200

*All the quantities are in mg

Bulk Density

Apparent bulk density was determined by pouring pre-sieved drug excipient blend into a graduated cylinder and measuring the volume and weight "as it is". It is expressed in g/ml and is given by:

$$D_b = M / V_0$$

Where, M is the mass of powder and V_0 is the Bulk volume of the powder.

Tapped density

It was determined by placing a graduated cylinder, containing a known mass of drug-excipient blend, on mechanical tapping apparatus. The tapped volume was measured by tapping the powder to constant volume. It is expressed in g/ml and is given by:

$$D_t = M / V_t$$

Where, M is the mass of powder and V_t is the tapped volume of the powder.

Powder flow properties

The flow properties were determined by Carr's Index (I):

It is expressed in percentage and is expressed by

$$I = \frac{D_t - D_b}{D_t}$$

Where, D_t is the tapped density of the powder and D_b is the bulk density of the powder.

Hausner ratio

It is expressed in percentage and is expressed by:

$$H = \frac{D_t}{D_b}$$

Where, D_t is the tapped density of the powder and D_b is the bulk density of the powder.

Lower Hausner ratio (< 1.25) indicates better flow properties than higher ones (>1.25).

Compression of tablet

Finally the tablets were compressed (9 mm diameter, round flat face punches) using 10 station Rimek tablet compression machine (M/s Karnawati Engg. Ltd. Ahemadabad). A minimum of 50 tablets was prepared for each batch.

Evaluation of tablet

All the tablets were evaluated for following different parameters which includes;

General appearance

Five tablets from different batches were randomly selected and organoleptic properties such as color, odor, taste, shape, were evaluated.

Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach).

Weight Variation

Twenty tablets from each formulation were selected at a random and average weight was determined. Then individual tablets were weighed and was compared with average weight.

Friability

Friability of the tablets was determined using Roche Friabilator. This device subjects the tablets to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were de dusted using a soft muslin cloth and re weighed. The friability (f) is given by the formula:

$$\text{Friability (f)} = 100 (W_0 - W) / W_0$$

Where W_0 is weight of the tablets before the test and W is the weight of the tablet after the test

Table 2: Results of Precompression Flow Properties of Losartan potassium powder blend

Formulation code	Angle of repose(θ)	Bulk density (g/cm ³)	Tapped density (g/cm ³)	Carr's index (%)	Hausner ratio (H _R)	Flowability
F1	28.1±0.01	0.57±0.01	0.71±0.04	19.0±0.01	1.24±0.01	good
F2	26.3±0.02	0.55±0.02	0.67±0.03	16.9±0.02	1.22±0.02	good
F3	27.6±0.03	0.55±0.01	0.70±0.01	19.9±0.02	1.27±0.03	good
F4	26.9±0.04	0.54±0.03	0.73±0.03	21.5±0.01	1.35±0.01	good
F5	26.9±0.05	0.53±0.04	0.67±0.03	20.8±0.02	1.26±0.02	good
F6	28.0±0.01	0.57±0.01	0.74±0.01	23.1±0.01	1.29±0.01	good
F7	32.6±0.04	0.56±0.01	0.74±0.02	23.7±0.01	1.30±0.04	good
F8	27.3±0.05	0.57±0.02	0.73±0.02	22.8±0.01	1.32±0.02	good
F9	27.9±0.01	0.58±0.03	0.72±0.02	18.7±0.02	1.24±0.01	good
F10	26.3±0.06	0.55±0.01	0.71±0.01	19.0±0.02	1.24±0.01	good

*All values are expressed as mean ± SD, n=3

Table 3: Results of Post Compression Properties of Losartan potassium matrix tablets

Formulation code	Thickness (mm) (n=5)	Hardness (kg/cm ²) (n=5)	Friability (%) (n=5)	Drug content (%) (n=10)	Weight variation (mg) (n=20)
F1	4.0±0.01	5.5±0.2	0.25±0.01	96.5±0.02	200±0.02
F2	3.9±0.02	6.0±0.1	0.30±0.06	98.0±0.01	199±0.04
F3	3.8±0.03	5.5±0.12	0.45±0.04	99.0±0.01	202±0.02
F4	4.0±0.01	6.0±0.16	0.55±0.02	99.5±0.05	200±0.06
F5	3.9±0.05	5.5±0.09	0.21±0.03	98.0±0.01	198±0.07
F6	3.7±0.01	6.0±0.08	0.35±0.03	99.0±0.01	201±0.03
F7	4.0±0.01	5.5±0.07	0.40±0.02	98.5±0.02	202±0.04
F8	4.1±0.02	6.0±0.12	0.25±0.03	99.5±0.02	200±0.02
F9	4.2±0.02	5.5±0.14	0.55±0.01	99.4±0.02	201±0.04
F10	4.0±0.02	6.0±0.09	0.65±0.01	97.0±0.02	202±0.06

Table 4: Kinetic Release Data of Different Model for Optimized Formulation (F10)

Model	Slope	R ²
Zero order	3.6415	0.8334
First order	0.0566	0.9899
Higuchi	32.979	0.9908
Korsmeyer-Peppas	0.9114	0.5858

Table 5: Stability study (40 °C/75%RH) of Optimized Formulation (F4)

Parameters	1 st month	2 nd month	3 rd month
Physical appearance	Off white, smooth, flat faced	Off white, smooth, flat faced	Off white, smooth, flat faced
Weight variation(mg)	101±0.01	101±0.01	101±0.01
Hardness (kg/cm ²)	6.0±0.16	5.8±0.16	5.7±0.15
Friability (%)	0.55±0.02	0.54±0.06	0.56±0.05
Drug content (%)	99.5±0.05	99.0±0.07	99.3±0.03
<i>In vitro</i> release (%) 24 h.	96.00	95.5	95.00

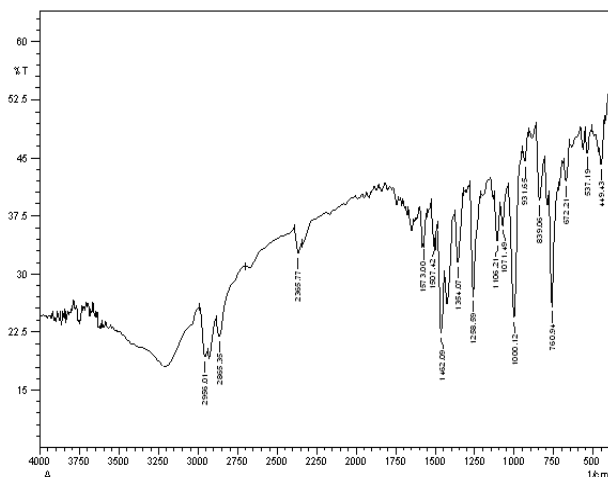


Figure 1: Infrared Spectrum of pure Losartan potassium

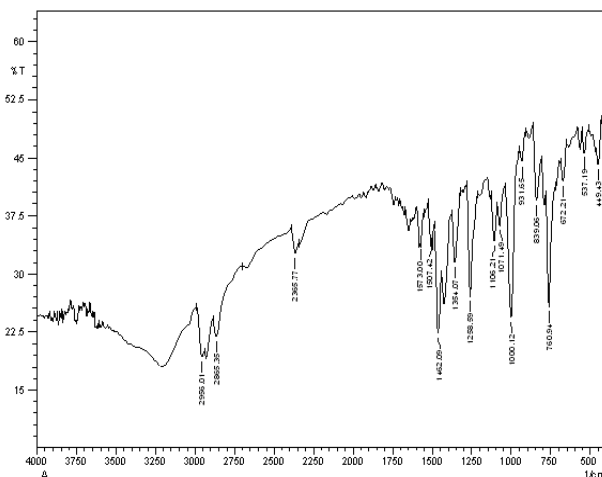


Figure 2: Infrared Spectrum of physical mixture of Losartan potassium and excipients

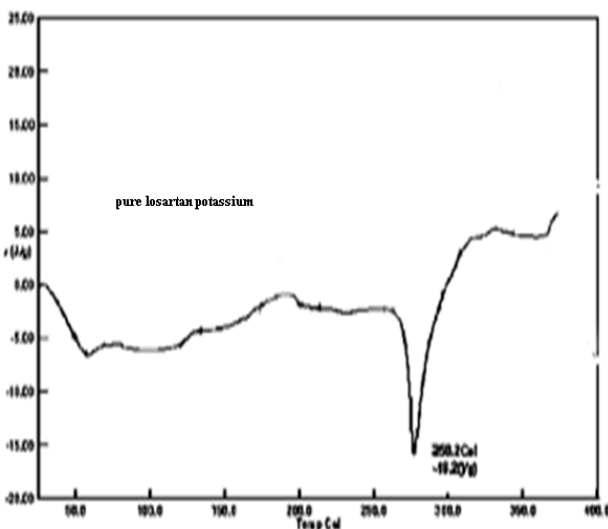


Figure 3: DSC Thermogram of pure Losartan potassium

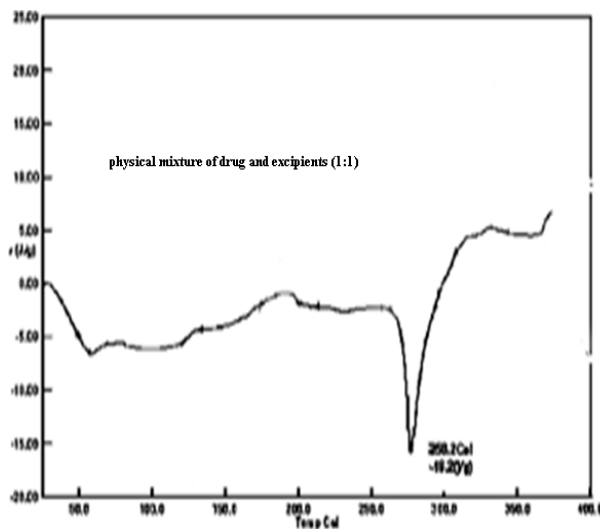


Figure 4: DSC Thermogram of physical mixture of Losartan potassium and excipients

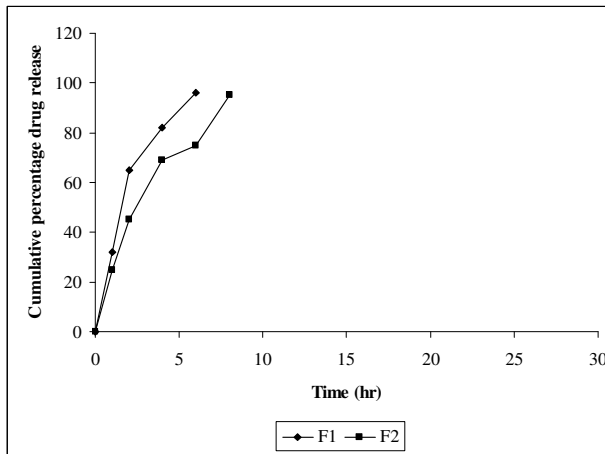


Figure 5: In vitro dissolution profile of sodium alginate containing Losartan potassium matrix tablets

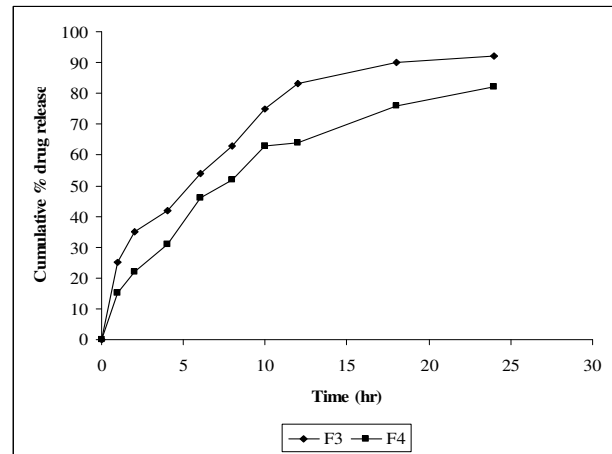


Figure 6: In vitro dissolution profile of xanthan gum containing Losartan potassium matrix tablets

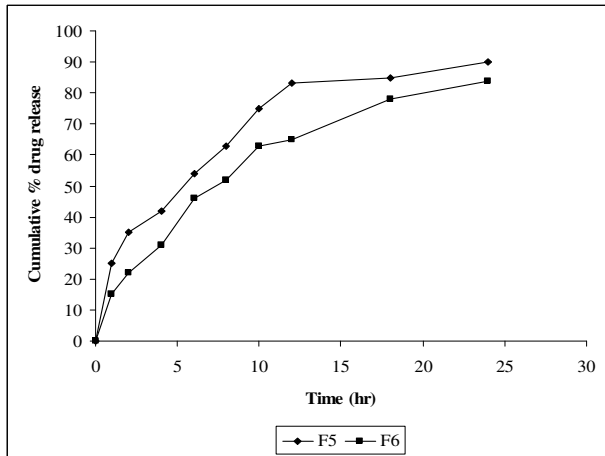


Figure 7: In vitro dissolution profile of Rosin gum containing Losartan potassium matrix tablets

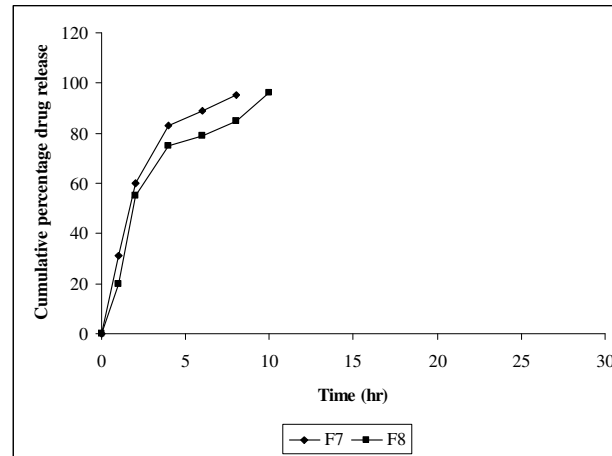


Figure 8: In vitro dissolution profile of pectin containing Losartan potassium matrix tablets

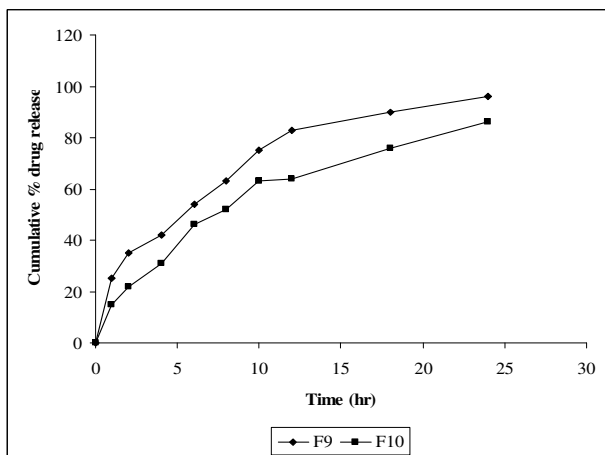


Figure 9: In vitro dissolution profile of Guar gum containing Losartan potassium matrix tablets

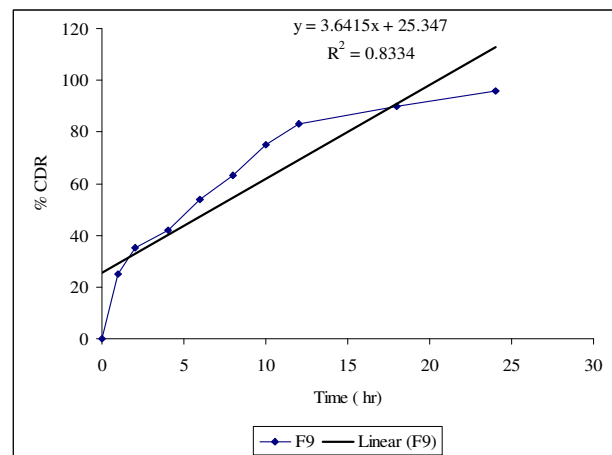


Figure 10: Zero order release kinetics of optimized formulation (F4)

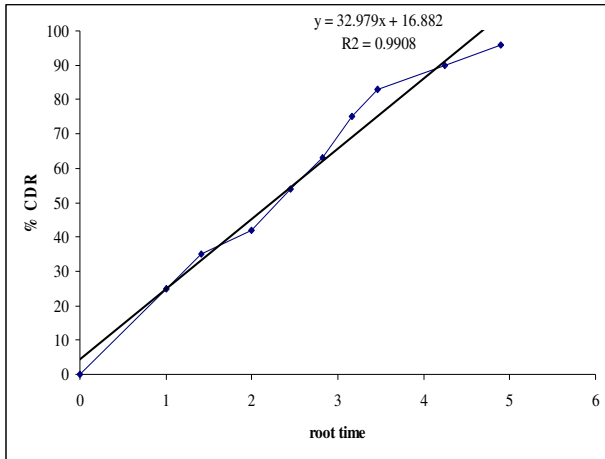


Figure 11: Higuchi matrix release kinetics of optimized formulation (F4)

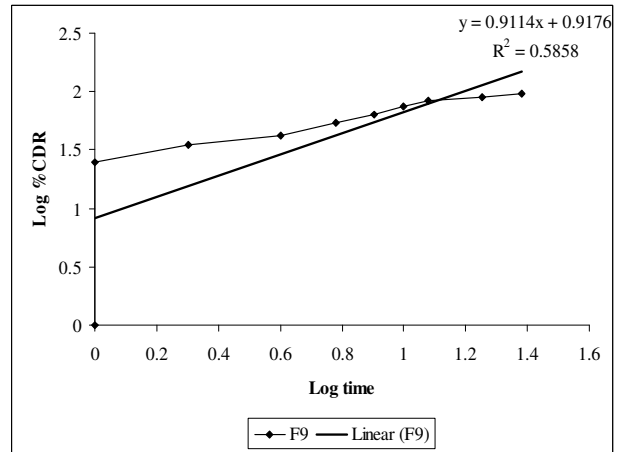


Figure 12: Korsmeyer and Peppas release kinetics of optimized formulation (F4)

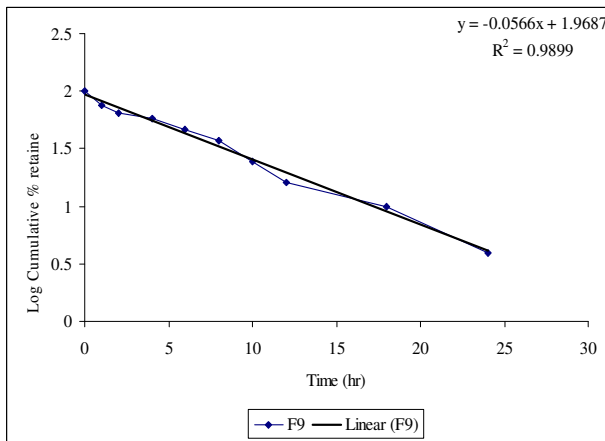


Figure 13: First order release kinetics of optimized formulation (F4)

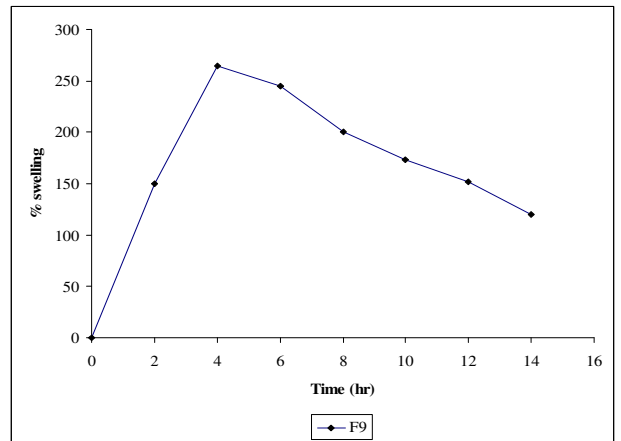


Figure 14: Swelling Study of Optimized Formulation (F4)

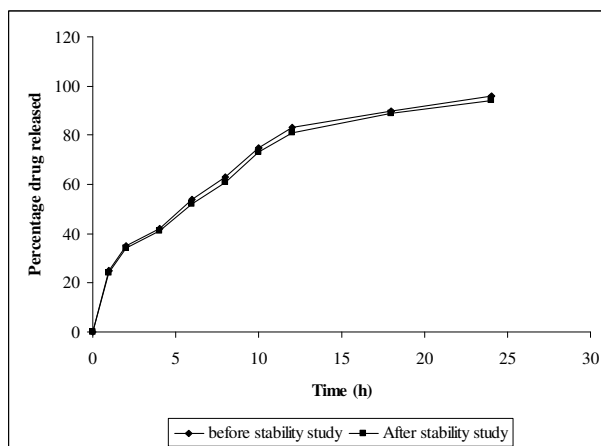


Figure 15: Comparison of invitro dissolution profile of Optimized Formulation (F4) before and after stability study

Thickness

Thickness of the tablets was determined using a Vernier caliper. Five tablets from each batch were used, and average values were calculated. It is expressed in mm.

Drug content ^[16]

Accurately weighed 20 tablets and crushing them in mortar, an accurately weighed quantity of powder equivalent to 50 mg of drug were transferred to a 100 ml volumetric flask. 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 0.1NHCl. Then absorbance of the resulting solution was determined by UV-Visible spectrophotometer at 205nm.

In vitro dissolution studies ^[15]

The prepared matrix tablets were subjected to in-vitro dissolution studies using USP XXIV type II dissolution apparatus (Electro Lab, TDT-O8L, Mumbai). The dissolution studies were carried out in pH 1.2 for 2 h & in pH 6.8 for next 22 h at 37 ± 0.50C and 75 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 205 nm for losartan potassium against blank using UV-Visible spectrophotometer. The amount of drug present in the samples was calculated using standard curve.

Mechanism of drug release

To know the mechanism of drug release from these formulations the data were treated according to first order¹⁶ (log cumulative percentage of drug remaining vs time) Higuchi's ^[17] (cumulative % drug release vs square root of time) and Korsmeyer et al's ^[18] (log cumulative % drug release vs log time) equations along with zero order ^[19] (cumulative amount drug release vs. time). Korsmeyer and Peppas model was fitted into the following equation:

$$M_t / M_\infty = K.t^n$$

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 (Swelling & Cylindrical Matrix).

Swelling Studies

The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behavior of all formulation was studied. One tablet from each formulation was kept in a petridish containing pH 6.8 phosphate buffer. At the end of 1 h, the tablet was withdrawn, soaked with tissue paper, and weighed. Then for every 2 h, weights of the tablet were noted, and the process was continued till the end of 24 h. % weight gain by the tablet was calculated by formula:

$$S.I = \{(M_t - M_0) / M_0\} \times 100,$$

Where, S.I = swelling index, M_t = weight of tablet at time 's' and M_0 = weight of tablet at time $t = 0$.

Stability Studies

To assess the drug and formulation stability, stability studies were done according to ICH guidelines ^[20]. The optimized formulation was subjected to stability study at 40 ± 2°C and 75 ± 5% RH for 90d. The samples were evaluated for physical changes, hardness, friability, drug content and percentage drug release during the stability studies.

RESULTS AND DISCUSSION

Sustained release dosage forms are designed to complement the pharmaceutical activity of the medicament in order to achieve better selectivity and longer duration of action. Sustained release preparations are helpful to reduce the dosage frequency and side effects of drugs and improve patient's convenience. Sustained release matrix tablet is relatively easy to fabricate by incorporating drug molecules in slowly disintegrating or inert porous materials. The most commonly used method of modulating the drug release is to include it in a matrix system.

Characterization of drug and excipients

The formulation additives in concentrations used did not affect the stability and Ultraviolet absorbance of the drug.

Fourier transforms infra red spectroscopy (FTIR) The interaction study between the drug and excipients in different formulations were performed using FTIR spectrophotometer. The pellets were prepared on KBr press. The spectra were recorded over the wave number range of 4000 to 650 cm⁻¹. The FTIR spectrum of Losartan potassium exhibits a characteristic peaks at 760cm⁻¹, 1000 cm⁻¹, 1462 cm⁻¹, 1575 cm⁻¹ and 2995 cm⁻¹ due to chloride moiety,

secondary hydroxyl group, aromatic ring, nitrogen moiety and an aliphatic chain respectively, which indicates groups is match with structure of drug and confirm the purity of the drug. FTIR-spectra of drug and its physical mixture with excipients are exactly same, and there is no shift of peaks or disappearance of principle peaks or modification of the principle peaks indicating that there is no interaction between the drug and excipients. FT-IR spectrum of pure drug and its physical mixture is represented in Figure 1 and Figure 2 respectively.

Differential Scanning Calorimetry (DSC)

Any possible drug polymer interaction can be studied by thermal analysis. The DSC thermogram of Losartan potassium was typical of a crystalline substance, exhibiting a sharp exothermic peak at 258°C corresponding to its melting and decomposition. The thermograms of the physical mixtures of Losartan potassium with other excipients (1:1) showed the existence of the drug exothermic peak which could indicate the absence of interaction between Losartan potassium and other excipients. The DSC thermogram of pure drug and its physical mixture is represented in Figure 3 and 4 respectively.

Pre-compression parameters of Losartan potassium powder blend

Powder 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 results were shown in Tables 2. Angle of repose was in the range of 26.3 ± 0.06 to 32.6 ± 0.04. The bulk density of the granules was in the range of 0.53 ± 0.04 to 0.58 ± 0.03 gm/ml; the tapped density was in the range of 0.67 ± 0.03 to 0.74 ± 0.02 gm/ml, which indicates that the granules were not bulky. The Compressibility index and Hauser ratio was found to be in the range of 16.9 ± 0.02 to 23.7 ± 0.01 and 1.22 ± 0.02 to 1.32 ± 0.02 respectively.

Post compression parameters of Losartan potassium sustained release matrix tablets

The results of Post compression parameters of Losartan potassium sustained release matrix tablets are shown in Tables 3. The thickness of matrix tablets was measured by vernier caliper and was ranged between 3.7±0.01 to 4.2±0.02 mm. The hardness of the matrix tablets was measured by Monsanto tester and was controlled

between 6.0±0.1 to 5.5±0.14 kg/cm². The friability was below 1% for all the formulations. Weight variations for different formulations were found to be 198±0.07 to 202±0.06mg. The percentage of drug content for F1 to F10 was found to be in between 96.5% to 99.5% of Losartan potassium it complies with official specifications. Thus all the physical attributes of the prepared tablets were found be practically within control. The Losartan potassium matrix tablets were off-white, smooth, and flat shaped in appearance.

Effect of Polymer Concentration on the Release Profile

Drug Release from Sodium alginate Matrices

The results of release studies of formulations F1 to F2 are shown in Figure 5. Formulation F1-F2 composed of drug polymer ratio of 1:1, 1:2, have extended the drug release only up to 8h. These formulations could not sustain the drug release.

Drug Release from Xanthan gum Matrices

The results of release studies of formulations F3 to F4 are shown in Figure 6. The release of drug depends not only on the nature of matrix but also upon the drug polymer ratio. As the percentage of polymer increased, the kinetics of release decreased. Formulation F3 to F4 composed of drug polymer ratio of 1:1, 1:2 have extended the drug release up to 24h. These formulations the swelling of the polymer is higher than that of guar gum matrices. F3 formulation showed the 30% of the drug is released in first one hour. Formulations with drug polymer ratios 1:2 (F4) have extended the drug release for 24h. The formulations prepared with drug: polymer (xanthan gum) ratio 1:1(F3) show 96% drug release in 22 h and formulations prepared with drug: polymer (xanthan gum) ratio 1:2 (F4) could retard the drug release up to desired time period. From the release study it is observed that as we increase the concentration of xanthan gum, the release of drug is decreased. This is possibly due to slower erosion of xanthan gum and may be due to the increased viscosity of xanthan gum which might have helped to keep the hydrated gel intact thus releasing the drug for 24 h.

Drug Release from Rosin gum Matrices

The results of release studies of formulations F5 to F6 are shown in Figure 7. The release of drug depends not only on the nature of matrix but also upon the drug polymer ratio. As the percentage of polymer increased, the kinetics of release decreased. Formulation F5-F6 composed of drug

polymer ratio of 1:1, 1:2 have extended the drug release up to 24h. Rosin gum is a hydrophobic natural polymer so it does not show any swelling behavior in dissolution study. It is moisture sensitive so when preparing the matrix tablets it shows the lamination and capping problems. So avoid the physical mixture exposed to moisture to avoid the lamination and capping problem.

Drug Release from Pectin Matrices

The results of release studies of formulations F7 to F8 are shown in Figure 8. Formulation F7-F8 composed of drug polymer ratio of 1:1, 1:2 have extended the drug release only up to 10h. These formulations could not sustain the drug release.

Drug Release from Guar gum Matrices

The results of release studies of formulations F9 to F10 are shown in Figure 9. The release of drug depends not only on the nature of matrix but also upon the drug polymer ratio. As the percentage of polymer increased, the kinetics of release decreased.

Hence it was concluded that F4 was the best among the ten formulations with a sustained release of 96 % at the end of 24 h. From the findings, obtained so far it can be concluded that xanthan gum in the concentration ratio of 1:2 (F4) was promising concentration for oral controlled release tablet of Losartan potassium.

Results of drug Release Kinetics

The drug release data of optimized formulation F4 was fitted to models representing zero order (cumulative amount of drug released vs. time), first order (log percentage of drug unreleased vs. time), Higuchi's (cumulative percentage of drug released vs. square root of time), and Korsmeyer's equation (log cumulative percentage of drug released vs. time) kinetics to know the release mechanisms. The results were shown in table 4 and in figure 10-13. As per table 4 optimized formulation F4 in this investigation could be best expressed by Higuchi's classical diffusion equation, as the plots showed high linearity ($R^2 : 0.9908$) indicates that the drug release follows diffusion mechanism. To confirm the diffusion mechanism, the data were fitted into Korsmeyer- Peppas equation. The optimized formulation F4 was showed values 0.91, indicating that non-Fickian/anomalous diffusion. (If the exponent $n=0.45$, then the drug release follows the Fickian diffusion, and if $0.45 < n < 0.89$, then it is said to be non-Fickian or anomalous release). From the Korsmeyer-Peppas study, the n value of the formulations show that

the release profile obeys nonfickian diffusion which shows that drug is released via, swelling, diffusion and erosion mechanism.

Results of swelling behavior of optimized formulation (F4)

The swelling index was calculated with respect to time. As time increases, the swelling index was increased, because weight gain by tablet was increased proportionally with rate of hydration up to 4 h. Later on, it decreases gradually due to dissolution of outermost gelled layer of tablet into dissolution medium. The direct relationship was observed between swelling index and gum concentration, and as gum concentration increases, swelling index was increased. It has been observed that the cumulative percent drug release decreases with increasing concentration of gum and swelling index. The reason attributed to this fact is slow erosion of the gelled layer from the tablets containing higher amount of xanthan gum. This slow release is because of the formation of a thick gel structure that delays drug release from tablet matrix As a result of rheology of hydrated product, the swollen particles coalesce. This results in a continuous viscoelastic matrix that fills the interstices, maintaining the integrity of the tablet, and retarding further penetration of the dissolution medium. The percentage swelling of optimized tablet was shown in Figure14.

Results of stability studies

The optimized formulation (F4) was selected for stability study on the basis of swelling study and in vitro drug dissolution studies. The tablets were investigated at 40°C/75%RH for 3mo. From the data, the formulation is found to be stable under the conditions mentioned before since there was no significant change in the percentage amount of drug content (Table 5 and figure 15). Formulation F4 did not show any significant changes in appearance, friability hardness and invitro dissolution profile after 3 mo Thus, it was found that the optimized formulation (F4) were stable under these storage conditions for at least 3 mo.

CONCLUSION

This study deals with the investigations carried out with the objective of developing oral sustained release formulations through matrix tablets for the widely used Losartan potassium is a potent, highly specific angiotensin II type 1 (AT1) receptor antagonist with antihypertensive activity using natural polymers viz; xanthan gum

guar gum sodium alginate, pectin and rosin gum and evaluation of their sustained release potential. Optimized formulation F4 (drug to polymer ratio 1:2) which includes xanthan gum has successfully sustained the drug release for 24 h. The release process involves anomalous diffusion mechanism, as indicated by the n value of 0.91 in Korsmeyer's plot. FTIR and DSC studies indicated that there was no interaction between the drug and excipients and stability studies had proved the integrity of the developed matrix tablets. The method of direct compression utilizes minimum machinery and man power. From the economical point of view, it may be beneficial for the local pharmaceutical firms to adopt such simple technologies for the preparation of sustained release product. Thus, sustained release matrix tablets of Losartan potassium using natural Biodegradable and biocompatible polymers were successfully formulated, evaluated and found to be suitable candidates in extending the release of the drug from the matrix tablets.

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