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Formulation and Evaluation of Sustained Release Matrix Tablet of a Model Anti-Hypertensive Drug Using Natural Polymers

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Abstract

The objective of the present study is to develop a sustained release matrix tablets of Losartan potassium, an anti hypertensive drug. The sustained release tablets were prepared by wet granulation and formulated using different drug and polymer ratios, formulations such as F1 to F9. Natural polymers like Xanthan Gum (XG), Guar gum, Cellulose were used. Compatibility of the drug with various excipients was studied. The compressed tablets were evaluated and showed compliance with Pharmacopeial limits. The optimized formulation is F2 on the basis of acceptable tablet properties and *in vitro* drug release. The resulting formulation produced robust tablets with optimum hardness, consistent weight uniformity and friability. In-Vitro dissolution studies have shown the sustained release for Losartan potassium i.e., 90.88% released at the end of 12h. A decrease in release kinetics of the drug was observed on increasing polymer ratio.

Keywords: Sustain release; Losartan Potassium; Anti Hypertensive; Wet Granulation; Natural Polymers.

Contents

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1. Introduction

Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation, etc. Many of the drug delivery systems, available in the market are oral drug delivery type systems. Oral drug delivery systems have progressed from immediate release to site-specific

delivery over a period of time. Every patient would always like to have a ideal drug delivery system possessing the two main properties that are single dose or less frequent dosing for the whole duration of treatment and the dosage form must release active drug directly at the site of action. Thus the objective of the pharmacist is to develop systems that can be as ideal system as possible. Attempts to develop a single- dose therapy for the whole duration of treatment have focused attention on controlled or sustained release drug delivery systems. The therapy of many chronic diseases requires a repeated dosing of a drug. Drugs having a short half-life have to be administered up to several times daily within short intervals. To reduce the application frequently sustained formulations have been developed [1].

Sustained Release Dosage Forms

Sustained release, sustained action, prolonged action, controlled release, extended action, timed release, depot and repository dosage forms are terms used to identify drug delivery system that are designed to achieve or prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose [2]. Basically there are three basic modes of drug delivery i.e. targeted delivery, controlled release and modulated release. Targeted delivery refers to the systemic administration of a drug carrier with the goal of delivering the drug to specific cell types; tissues or organs. Controlled release refers to the use of a delivery device with the objective of releasing the drug into the patient's body at a predetermined rate, or at specific release profiles. On the other hand modulated release implies use of as drug delivery device that releases the drug at a variable rate controlled by environment conditions, biofeedback, sensor input or an external control device [3]. Many times sustained release and controlled release terms are used interchangeably. However sustained release system deliver the active agent although at slower than a conventional formulation but the release is substantially affected by external environment. Sustained release dosage forms are generally administered by four delivery modes, namely Oral controlled drug delivery, transdermal drug delivery, implantable drug delivery and particulate drug delivery.

Drug Properties Relevant To Sustained Release Formulations [4-7]:

During design of sustained release delivery systems, variables such as the route of drug delivery, the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug, are considered. Of particular interest to the scientist designing the system are the constraints imposed by the properties of the drug.
These properties are classified as

(a) Physicochemical
(b) Biological properties

These properties have the greatest effect on the behavior of the drug in the delivery system and in the body. There is no clear cut distinction between these two categories since the biological properties of a drug are a function of its physicochemical properties. By definition, physicochemical properties are those that can be determined from *in vitro* experiments and biological properties will be those that result from typical Pharmacokinetic studies of the absorption, distribution, metabolism, and excretion (ADME) characteristics of a drug and those resulting from pharmacological studies. In the recent years extensive efforts have been made in various pharmaceutical research laboratories of sustained release drug delivery systems, with an aim of improved patient compliance, better therapeutic efficacy, less side effects and reduced dosage regimen with less toxicity for treatment for many acute and chronic diseases [8-10]. Losartan potassium is a potent, highly specific angiotensin II type 1 receptor antagonist with antihypertensive activity. It is readily absorbed from the gastrointestinal tract with oral bioavailability of about 33% and plasma elimination half-life ranging from1.5 to2.5 hours [11]. Matrix tablets composed of drug and polymer as release retarding material offer the simplest approach in designing a sustained release system. The present study aims to develop sustained release matrix tablets using natural polymers along with drug in varying proportions by wet granulation method [12].

2. Materials and Methods

Materials:

Losartan potassium was obtained from Chandra labs kukatpally. Guar gum and Xanthan gum from wonder herbs, Hyderabad, India. Cellulose from Loba chemie Pvt.ltd, Mumbai. Microcrystalline cellulose,PVP, Magnesium stearate and talc from S.D. Fine Chem. Ltd, Mumbai, India.

Drug- Polymer Interaction

It was carried out by taking FT-IR Infrared spectra of pure drug, and drug-polymer by KBr pellet technique and was recorded in the range of 4000 – 400 cm-1 using FT-IR Spectrophotometer.

Methods:

Preparation of Losartan Potassium Tablets by Wet Granulation:

The active ingredient, disintegration agents are weighed as mentioned in the table 1 and mixed. The wet granulate is prepared by adding binder solution i.e., PVP, then damp mass is screened to get the granules. The granules obtained

are dried in hot air oven at 60^0C for one hour. After the granules are dried, they are passed through a screen of smaller size than the one used for the wet mass to select granules of uniform size to allow even fill in the die cavity. A dry lubricant is added to the granules either by dusting over the spread-out granules or by blending with the granules. The granules are fed into the die cavity and then compressed between a lower and an upper punch. 7.5mm size punches were used for punching tablets.

Table 1. Master formulation for Losartan potassium tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Losartan potassium	50	50	50	50	50	50	50	50	50
Xanthan gum	50	100	150	-	-	-	-	-	-
Guar gum	-	-	-	50	100	150	-	-	-
Cellulose	-	-	-	-	-	-	50	100	150
MCC	225	175	125	225	175	125	225	175	125
PVP	20	20	20	20	20	20	20	20	20
Iso propyl alcohol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Talc	3	3	3	3	3	3	3	3	3
Magnesium stearate	2	2	2	2	2	2	2	2	2
Total weight(mg)	350	350	350	350	350	350	350	350	350

Evaluation Parameters

A) Precompression Parameters

The prepared granules were evaluated for various precompression parameters such as bulk density, tapped density, angle of repose, hausner's ratio, compressibility index to determine the flow properties of the powdered blend.

B) Post compression Parameters [13]

Hardness:

The hardness of the tablet was determined using a Monsanto hardness tester. It is expressed in **Kg / cm^2.**

Friability (F):

The friability of the tablet was determined using Roche Friabilator. It is expressed in percentage (**%)**. 10 tablets were initially weighed ($W_{initial}$) and transferred into the friabilator. The friabilator was operated at 25 rpm for four mins. The tablets were weighed again (W_{final}). The percentage friability was then calculated.

Weight Variation:

Ten tablets were selected randomly from the lot and weighed individually to check for weight variation. IP limit for weight variation in case of tablets weighing more than 325mg is ± 5%.

Thickness:

The thickness of the tablets was measured by screw gauge. It is expressed in **mm.**

Content uniformity test:

Ten tablets were weighed and powdered, a quantity of powder equivalent to 10 mg of formulation was transferred to a 25 ml volumetric flask and 15 ml water is added. The drug is extracted in water by vigorously shaking the stoppered flask for 15 minutes. Then the volume is adjusted to the mark with distilled water and the liquid is filtered. The drug content was determined by measuring the absorbance at 234 nm after appropriate dilution. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated.

***Invitro* dissolution studies:**

The Dissolution study was carried out using dissolution test apparatus USP type II (Paddle). The dissolution medium used was 900 ml of simulated intestinal fluid at 37±0.5º. The paddle speed was kept at 50 rpm throughout the study. Aliquot of 5 ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain a constant volume. After each sampling and suitably diluted with buffer, solutions were analyzed spectrophotometrically at 234nm against suitable blank using UV-visible spectrophotometer.

Kinetics modeling of drug dissolution profiles [14]:

To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The dissolution profile of the all formulations were fitted to zero order, first order, Higuchi and Korsmeyer equation / Peppa's model to ascertain the kinetic modeling of the drug release.

$C = K_0t$

Where, K_0 = Zero-order rate constant and t = Time

$LogC = LogC_0 - Kt / 2.303$
Where, C_0 = initial concentration of drug and K = First order constant.
$Q = K t1/ 2$
Where, K = Constant and t = Time.
$M_t / M_\alpha = Kt^n$
$Log M_t / M_\alpha = Log K + n Log t$
Where, $M_t / M\alpha$ = the fraction of drug released at time't', K = Constant incorporating the structural and geometrical characteristics of the drug / polymer system and N = Diffusion exponent related to the mechanism of the release.

3. Results and Discussion

Determination of Interaction between Drug and Polymers:

Compatibility studies were performed using FT-IR spectrophotometer. The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicates that the drug is compatible with the formulation components. Pure drug Losartan potassium has exhibited IR spectrum indicating the presence of C-H group at 3055.35cm $^{-1}$ and 2943.49cm^{-1}, C=C group at 1575.89cm^{-1} to 1733cm^{-1}, C-O peak at 1631cm^{-1}. The IR spectrum of pure drug losartan potassium is shown in Figure 1. In the IR spectra of drug and different polymers obtained, there is no interaction found in between drug and polymers. The drug functional groups are observed in each of IR spectra of combination of drug and polymers. IR spectra of pure drug and drug with other excipients are shown in figures 1, 2, 3, 4.

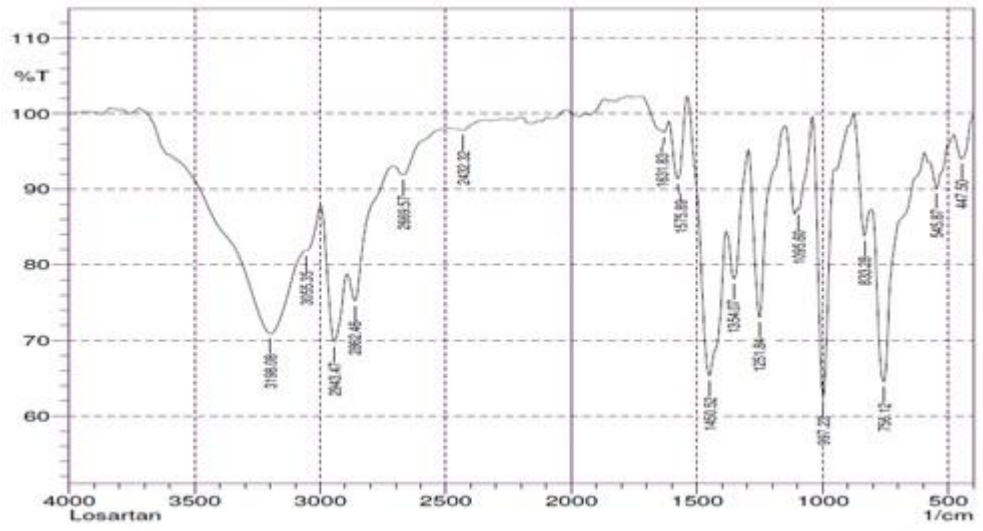

Figure 1. FTIR for pure drug of losartan potassium

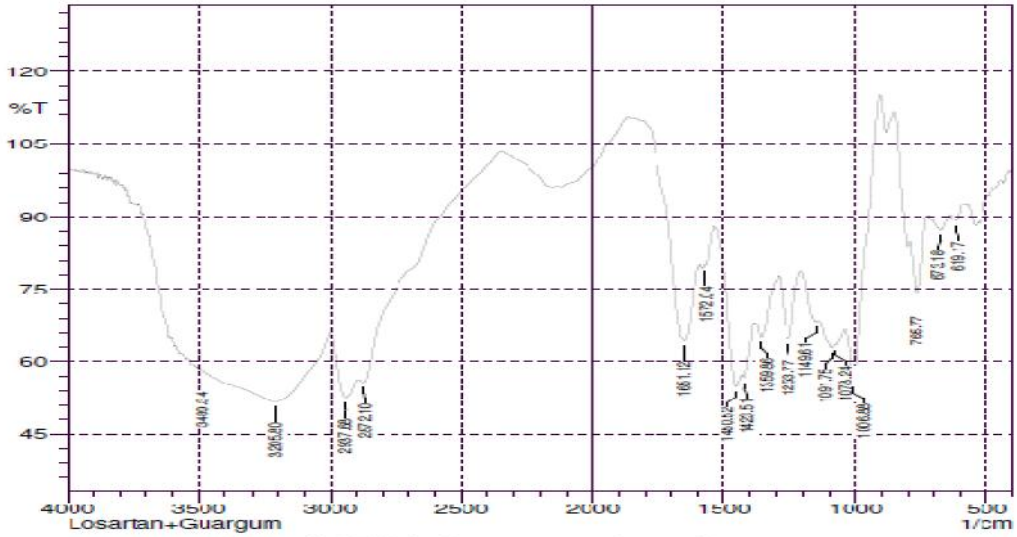

Figure 2. FTIR for losartan potassium + Guar gum

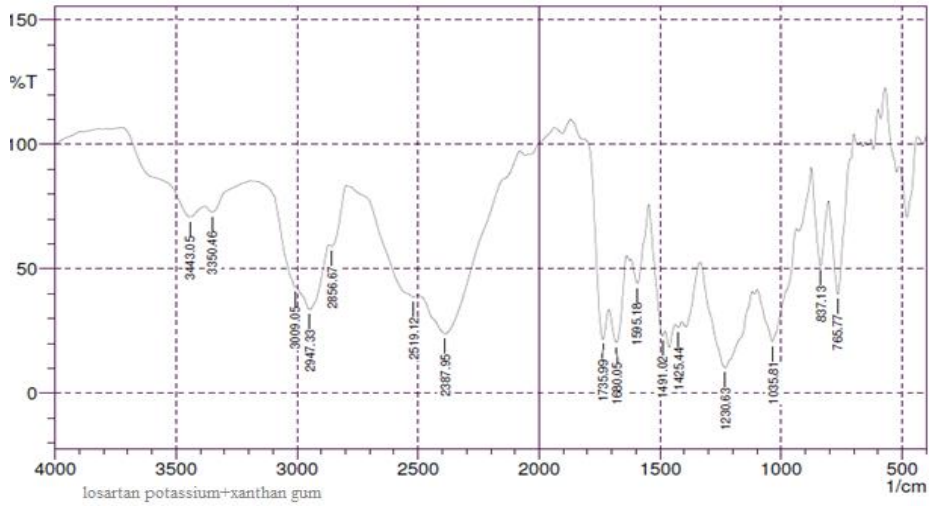

Figure 3. FTIR for losartan potassium + xanthan gum

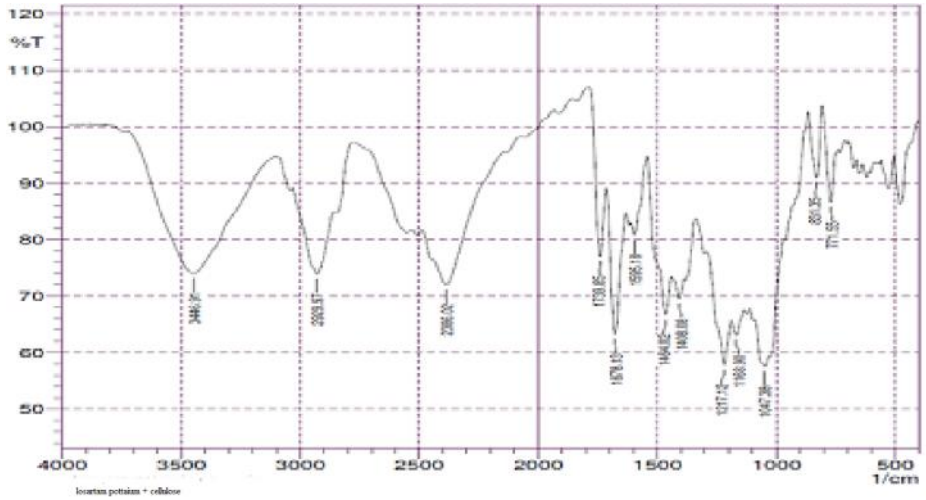

Figure 4. FTIR for losartan potassium + cellulose

Precompression Parameters: The method employed for tabletting in this study was wet granulation for which the drug or the mixture of drug and polymer should possess good flow properties. Granules ready for compression containing drug and various excipients were subjected for pre-compression parameters (Micromeritic properties) to study the flow properties of powder blend, to achieve constant uniformity of tablet weight. The data obtained for angle of repose for all the formulations were tabulated in the table no.2 The values were found to be in the range of 22°.69′ and 26°.95′. All the formulations showed the angle of repose less than 30°, which reveals the good flow property. The results of Carr's consolidation index or compressibility index (%) for the entire formulation blend ranged from 14.28 to 16.92 %. the powder blend showed excellent compressibility index values up to 15% result in good to excellent flow properties.

Table 2. Precompression studies for the granules

Formulation	Angle of repose (θ)	Carr's Index (%)	Hausner's ratio	Drug uniformity* (%)
F1	26°.95′	15.15	1.178	98.94±0.40
F2	24°.56′	14.35	1.182	99.31±0.32
F3	25°.94′	16.42	1.196	99.75±0.33
F4	23°.96′	16.92	1.204	96.31±0.41
F5	24°.14′	16.42	1.196	98.69±0.22
F6	25°.91′	16.67	1.2	99.75±0.34
F7	22°.69′	14.28	1.167	99.75±0.21
F8	23°.58′	16.67	1.2	98.94±0.25
F9	25°.95′	14.92	1.175	99.75±0.34

Post Compression Parameters:

Hardness: The hardness of the tablet formulations was found to be in the range of 5.1 to 6.1 kg/cm^2.

Friability: The friability values were found to be in the range of 0.141 to 0.191 %.

Uniformity of weight: All the prepared tablets of losartan potassium were evaluated for weight variation. The weight of all the tablets was found to be in the range of 345 to 358%.

Uniformity of drug content: The low values of standard deviation indicates uniform drug content within the tablets The percent drug content of all the tablets was found to be in the range of 97 to 99 %. The values are represented in the table 3.

Table 3. Post formulation studies of all formulations

Formulations	Diameter* (mm)	Thickness* (mm)	Weight variation (mg)	Hardness* (kg /cm^2)	Friability (%)	Drug content* (%)
F1	10.05±0.030	4.45±0.11	351±5	5.1 ± 0.12	0.191	97.00±0.24
F2	10.06±0.040	4.50±0.04	350±5	5.5 ± 0.24	0.149	98.90±0.22
F3	10.04±0.030	4.49±0.05	354±5	5.8 ± 0.21	0.146	97.86±0.34
F4	10.02±0.030	4.45±0.12	345±5	5 .2± 0.23	0.149	98.75±0.32
F5	10.02±0.054	4.46±0.03	347±5	5.9 ± 0.12	0.145	96.26±0.46
F6	10.05±0.064	4.54±0.23	351±5	6.1 ± 0.14	0.191	98.45±0.26
F7	10.07±0.022	4.52 ±0.2	352±5	5.2 ± 0.18	0.193	98.00±0.28
F8	10.05±0.035	4.51±0.12	349±5	5.4 ± 0.22	0.146	99.72±0.30
F9	10.04±0.059	4.53 ±0.3	348±5	6 .1± 0.21	0.191	98.82±0.34

In vitro Drug Release Profile:

In vitro drug release studies were carried out on dissolution test apparatus in 900ml of 0.1N HCl for 2 hours and phosphate buffer 6.8 pH for the next remaining hours. The release rate of the drug from the matrix tablets decreased with an increase in polymer proportion because of increase in gel strength as well as the formation of a gel layer with a longer diffusional path. Results are given in the table 4,5 and represented in the figure 5,6 and 7.

The order of release was found to be: F2>F1>F5> F4>F3>F8 >F7>F9

The formulation F2 has shown better drug release than other formulations. In the formulation F2 having swellable polymer as guar gum showing better drug release profile than other polymer (xanthan gum, cellulose). Hence the natural polymer guar gum is better suitable for sustained release delivery than other natural polymers.

Table 4. Dissolution table of formulations in 0.1N HCL Acid stage

Time in hrs	1hr	2hr
F1	19.24	27.42
F2	18.64	26.46
F3	17.44	24.82
F4	18.82	26.72
F5	17.12	24.12
F6	16.41	23.12
F7	17.12	25.12
F8	16.42	22.18
F9	15.12	22.01

Table 5. Dissolution table of formulations in 6.8 Phosphate buffer buffer stage

Time in hrs	4hr	6hr	8hr	10hr	12hr
F1	40.12	65.42	72.12	80.52	87.12
F2	39.73	62.84	74.52	82.12	90.88
F3	36.42	55.42	62.45	74.45	83.52
F4	39.42	61.24	68.62	76.96	84.22
F5	39.92	61.12	72.52	79.89	86.17
F6	33.12	52.42	60.86	72.85	80.33
F7	38.12	50.19	67.62	74.62	80.14
F8	38.80	60.40	69.75	77.75	82.55
F9	31.45	51.09	59.36	70.46	78.26

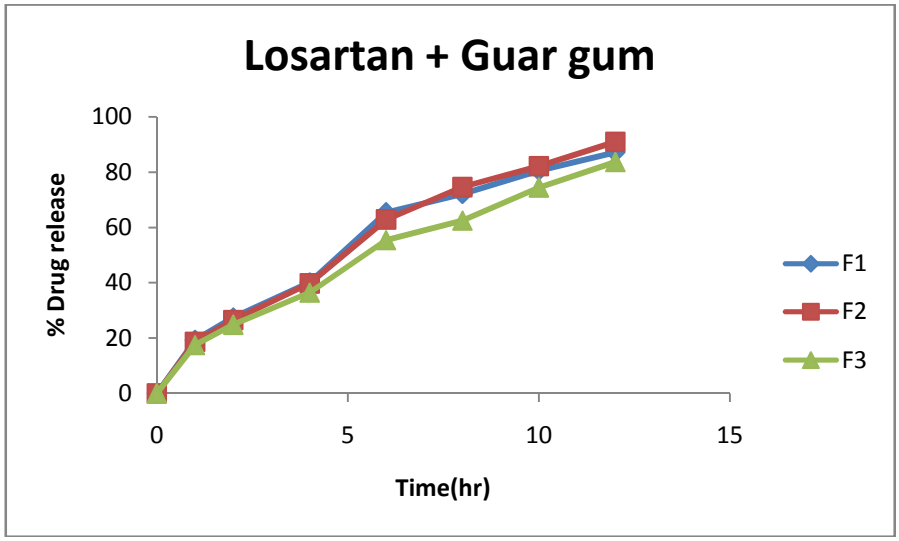

Figure 5. Dissolution for losartan potassium with guar gum

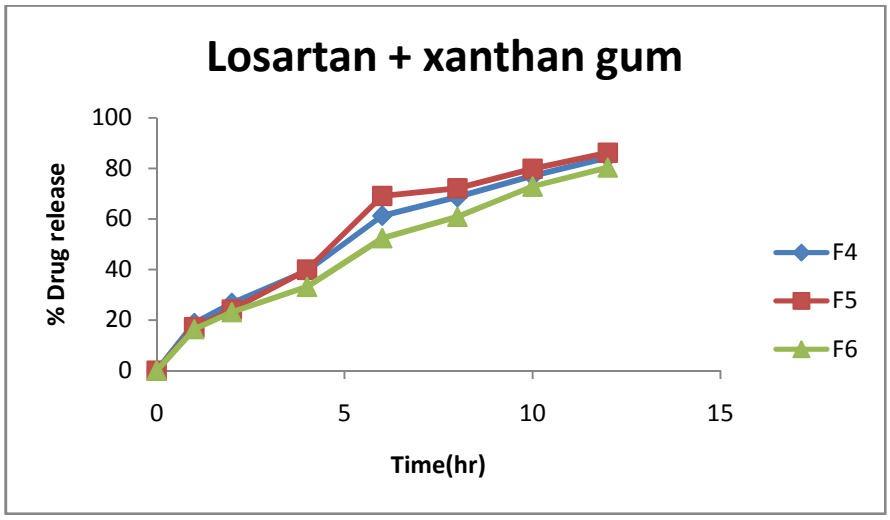

Figure 6. Dissolution for losartan potassium with xanthan gum

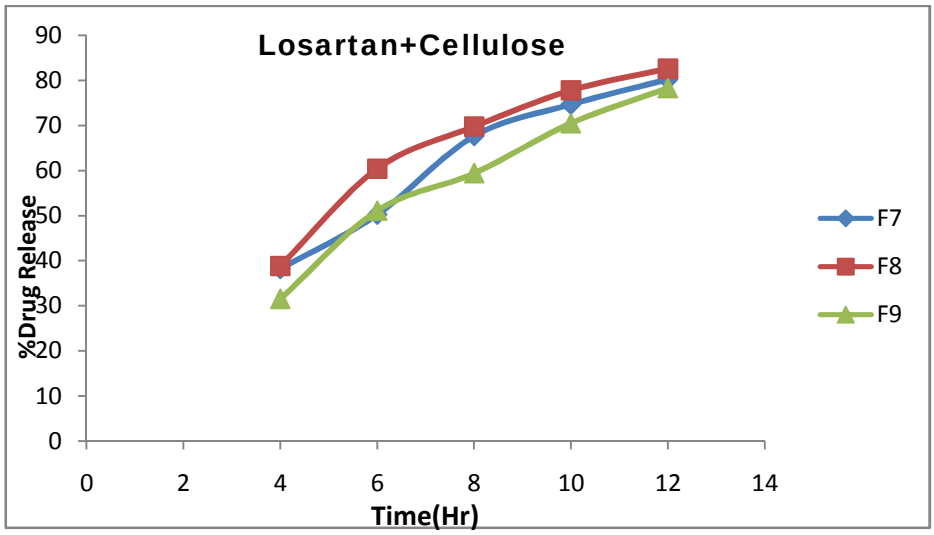

Figure 7. Dissolution for losartan potassium with cellulose

Release Kinetics:

The data obtained from *in-vitro* release of best formulation F2 were fitted into equations for the zero order and first order, Higuchi and Krosmeyer release models; the interpretation of the data was based on the values (Table 6) of the resulting regression co-efficient. Result obtained from the release kinetics shows that the formulation F2 follows the first order and Krosmeyer Peppas plots were found to be fairly linear and the 'r' coefficient value for pure drug losartan potassium and its formulations with guar gum (1:2). So the regression data of first order and Krosmeyer Peppas plots indicates that the drug was released by first order kinetics and non fickian.

Table 6. Release kinetics of formulation F2

Formulation	Zero order R^2 value	First order R^2 value	Higuchi R^2 value	Krosmeyer Peppas	
				R^2 value	'n'value
F-2	0.964	0.981	0.976	0.987	0.670

4. Conclusion

Sustained release matrix tablets of losartan potassium were successfully formulated and evaluated. Sustained release matrix tablets of losartan potassium were successfully prepared by wet granulation using guar gum, xanthan gum, cellulose, CMC as polymers and PVP as binder. The isopropyl alcohol was used as granulating fluid for binder. Sustained release tablets were evaluated for pharmacopeial and non-pharmacopeial (industry specified) tests. The drug content was uniform in all the formulations of tablets prepared. The low values of standard deviation indicate uniform distribution of drug. Based on the results, F-2 was identified as better formulation among the developed formulations. In F-2 formulation drug release was found to be 90.83% at the end of 12hrs. The drug release profile of F2 (guar gum) is higher than rest of the formulations made by using xanthan gum and cellulose. In the formulation 2 having swellable polymer as guar gum showing better drug release profile than other polymer (xanthan gum and cellulose). Hence the natural polymer guar gum is better suitable for sustained release delivery than other polymers.

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