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DESIGN AND DEVELOPMENT OF CONTROLLED RELEASE TABLET OF LOSARTAN POTASSIUM

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ABSTRACT:
The goal of the study was to formulate controlled release matrix tablets of losartan potassium by using a combination of HPMCK100M, eudragit L-100 and eudragit S-100. Losartan potassium is used in the treatment of hypertension. It has a short half life(2 hrs). Losartan potassium 50mg controlled release matrices were prepared by direct compression method and evaluated for thickness, hardness, weight variation, friability, drug content and *in-vitro* release of drug. *In-vitro* drug release was carried out using USP type II apparatus at 50 rpm in 900ml of dissolution media for 12 hrs. Mean dissolution time is used to evaluate drug release rate from a dosage form and indicates the drug release retarding efficiency of polymer. Various kinetics model were applied to the dissolution profile to determine the drug release kinetics. All the physical characteristics evaluated for the tablets were obtained to be within the acceptable limits. The release profile of optimized formulation of losartan potassium were close to zero order release pattern. Irrespective of the polymer type and its concentration, the prepared optimized matrix tablets showed non fickian (anomalous) release. Finally it was clear that HPMCK100M, eudragit L-100 and eudragit S-100 are good candidates for preparing controlled release matrix tablets of losartan potassium.
Keywords: Hypertension, *In-Vitro* release, Controlled release, Kinetics

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INTRODUCTION

The expenditure and difficulties included in marketing new drug delivery system have increased so greater research has been focused on fabrication of controlled release drug delivery system. The conventional drug delivery systems like as tablet, capsules, suspensions, ointments, liquids and aerosols are widely used, mainly conventional drug are effective but some drugs are unstable, toxic, narrow therapeutic ranges. To overcome these problems controlled drug delivery system were introduced in past years.[1-4] The objectives of fabrication of controlled release drug delivery system is to decrease the dosing frequency of drug, reduce the dose and administering the uniform drug delivery, so controlled release formulation is a dosage form that release the drug for predetermined rate for a specific time period. It is assist good control of plasma drug level. The hydrophilic polymers are widely used in fabrication of controlled release formulation. The ideal characteristics of dosage form is to assist proper amount of drug at specific time period, it is target oriented drug delivery system. In recent years empirical and technical advancement have been made in the design and fabrication of rate controlled drug delivery system by combat physiological adversities, such as short gastric residence time and unpredictable gastric emptying times.[5-7]

MATERIALS AND METHOD

Materials

Losartan potassium was obtained as a gift sample from XL laboratories pvt. ltd. bhiwadi. The eudragit L-100 and eudragit S-100 were obtained as gift samples from evonik. All polymers and chemicals were of analytical grade and used.

Preparation of matrix tablet

The matrix tablets containing losartan potassium was prepared by a direct compression process. HPMC

K100M, eudragit L 100 and eudragit S 100 were used as swellable polymers which control drug release. The controlled release tablet formulations consisted of a drug and polymer were prepared in different ratios. Microcrystalline cellulose was added as diluent at different proportions to the matrix tablets to achieve uniform weight. The drug, polymers and diluent were screened through 45 sieves and pre blended in a lab scale. The lubricant such as magnesium stearate in the concentration of 2 % was added and the blend was mixed again prior to compression. The drug mixture were directly compressed by using rotary compression machine with a constant compression force. The excipients were taken according to drug weight. The different forms of tablets compressed together with their compositions are given in following table 1.

Table 1: Compositions of various matrix tablet formulation of losartan potassium

Batch	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg
HPMC K100M	20%	20%	20%	20%	20%	20%	30%	30%	30%	30%	30%	30%
EL-100	10%	20%	30%	-	-	-	10%	20%	30%	-	-	-
ES-100	-	-	-	10%	20%	30%	-	-	-	10%	20%	30%
MS	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%
MCC	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

CHARACTERIZATION OF DRUG AND EXCIPIENTS

Fourier transforms infra red spectroscopy (FTIR)[8-10]

The primary objective of this investigation was to identify a stable storage condition for drug in solid state and identification of compatible excipients for formulation. The FTIR spectra of losartan potassium was done and given in figure no.1.

Differential scanning calorimetry (DSC)[11,12]

DSC is a thermo analytical technique in which the difference in the amount of heat required to increase the temperature of a reference and sample are measured as a function of temperature. Both the sample and reference are maintained at nearly the same temperature throughout the study. Mainly, the temperature program for a DSC analysis is designed such that the sample holder temperature increases linearly as a function of time. The DSC analysis of losartan potassium was given in figure no. 2

Pre compression characterization[13-17]

The tapped density, bulk density, hausner's ratio, carr's index and angle of repose is the pre compression characterisation of controlled release matrix tablet.

Angle of repose

The frictional force in the powder can be measured by the angle of repose. Angle of repose was obtained by fixed funnel method. Angle of repose can be calculated by using following formula:

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

θ = Angle of repose, h = Height of heap in cm, r = Radius of heap in cm

Bulk density

Weigh accurately 10 gm of drug and transfer in 50 ml measuring cylinder. The level of powder carefully record unsettled volume. Calculate bulk density in gm/ml by following formula.

Bulk Density = Weight of Powder/Bulk Volume

Tapped density

Weight accurately 10 gm of drug and transfer in 50 ml graduated cylinder. Then after 100 tapping the volume of powder in measured carefully. Calculate tapped density in gm/ml by following formula.

Tapped Density = Weight of powder / Tapped volume

Carr's index

The Carr's/compressibility index are measurement for find out tendency of powders to be compressed. Carr's/compressibility index can be calculated as follows: %Carr's Index

= (Tapped Density – Bulk Density) / Tapped Density $\times$ 100

Hausner's ratio

It is correlated to the flow ability of powder or granular material and it was calculated by following formula.

Hausner's Ratio = Tapped Density / Bulk Density

Post compression characterization[18-29]

The thickness, weight, friability and hardness are the post compression characterisation of controlled release matrix tablet.

Thickness

The diameter and thickness of the tablets of all of the formulations were determined with vernier calliper.

Tablet weight variation

Every individual tablet in a batch should be in uniform weight and weight variation within permissible limits. Weight control is based on a sample of 20 tablets. Twenty matrix tablets were randomly selected and accurately weighed using an electronic balance.

Hardness

The hardness of the tablets was determined using a hardness testing apparatus (Monsanto Type). A tablet hardness of about 4-6 kg/cm^{2}is considered adequate for mechanical stability.

Friability

The friability of the tablets was measured in a Roche friabilator. Tablets of a known weight (W0) or a sample of 10 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given

in equation as below. The limit of friability is 1% w/w and weight loss not more than of this limit.

% Friability = (W0 −W)/W0 ×100

Where, Wo is intial weight of tablet & W is final weight of tablet

Drug content

10 tablets were weighed and powdered then powder equivalent to 10 mg of drug was taken and dissolved in 0.1N HCl and made the volume up to 10 mL. After that 10 ppm solution was prepared and absorbance was measured at 250.2 nm by using SHIMADZU UV-1800 spectrophotometer.

In vitro drug release characteristics

Drug release from the matrix tablets was assessed by dissolution test using USP type II dissolution apparatus equipped with paddles at 37°C ±0.5°C with an rpm of 50. The test was performed using 900 ml of 0.1 N HCl (for 2hrs) and phosphate buffered solution, pH 6.8 (up to 12 hrs) as dissolution media. After that 5 ml samples were withdrawn at regular time intervals, filtered and assayed spectrophotometrically at 250.2 nm.

Drug release kinetics[30-40]

The release kinetic was studied by various kinetic models as first order plot, zero order plot, korsmeyer-peppas and higuchi plot. In order to identify a particular release mechanism, experimental data of statistical significance are compared to a solution of the theoretical model. It is clearly that only a combination of precise and accurate data with models accurately depicting the physical situation will provide an insight into the actual mechanism of release. To examine the mechanism for the drug release and drug release rate kinetics of the dosage form, the data obtained was fitted into first order, zero order, korsemeyer-peppas, higuchi matrix,. The comparing the R^2 values find out from the relese equations, the best-fit model was obtained.

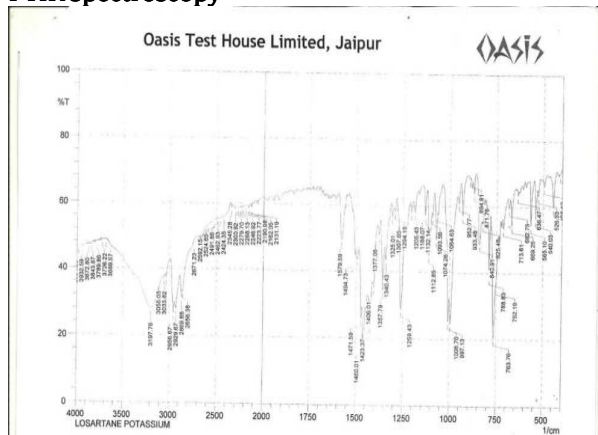## RESULT AND DISCUSSION

FTIR spectroscopy

Figure 1: IR spectra of losartan potassium

Table 2: IR interpretation of drug (losartan potassium)

S.no	Functional group	Range	Observed peak
1	C- N (Streching)	1375-1275	1357.79
2	C=C (Aromatic)	1450	1460.01
3	C-H (Aromatic)	840-800	840.91
4	C-Cl	800-600	763.76
5	N-H (Streching)	3180	3197.76

The above table shows the IR interpretation of losartan potassium. According to this interpretation the observed peak of drug was found in the range.
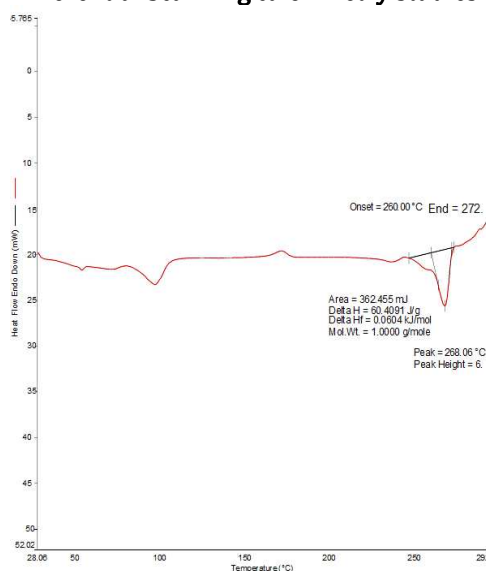
Differential Scanning calorimetry studies

Figure 2: DSC analysis of losartan potassium

On the basis of DSC analysis the melting point of losartan potassium was found to be 268.6 ^{0}C.

Pre compression characterization

The bulk density, tapped density, carr's index, hausner's ratio and angle of repose of floating tablet are given in table no. 3.

Table 3: Pre compression characterisation

Batch	Bulk density (gm/ml)±SD	Tapped density (gm/ml)±SD	Carr's Index±SD	Hausner's ratio±SD	Angle of repose±SD
F1	0.71±0.020	0.81±0.015	12.34±1.87	1.14±0.026	23.74±1.50
F2	0.70±0.015	0.78±0.025	10.25±2.30	1.11±0.040	23.74±0.72
F3	0.68±0.015	0.76±0.036	10.52±2.17	1.11±0.040	22.29±1.46
F4	0.69±0.026	0.80±0.035	13.75±1.61	1.15±0.030	25.17±1.42
F5	0.68±0.030	0.81±0.026	16.04±1.86	1.19±0.025	25.64±1.17
F6	0.71±0.015	0.83±0.015	14.85±1.14	1.16±0.041	26.56±1.41
F7	0.68±0.015	0.80±0.015	15±1.11	1.17±0.030	27.47±1.36
F8	0.70±0.015	0.80±0.015	12.5±1.25	1.14±0.035	27.47±0.92
F9	0.71±0.015	0.80±0.020	11.25±1.13	1.12±0.025	22.29±1.46
F10	0.71±0.036	0.83±0.030	14.45±1.61	1.16±0.020	23.26±2.23
F11	0.74±0.036	0.85±0.051	12.94±1.60	1.14±0.015	24.70±1.64
F12	0.74±0.035	0.86±0.050	13.95±1.36	1.16±0.026	25.17±1.54

For each fabricated formulation, mixtures of drug and excipients were prepared and characterised for

micromeritic properties and were tabulated in table no 3.

These parameters were show that the prepared mixtures of all formulation have well to excellent flow property range. The angle of repose is identifying to be determining of flow ability and the angle of repose of all formulation was shows excellent to good flow.

Post compression characterization

All batches of formulation were evaluated for various physical parameters and results tabulated in table no. 4

Table 4: Post compression characterisation

Batch	Thickness±SD (mm)	Weight±SD (mg)	Friability±SD (%)	Hardness (kg/cm²)
F1	4.17±0.005	195.6±1.55	1.12±0.213	4.4
F2	4.15±0.005	195.4±1.58	0.66±0.076	4.2
F3	4.16±0.005	194.8±1.50	0.77±0.077	4.4
F4	4.16±0.010	197.1±1.16	0.65±0.083	4.4
F5	4.17±0.005	198.2±1.70	0.70±0.055	4.4
F6	4.16±0.010	198.4±1.15	0.60±0.111	4.6
F7	4.15±0.010	197.8±2.20	0.55±0.113	4.2
F8	4.17±0.005	194±1.90	0.61±0.092	4.4
F9	4.17±0.010	195.9±1.51	0.66±0.081	3.8
F10	4.17±0.010	194.8±1.90	0.71±0.050	4
F11	4.16±0.005	195.5±1.73	0.40±0.137	4.2
F12	4.16±0.005	195.4±1.70	0.56±0.109	4

All batches of formulation were evaluated for various physical parameters and tabulated in table no 4. The weight variation of each formulation was found in range. According to thickness of all formulation it was found in uniform size. The hardness of tablet was within range of 3.8 to 4.6 kg/cm² and friability found in less than 1%. These all parameters were satisfactory as specified in the pharmacopoeia.

In-vitro drug release study

The % CDR and drug content are given in table no. 5 and the *in-vitro* drug release profiles of F1-F12 are shown in fig. 3 and 4
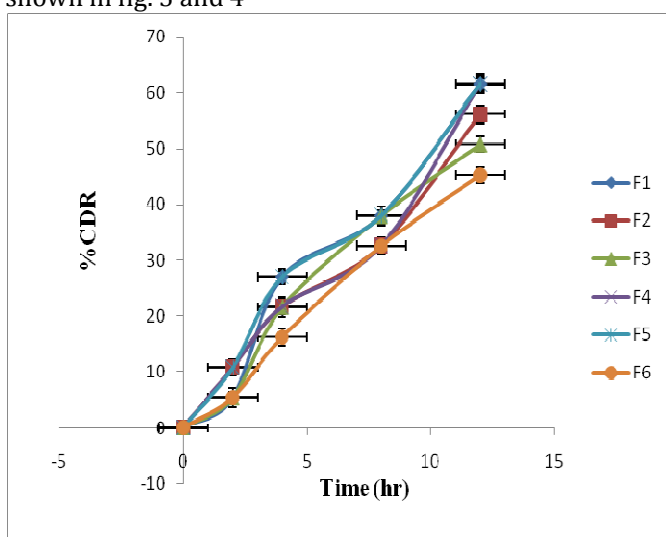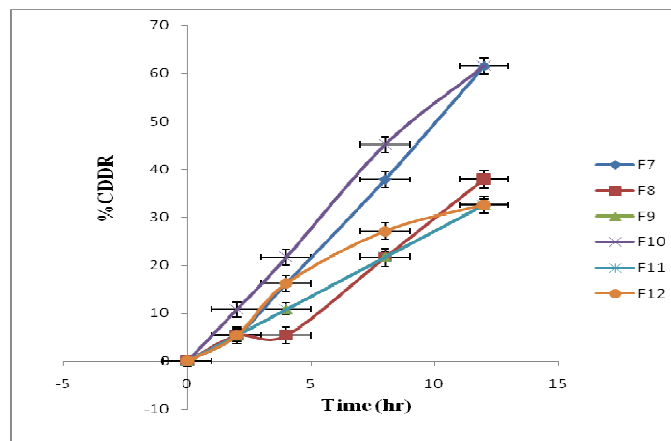

Figure 3: Drug release curve (F1-F6)

Figure 4: Drug release curve (F7-F12)

Table 5: Drug release and drug content data (F1 to F12)

Formulation	%CDR (12hr)±SD	Drug content±SD
F1	61.56±1.39	94.8±1.08
F2	56.16±1.25	95.4±2.01
F3	50.74±1.18	97.5±1.41
F4	61.56±1.11	96.3±1.35
F5	61.6±1.12	95.7±1.83
F6	45.28±1.03	94.8±1.87
F7	61.5±1.40	102.1±1.70
F8	37.96±1.51	103.3±1.61
F9	32.60±1.35	100.6±1.35
F10	61.62±1.65	98.4±1.86
F11	32.60±1.36	96.9±1.65
F12	32.64±1.20	95.1±1.41

All formulation of losartan potassium matrix tablet was manufacture under same condition to except the processing variables. All matrix tablet of losartan potassium were containing different % of HPMC K100M, eudragit L-100 and eudragit S-100. HPMC H100M retains its drug release property due to its gelling property. Drug release for 12 hrs of all formulation from F1 to F12 were shown in figure no 3 &4.

In formulation of F1 to F3, the mixture of HPMC K100M and eudragit L-100 were 20% and 10-30% respectively. The release of F1, F2 and F3 are 61.56%, 56.16% and 50.74% respectively. Eudragit L-100 controls the release of drug and the eudragit L-100 concentration was increased thus the release in formulation F1 to F3 was varied. In the formulation F4 to F6, the eudragit L-100 was replaced by eudragit S-100 and HPMC K100M 20 % was used and the drug release of this formulation was 61.56%, 61.6% and 45.28% respectively.

In the formulation F7 to F9, the mixture of HPMC K100M (30%) and eudragit L-100 (10%-30%) was used. Then the release of F7, F8 and F9 was obtained 61.5%, 37.96% and 32.60% respectively for 12 hrs. In formulation F8 and F9, the release is very less due to increased in concentration of HPMC K100M. In

formulation F10 to F12, again the eudragit L-100 was replaced by eudragit S-100 and the release was 32.60 to 61.62 % obtained.

The drug content in each formulation was found in a uniform range and the range was 94.80% to 103.30%. This range is uniform and satisfactory the specifications of pharmacopoeia. The individual drug content of each formulation was shown in above table.

According to this whole discussion, the best formulations were found to be F3 and F6. F3 is best because of its 97.5 % drug content and 50.74 % drug release for 12 hrs. F6 is having 94.8 % drug content and 45.28 % drug release. Finally the optimized formulation F3 was obtained.

Drug release kinetics

Data of drug release kinetics is shown in table no.6.

Table 6: Data of release kinetics

Batch	Zero order		First order		Higuchi		Korsmeyer peppas	
	R^2	$K_0(-)$ $(1/S)$	R^2	$K_1(-)$ $M/L.S$	R^2	K_H	R^2	n
F1	0.970	5.120	0.120	0.177	0.887	17.79	0.936	0.72
F2	0.984	4.445	0.237	0.191	0.908	16.23	0.878	0.71
F3	0.978	4.397	0.247	0.195	0.911	14.66	0.945	0.79
F4	0.974	4.840	0.214	0.181	0.876	17.79	0.886	0.69
F5	0.980	4.938	0.215	0.179	0.922	17.80	0.877	0.70
F6	0.993	3.902	0.261	0.202	0.903	13.08	0.957	0.82
F7	0.992	5.254	0.202	0.177	0.851	17.77	0.976	0.72
F8	0.960	3.178	0.285	0.216	0.794	10.97	0.937	0.85
F9	1.000	2.718	0.300	0.223	0.906	9.42	0.953	0.90
F10	0.995	5.225	0.204	0.175	0.920	17.80	0.901	0.71
F11	1.000	2.718	0.300	0.223	0.906	9.42	0.953	0.90
F12	0.956	2.813	0.301	0.221	0.939	9.43	0.927	1.04

The data were treated according to zero order, first order, higuchi model and korsmeyer peppas pattern for kinetics of drug release during dissolution process. The

regression equation of optimized formulation F3 was find out according to zero order equation 0.978, first order equation 0.247 and higuchi model 0.911. These values clearly indicate that the formulation showed to be best expressed by zero order kinetics. It was follow the zero order release pattern.

The dissolution data was also fitted to the well known exponential equation (Koresmeyer peppas equation), which is often used to describe the drug release behavior from polymeric system. According to this model a value of n<0.45 indicates fickian release, n>0.45 but n<0.89 for non-fickian (anomalus) release and n>0.89 indicates super case II generally refers to the erosion of the polymeric chain and anomalus transport (non-fickian) refers to a combination of both diffusion and erosion controlled drug release. The n value described in table no 6. On the basis of n value the best formulation (F3) exhibited non fickian type drug release

CONCLUSION

Losartan potassium controlled release matrix tablets were successfully formulated using the mixture of HPMCK100M with eudragit L-100 and eudragit S-100 for delivery of drug over an extended period of time. This study demonstrates that the mixture of HPMCK100M with eudragit L-100 and eudragit S-100 led to prolonged release of drug. Ideal features of this system are the potential for generating constant drug release and maintain the plasma drug level. These controlled release matrix tablets are improved patient compliance and therapeutic efficacy. From this study, it is possible to develop oral controlled release matrix tablets containing losartan potassium for the management of hypertension.

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