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DEVELOPMENT AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF LOSARTAN POTASSIUM BY USING NATURAL AND SYNTHETIC POLYMERS

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ABSTRACT

The objective of the study was to develop a sustained release matrix tablets of Losartan potassium, an antihypertensive drug. The sustained release tablets were prepared by wet granulation and formulated using drug and different polymer ratios, nine different formulations were prepared from F1 to F9. Hydrophilic polymer & hydrophobic polymer like natural polymer like Xanthan Gum (XG), Guar Gum, and Karaya gum were used. Compatibility of the drug with various excipients was studied by using FTIR and DSC. The compressed tablets were evaluated for compliance with Pharmacopoeia limits. The formulation (F1) is optimized 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.

The results of dissolution studies indicated that formulations F1, F2 & F3 have shown better drug release profile than compared other formulations. Among all other formulations the formulation F1 (drug to polymer 1:1) was found to be the most successful and the study exhibited sustained release of Losartan potassium with 96.45% released at the end of 24 hours. A decrease in release kinetics of the drug was observed on increasing polymer ratio. Applying exponential equation, all the formulation tablets (except F1) showed diffusion-dominated drug release. The drug release kinetics was found to be Non-Fickian super case II

KEYWORDS: Losartan Potassium, Xanthan gum, Sustained release, Matrix Tablets.

INTRODUCTION

Oral sustained-release (SR) drug delivery systems are designed to deliver therapeutically effective concentrations of drug to the systemic circulation over an extended period of time. Matrix tablets are considered to be the commercially feasible sustained action dosage forms that involve the least processing variables, utilize the conventional facilities and accommodate large doses of drug. There remains an interest in developing novel formulations that allow for sustained release of drug using readily available, inexpensive excipients by matrix based formulation. During the last two decades there has been remarkable increase in interest in sustained release drug delivery system.[1]

It includes any drug delivery system achieves release of drug over an extended period of time, which not depend on time. Hydrophilic polymer matrix is widely used for formulating a Sustained dosage form. The role of ideal drug delivery system is to provide proper amount of drug at regular time of interval & at right site of action to maintain therapeutic range of drug in blood plasma. The IR drug delivery system lacks some features like dose maintenance, sustained release rate & site targeting. The oral Sustained drug delivery has some potential advantage like Sustained release rate & dose maintenance in plasma. The SR formulations have some swelling polymer or waxes or both which controls the release rate.[2] The use of reservoir system is also well known for controlling release rate. Shows the relation between plasma concentration verses time.

Losartan potassium is a selective, competitive angiotensin II receptor type 1 (AT_1) antagonist, reducing the end organ responses to angiotensin II. Losartan administration results in a decrease in total peripheral resistance (afterload) and cardiac venous return (preload). All of the physiological effects of angiotensin II, including release of aldosterone, are antagonized in the presence of losartan. Reduction in blood pressure occurs independently of the status of the renin-angiotensin system.[3]

The absolute bioavailability of losartan is up to 25-35 % through oral route, Half-life of the losartan is 1-2.5 hours and protein binding of losartan is 99.7 %.[3] To overcome the adverse effects of the losartan and bioavailability problems we are planned to design sustained release dosage forms. In the present study we are proposing natural gums such as Xanthan gum, Guar gum and Karaya gum as natural polymers and their combination were used. The study may show different pattern of drug release and also chances to reduce the cost of the preparation by replacing costlier gums with cheaper gums.

The objective of the present work is to develop and evaluate sustained release matrix tablets of losartan by using natural gums. The effect of natural polymers on the *in vitro* release rate were analysed.

MATERIALS AND METHODS

Materials

Losartan Potassium was obtained as gift sample from Emcure Pharmaceutical, Pvt. Ltd, Pune, India. Xanthan Gum, Guar gum and Microcrystalline cellulose were purchased from S.D. Fine chem. Ltd. Mumbai. Karaya gum and Sodium hydroxide pellets, procured from Loba Chemicals, Mumbai. Talc and Magnesium stearate were purchased from Apex Chemicals, Ahmedabad, India.

Table I: Tablet Composition of Losartan Potassium Sustained Release Matrix Tablets Prepared with Different Release Retardant Natural Matrices (in mg) (F1 to F9).

Ingredients/Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug(mg)	50	50	50	50	50	50	50	50	50
Xanthan Gum(mg)	50	75	100	-	-	-	-	-	-
Guar Gum (mg)	-	-	-	50	75	100	-	-	-
Karaya gum(mg)	-	-	-	-	-	-	50	75	100
MCC(mg)	125	100	75	125	100	75	125	100	75
Magnesium Stearate(mg)	2	2	2	2	2	2	2	2	2
PVP(mg)	20	20	20	20	20	20	20	20	20
Talc(mg)	3	3	3	3	3	3	3	3	3
Total Weight(mg)	250	250	250	250	250	250	250	250	250

Method of preparation sustained release matrix tablets of losartan potassium

The matrix tablet was prepared from granules by conventional wet granulation method. A non-aqueous granulation process was adopted to prepare Losartan potassium matrix tablets. The drug and all other ingredients were sifted through sieve # 22. Then the sifted ingredients were mixed thoroughly in a mortar with pestle for 15min. IPA with PVP was added into well mixed powder till the desired wet mass was formed. This wet mass was sifted through sieve # 22 then granules are prepared. The prepared granules were dried at 70ºC for 15 minutes in hot air oven, for lubrication add the magnesium stearate and talc were sifted through sieve #22 and mixed with the prepared granules in a polybag for 5min. Finally, tablets were compressed at 250 mg weight on a 10 station mini rotary tableting machine.[4]

Evaluation of granules

The angle of repose was measured by using funnel method which indicates the flow ability of the granules. Loose bulk density (LBD) and tapped bulk density (TBD) were measured using the formula: LBD= weight of the powder/volume of the packing. TBD= weight of the powder /tapped volume of the packing. Compressibility index of the granules was determined by using the formula: CI (%) = [(TBD-LBD/TBD)] ×100 [5]. The physical properties of granules were shown in Table II.

Evaluation of tablets

All prepared matrix tablets were evaluated for its uniformity of weight, hardness, friability and thickness according to official methods shown in Table 3.[6]

Uniformity of drug content

Accurately weighed quantity of the powder tablet equivalent to 25 mg of the drug was transferred to 100 ml volumetric flask.100 ml of water are added in 100 ml of volumetric flask . Mix with the aid of ultrasound for 15 min, and then the volume was made up to 100 ml with the same water, mixed solution was filtered through the membrane filter disc with an average pore diameter not greater than 0.55µm. 5 ml of the filtrate was diluted to 100 ml with same water solution and examined under UV Spectrophotometer at 234 nm.[7]

Drug release kinetics

Various mathematical equations have been proposed for kinetic analysis of drug release from the evaluated formulations. The zero order rate Eq. 1 describes the systems where the drug release is independent of its concentration. The first order rate Eq. 2 describes drug release from systems where the release is concentration dependent. According to the Higuchi model Eq. 3, drug release from the insoluble matrix is directly proportional to the square root of time and is based on Fickian diffusion:

$$\mathbf{At = A_0 - K_0 t \ldots\ldots\ldots\ldots\ldots\ (1)}$$

$$\mathbf{Log\ C = Log\ C_0 - Kt / 2.303 \ldots\ldots\ldots\ldots\ldots\ (2)}$$

$$\mathbf{Q = Kt^{1/2} \ldots\ldots\ldots\ldots\ldots\ (3)}$$

Where,

At is the amount of drug released at time t, A_0 is the initial amount of drug in the tablet and k_0 and k_1 are release rate constants for the zero order and first order respectively. In order to define a model that will represent a better fit for the formulations, dissolution data can be further analyzed by the Peppa's and Korsemayer's equation:

Log Mt/Ma = Log K + n Log t ……. (4)

Where,

Mt corresponds to the amount of drug released at time t, K is the constant incorporating the structural and geometrical characteristics of the drug / polymer system. And n is the diffusion exponent related to the mechanism of the release.[8]

Stability Study

The optimized formulation was subjected to stability at 25^{o}C± 2^{o}C / 60% ± 5% RH, 30^{o}C ± 2^{o}C / 65% ±5% RH and 40^{o}C ± 2^{o}C / 75% ± 5% RH for period of 90 days. After each month tablet sample was analyse for physical characteristics and drug release profile.

RESULTS AND DISCUSSION

Discussion on FT-IR

FT-IR spectrum of losartan potassium showed in Figure I, drug polymer interaction was checked by comparing the IR spectra of the formulation with the IR spectra of the pure drug. There was no significant change in the functional groups between the IR spectra of the pure drug and also no additional peaks were seen in the selected formulation. This confirms that no interaction between drug and excipients.[9]

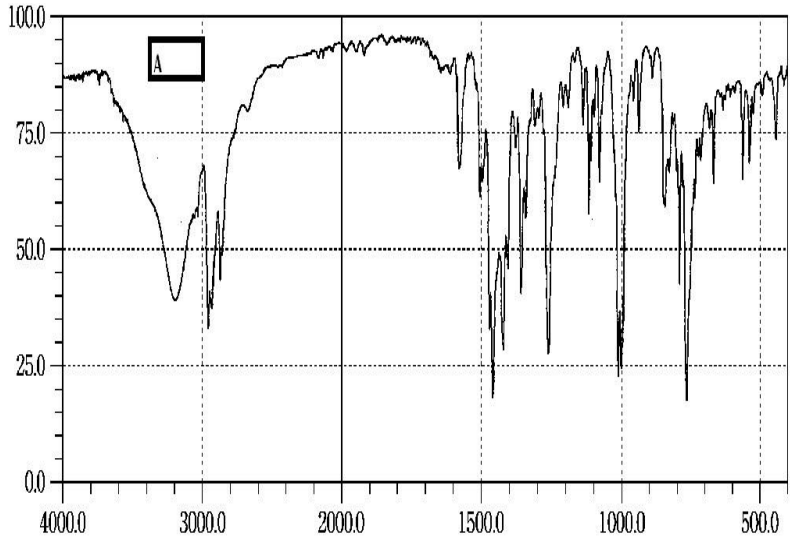

Figure I: FT-IR Spectroscopy of Losartan potassium.

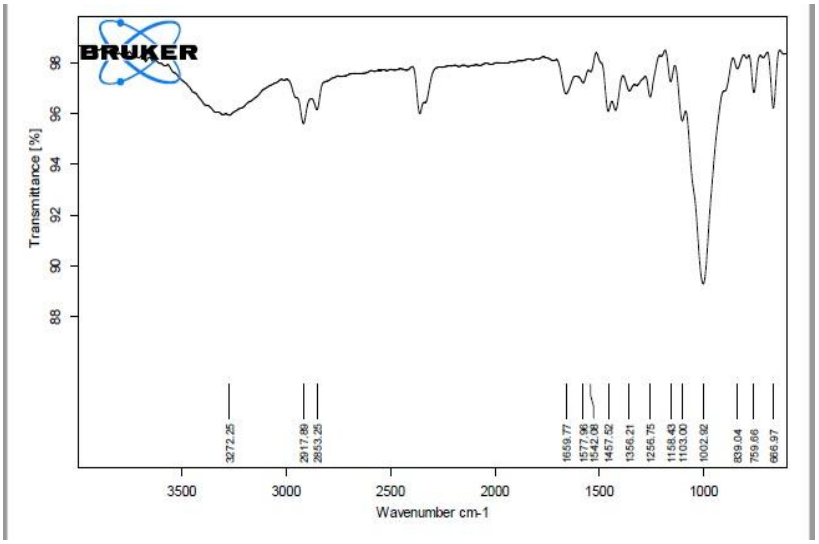

Figure II: FT-IR Spectroscopy of Xanthan Gum+ MCC+PVP+ Magnesium Stearate+ Talc.

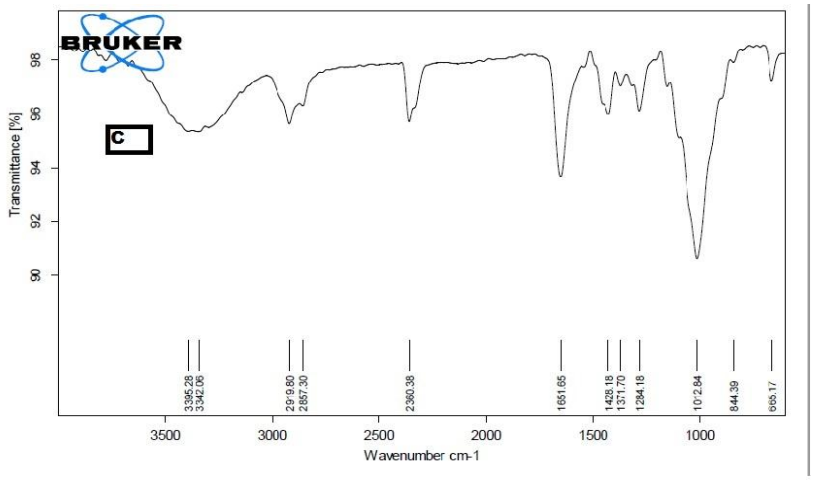

Figure III: FT-IR Spectroscopy of Formulation F1.

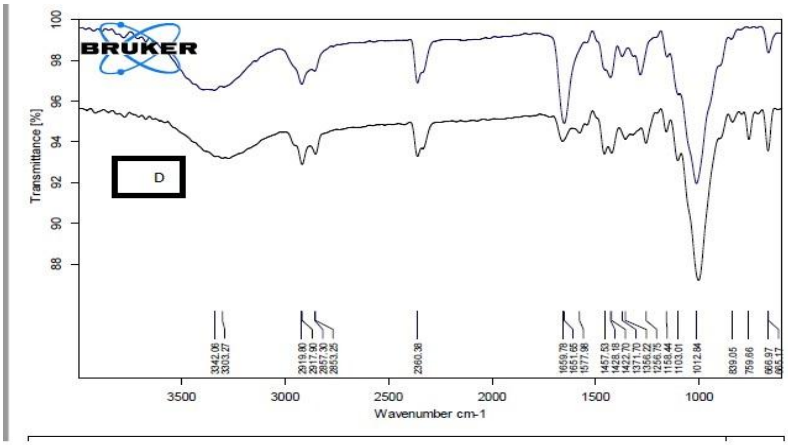

Figure IV: FT-IR Spectroscopy of Formulation F1 and FT-IR Spectroscopy of Xanthan Gum+ MCC+PVP+ Magnesium Stearate+ Talc.

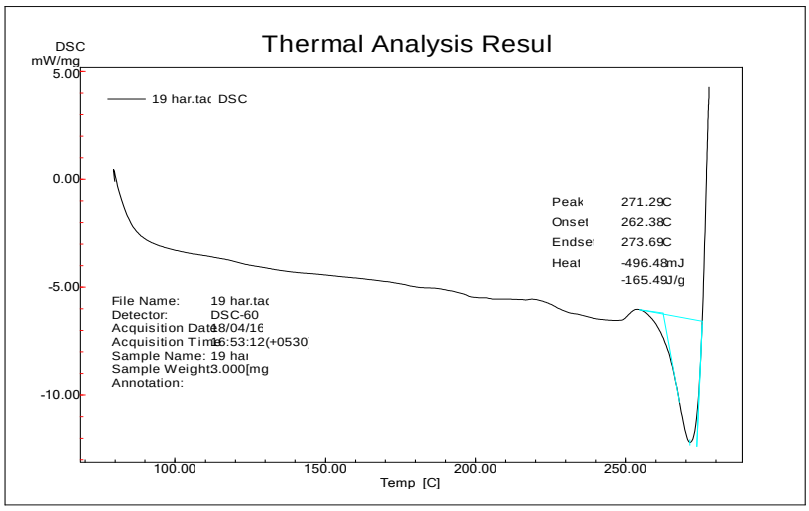

Figure V: DSC of Losartan potassium.

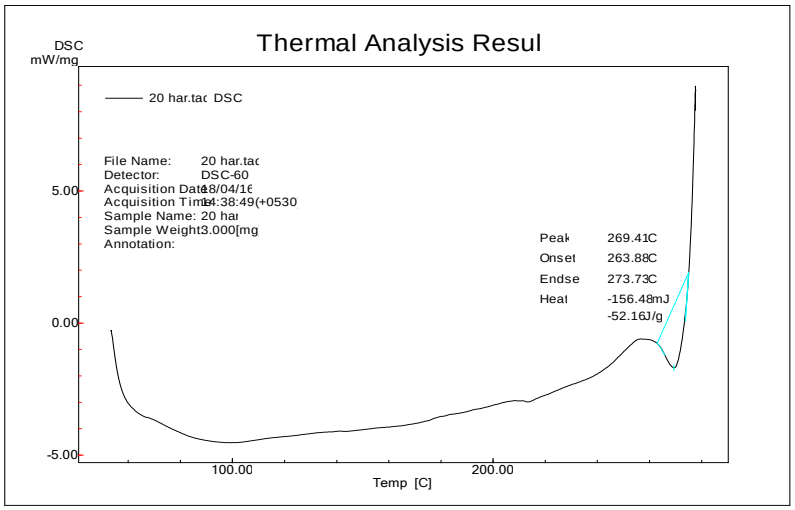

Figure VI: DSC of Losartan potassium + Xanthan gum.

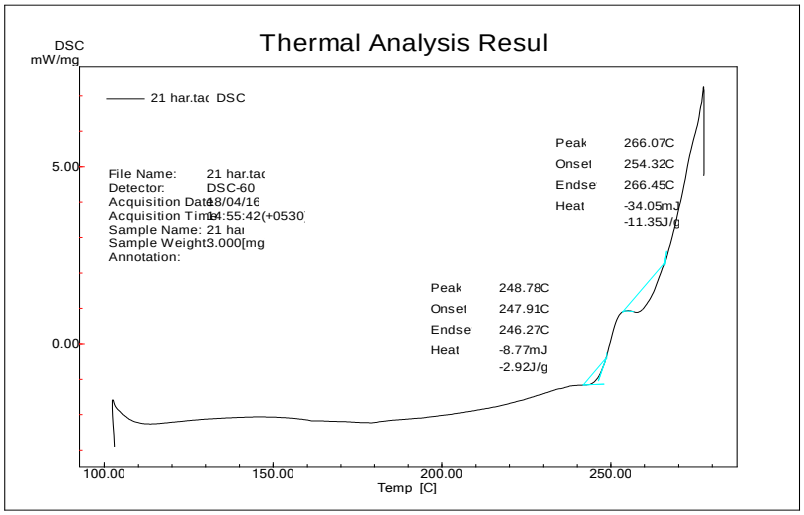

Figure VII: DSC of Losartan potassium + Guar gum.

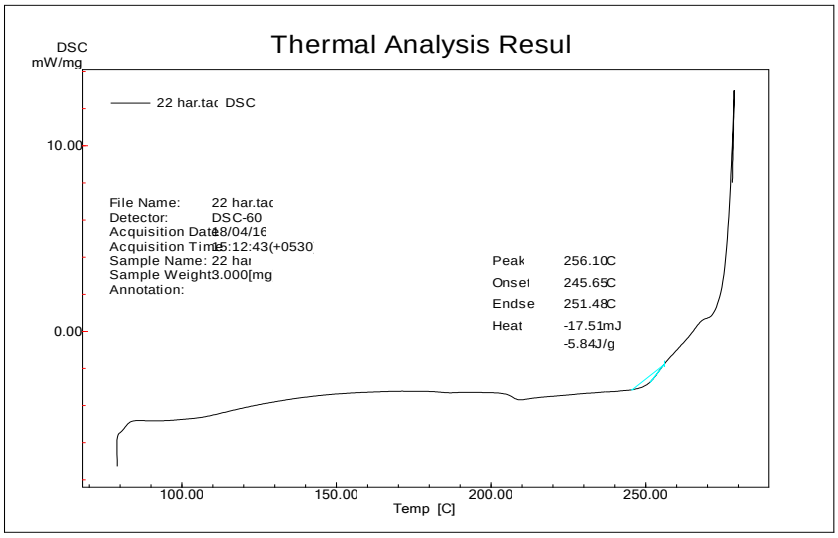

Figure VIII: DSC of Losartan potassium + Karaya gum.

Characterization of granular properties

Granules prepared for compression of matrix tablets were evaluated for their flow properties, the results were shown in Table III. Angle of repose was in the range 24.30° to 26.19°, which indicates excellent flow of the powder for all formulations. The bulk density of the powder formulation was in the range of 0.315 to 0.333 gm/cc, the tapped density was in the range of 0.348 to 0.365 gm/cc, which indicates that the powder was not bulky. The Carr's index was found to be in the range of 13.68 to 17.34 indicating compressibility of the tablet blend is good. These values indicate that the prepared granules exhibited good flow properties.[10]

Table II: Data for blend evaluation of formulation (F1 to F9).

Formulation	Bulk density	Tap density	Carr's index(%)	Hausner's Ratio	Angle of repose
F1	0.315	0.365	13.68	1.158	25.86
F2	0.306	0.370	17.34	1.209	25.70
F3	0.309	0.365	16.32	1.181	17.52
F4	0.333	0.361	8.88	1.084	21.52
F5	0.303	0.357	10.90	1.178	21.44
F6	0.277	0.326	14.81	1.176	24.30
F7	0.329	0.357	7.92	1.085	23.80
F8	0.319	0.348	13.68	1.090	26.19
F9	0.309	0.333	10.20	1.077	25.40

Physicochemical evaluation of matrix tablets

1. Physical parameters (hardness & friability)

Tablets with a weight of 250 mg were subjected to quality control tests such as hardness, thickness and friability (Table III). Hardness of the tablets was found to be in the range of 6.4

to 7.2 Kg/cm^2. It was within the range of monograph specification. Thicknesses of the tablets were found to be in the range of 4.0 to 4.08 mm. The friability of the tablets was found to be less than 1 % and it was within the range of standard specification.[11]

2. Weight variation and drug content

The average weights of the tablets were found to be within the prescribed official limits (IP). The drug content for all the batches was found to be in the range of 94.21% to 98.12% Table III.

Table III: Physical properties of tablet formulation (F-1 to F- 9) of losartan potassium sustained release matrix tablets.

Formulations	Weight (mg)	Hardness (Kg/cm^2)	Friability (%)	Thickness (mm)	Drug Contents (%)
F1	250	6.9	0.7	4.0	98.12
F2	250	7.2	0.51	4.08	97.20
F3	251	7.0	0.452	3.98	95.30
F4	250	7.1	0.4	4.04	94.64
F5	249	6.8	0.78	4.00	95.45
F6	250	7.0	0.39	3.98	96.00
F7	250	6.5	0.78	4.0	96.00
F8	250	6.4	0.73	4.0	96.27
F9	250	6.4	0.92	3.98	94.21

***In-Vitro* Release Study**

In-vitro release studies were carried out for all the formulations by using USP dissolution apparatus II employing basket at 100 rpm using 900ml of pH 6.4 phosphate buffer as dissolution medium. The results were evaluated for 24 hrs. The temperature was maintained at 37 ±0.5^{0}C throughout the experiment. 5 ml of sample was withdrawn at predetermined time interval replacing with equal quantity of same buffered solution. The samples were filtered through 0.45µm membrane. Take 1ml filtrate in 10ml volumetric flask and volume made up to mark with same buffered solution. Drug content in each sample was analyzed after suitable dilution by UV/Visible spectroscopy at 234nm.[12]

The results of dissolution studies of these tablets indicates decrease in drug release from the formulation F-1 to F-3 by using xanthan gum which gave better controlled release for 24 hrs. Reason for the above could be because of low permeable nature of xanthan gum.

Incorporation of MCC in the formulations F-8 to F-9 showed better retarded the release rate of drug compared to xanthan gum formulation and drug release was decreased with increased polymer concentration.

The present study revealed that the natural polymer of xanthan gum in formulation of F1 proved to be potential and economical sustained release retarding agent in the development of controlled release solid dosage forms.

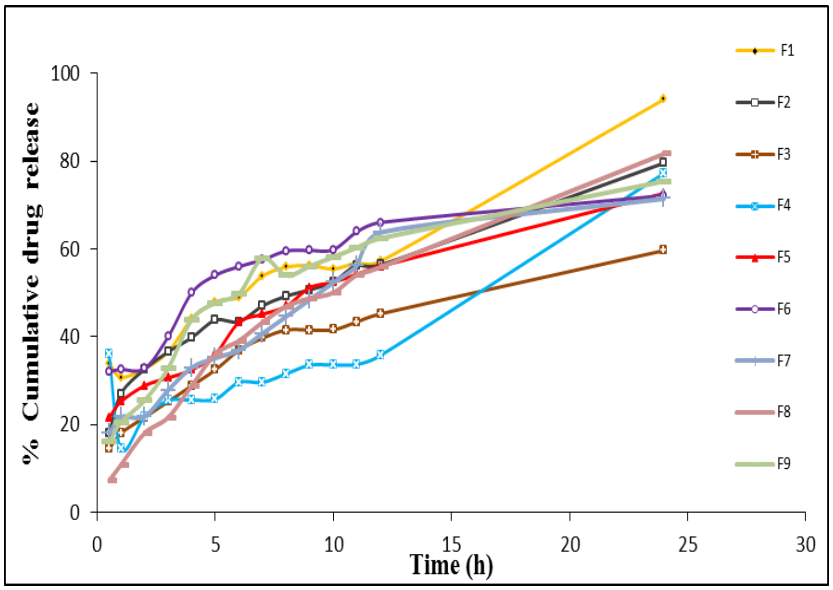

Figure IX:- *In-vitro* Dissolution Profile Release Study of Losartan Potassium Matrix Tablets (F1 to F9) Formulation.

Drug release kinetics

The release data was fitted to various mathematical models to evaluate the kinetic & mechanism of drug release. The kinetics data of all formation F1, F2, F6 & F8 could be best expressed by first order equation as the plots showed linearity (R^2: 0.6073 to R^2: 0.9002) then zero order release kinetics (R^2: 0.7012 to R^2:0.9587) of formulations F5 & F9. The n values obtained from korsmeyer peppas plots range from (1.638 to 1.743) indicates that mechanism of release from the formulations F1to F9 was Non- Fickian super case II.

Table IV: Release kinetic Data of the of the formulation from F1 to F9.

Formulations	Zero Order		First Order		Higuchi		Peppas	
	R^2	K_0	R^2	K_1	R^2	K	R^2	n
F1	0.7965	3.29	0.9587	0.026	0.929	16.21	0.359	1.971
F2	0.8194	2.73	0.9463	0.025	0.9721	18.23	0.4686	1.743
F3	0.7839	2.37	0.8871	0.016	0.9780	16.17	0.5054	1.638
F4	0.777	2.47	0.7946	0.021	0.4701	15.18	0.322	1.555
F5	0.7943	2.84	0.7846	0.052	0.9717	20.10	0.4335	1.712
F6	0.6073	2.75	0.7610	0.023	0.8845	27.88	0.354	1.798
F7	0.8202	3.02	0.920	0.023	0.9702	18.58	0.4993	1.695
F8	0.9002	3.53	0.993	0.069	0.9902	20.71	0.7247	1.716
F9	0.7305	3.17	0.060	0.071	0.9552	21.40	0.5268	1.778

CONCLUSION

Matrix tablet of losartan can be prepared by wet granulation method using polymers like Guar gum, Xanthan gum and karaya gum in different ratios.

The prepared tablets were evaluated for hardness, friability, drug content, Fourier transform infrared spectroscopy, Differential scanning calorimeter, and *in-vitro* drug release. All prepared tablets formulations were found to be good without capping and chipping. In all the formulations 8% PVP solution in isopropyl alcohol was used as binder which showed acceptable hardness of tablets. IR spectroscopy studies and DSC studies indicated that there are no drug-excipients interactions. Formulations of F1, had good strength and ability to sustained release of the drug from the matrix over 24 hrs period.

Among all the nine formulations F1 found to be optimized formulation in this present work.

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