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Formulation and Evaluation of Hydrogel Based Oral Controlled Drug Delivery System for Antihypertensive Drug

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Abstract

The objective of the study was to develop controlled release matrix tablets of Losartan potassium by simplex lattice design and evaluating the relationship and influence of different content levels of HPMC, Eudragit RSPO, Eudragit RLPO and ethylcellulose, in order to achieve a zero-order release of Losartan potassium. Tablets were prepared by wet granulation process. *In-vitro* drug release study revealed that HPMC causes initial burst release of drug hence combining HPMC with Eudragit sustained the action for 8hrs (95.92±0.57% release). Fitting the *in-vitro* drug release data to Korsmeyer equation indicated that diffusion along with erosion could be the mechanism for drug release. In conclusion, results suggest that drug release kinetics from these formulations corresponded best to zero-order kinetics. Compared to conventional tablets, release of model drug from these HPMC matrix tablets was prolonged, leading to achieve an effective therapy with low dosage of the drug, to reduce the frequency of medication.

Keywords: Losartan potassium, Hydrogel, Eudragit, Matrix tablet, Simplex lattice design.

INTRODUCTION

High patient compliance and flexibility in designing dosage forms attracted the oral drug delivery systems to be the most convenient mode of drug administration when compared to other dosage forms. Of these, matrix systems have gained widespread importance in controlled drug delivery due to cost-effective manufacturing technology. Matrix drug delivery systems are of two types: diffusion/swellable systems and dissolution systems. In diffusion systems, drug release is mainly governed by the hydration of matrices followed by diffusion of the drug molecules from the hydrated layer to the surrounding bulk solution, and sometimes, partially by erosion/dissolution. Cellulose ethers, Eudragits and Carbopols are the best examples of such systems. With dissolution systems, drug release is mainly due to dissolution/erosion of the matrix and hence, achievement of constant drug delivery rate is easier by this systems.[1]

Hydrophilic matrix tablets are among the most popular delivery systems for oral controlled-release dosage forms. These hydrophilic matrices are widely accepted because of their biopharmaceutical and pharmacokinetics advantages over conventional dosage forms. This is largely because they offer precise modulation of drug release as a result of hydration of the constituent polymer(s), flexibility to obtain desired drug release profiles, cost effectiveness, patient compliance, providing a constant, prolonged, and uniform therapeutic effect and broad Food and Drug Administration (FDA) acceptability. The swelling rate and erosion of HPMC-based matrix tablet in aqueous media are very crucial in terms of achieving the desired release profiles, and are affected by parameters such as the physicochemical properties of the polymer and the drug, processing conditions, the testing medium used and the formulation composition.

Losartan potassium (LP) is a potent, highly specific angiotensin II type 1 (AT1) receptor antagonist with antihypertensive activity. It is readily absorbed from the gastrointestinal tract with oral bioavailability of about 33% and a plasma elimination half-life ranging from 1.5 to 2.5 h. Administration of LP in a controlled release dosage form with an extended release over 8 h, would be more desirable as these characteristics would allow a rapid onset followed by protracted anti-hypertensive effects by maintaining the plasma

concentrations of the drug well above the therapeutic concentration.

The current study aimed at developing and optimizing an oral sustained release dosage form of LP using computer-aided optimization technique i.e. simplex lattice statistical design with constraints on cumulative percentage release of drug after 8hrs(95.92±0.57%). The Independent variables for the present study were: amount of Eudragit RSPO(A), amount of Eudragit RLPO(B), amount of HPMC 15cps(C), amount of Ethyl cellulose(D). The dependent variables studied were the1 hour drug release(R_1), 4 hr drug release(R_2), 8 hr drug release(R_3) and $T_{50\%}$ -Time required for 50% drug release(R_4).[2]

MATERIALS AND METHODS

Losartan potassium was provided ex gratia by KAPL, Bangalore. HPMC 15cps and Ethyl cellulose were supplied by S.D. Fine chemicals Ltd, India. Eudragit RSPO and Eudragit RLPO were received as a gift sample from Evonik Degussa India Pvt. Ltd., Mumbai.

Preparation of Controlled release matrix tablets

The tablets were prepared by wet granulation method. The different stages involved in the process are:

All the raw materials were passed through sieve no. 60 and weighed accurately as per the formulae. Losartan Potassium, Polymers (HPMC 15cps, ERSPO, ERLPO and Ethyl cellulose), PVP, Aerosil and Lactose were mixed thoroughly by trituration in mortar and pestle to get uniform mix. The thoroughly mixed powder was kneaded for 10 minutes with Isopropyl alcohol solution till it forms dough mass. This mass was passed through sieve no. 20 to form granules. The granules were spread on the tray and kept for drying at 50˚C for 30min using hot air oven. The dried granules were passed through the sieve no. 40 to get fines and uniform sized granules and blended with magnesium stearate. The precompression parameters were studied. The controlled release matrix tablets were prepared using 8mm biconcave round punch in 10 station rotary compression machine.

Working formula is given in table 1 & 2.

EVALUATION PARAMETERS

Evaluated for both precompression and post compression parameters, they includes -

Bulk density, Tapped density, Carr's Index, Angle of Repose, Hardness, Friability, Weight variation test, Thickness.[3]

Drug Content:

Five tablets were powdered in a mortar. Weighed accurately the quantity equivalent to 50mg of Losartan potassium and transferred to a 100ml volumetric flask containing few ml of distilled water and mixed well, made up the volume up to 100ml with distilled water. Pipette out 10 ml from the stock solution into another 100 ml volumetric flask and made up the volume with distilled water. From the above solution withdrew the aliquots of 2ml, 2.4ml and 3.2ml (as per Beer's range 2-20 µg/ml) and the volume was made up to 10 ml with distilled water. The absorbance was measured at 236 nm using distilled water as blank.

In-vitro Release studies:

The *in-vitro* dissolution profile of the designed formulations of controlled release tablets was carried out using USP type II apparatus under conditions specified (temp 37± 0.5^{o}C, 75rpm). Tablets were subjected to dissolution for first two hrs in 0.1 N HCl, followed by pH 7.4 phosphate buffer for next six hrs till the end of dissolution studies. From the dissolution medium withdrawn and replaced 1 ml for every 1 hour, for the solution withdrawn volume was made up to 10 ml with distilled water and absorbance was measured at 236 nm using distilled water as blank. Dissolution profiles of the formulations were analyzed by plotting drug release versus time plot.

CURVE FITTING ANALYSIS [4, 5, 6]

Dissolution profiles of the formulations were fitted to various mathematical models for describing the release mechanism; Korsmeyer-Peppas, Zero-order and Higuchi release models.

STABILITY STUDIES: [7]

The optimized formulations were packed in amber colored bottles, which were tightly plugged with cotton and capped. They were then stored at 45^0C/75% RH and 30^0 C/65% RH for 2 months. The samples were withdrawn at 15 days intervals and checked for physical changes, drug content and *in vitro* drug release studies.

Table 1: Working Formula: F1 – F9 by wet granulation method

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	50	50	50	50	50	50	50	50	50
HPMC 15cps	0	100	50	12.5	12.5	0	50	50	62.5
ERSPO	100	0	50	62.5	12.5	0	0	0	12.5
ERLPO	0	0	0	12.5	12.5	0	50	50	12.5
Ethyl cellulose	0	0	0	12.5	62.5	100	0	50	12.5
PVP	5	5	5	5	5	5	5	5	5
Mg stearate	4	4	4	4	4	4	4	4	4
Aerosil	1	1	1	1	1	1	1	1	1
Lactose	40	40	40	40	40	40	40	40	40
Total Wt	200	200	200	200	200	200	200	200	200

The above quantities are expressed in terms of mg per tablet

Table 2: Working Formula: F10 – F17 by wet granulation method

Formulation code	F10	F11	F12	F13	F14	F15	F16	F17
Drug	50	50	50	50	50	50	50	50
HPMC 15cps	0	12.5	0	25	0	0	0	0
ERSPO	0	12.5	100	25	50	0	0	50
ERLPO	100	62.5	0	25	50	50	100	0
Ethyl cellulose	0	12.5	0	25	0	50	0	50
PVP	5	5	5	5	5	5	5	5
Mg stearate	4	4	4	4	4	4	4	4
Aerosil	1	1	1	1	1	1	1	1
Lactose	40	40	40	40	40	40	40	40
Total Wt	200	200	200	200	200	200	200	200

The above quantities are expressed in terms of mg per tablet

RESULTS & DISCUSSION:

Compatibility Studies

In order to investigate the possible interactions between Losartan potassium and distinct polymers and/or diluents, FT-IR and DSC studies were carried out.

FT-IR results proved that the drug was found to be compatible with excipients as wave numbers are almost similar for pure drug and also drug excipients mixture.

DSC studies indicate that chosen excipients for the formulation were found to be compatible with the active ingredient as the melting endothermic peaks are in the range of 170-240^{o}C which is same as the melting point of Losartan potassium

Evaluation of pre-compression parameters:

Based on the results of pre-compression tests, all the formulations showed angle of repose ranging from 22.21^{o} ± 0.84 to 27.5^{o} ± 0.94 indicating a good flow property (Table 3) and Carr's index ranging from 10.53 ± 0.01 to 23.22 ± 0.22%, indicating compressibility of the granules is fairly passable (Table 3).

Evaluation of post-compression parameters:

The tablets of different formulations were subjected to various evaluation tests, such as thickness, uniformity of weight, hardness, friability, and drug content and the result are shown in Table 4. All the formulations showed uniform thickness. The thickness and hardness of the tablets were in the range of 4.19 ± 0.01 to 4.22 ± 0.01 mm and 8.66 ± 0.40 to 9.33 ± 0.40 kg/cm^2 respectively. The percentage friability was found to be less than 1% indicating that the friability is within the prescribed limits. In weight variation test, the average percentage deviation of all tablet formulations was found to be within the limit, and hence they met the test as per official requirements and were found to contain 45.32 ± 0.66 to 54.17±0.47 mg of the labeled amount of Losartan potassium indicating uniformity of drug content.

Table 3: Pre-compression parameters of matrix tablets

Formula	Parameters			
	Bulk density (g/cc)	Tapped density (g/cc)	Carr's Index (%)	Angle of repose (˚)
F1	0.46±0.00	0.53±0.00	14.16±0.03	26.79±1.15
F2	0.41±0.00	0.49±0.00	18.54±0.03	25.86±0.22
F3	0.47±0.00	0.52±0.00	10.54±0.01	27.06±1.01
F4	0.46±0.00	0.56±0.00	10.53±0.01	22.88±1.08
F5	0.38±0.00	0.45±0.00	14.85±0.04	26.37±1.17
F6	0.32±0.00	0.38±0.00	16.13±0.05	27.5±0.94
F7	0.42±0.00	0.48±0.00	12.59±0.10	23.12±1.32
F8	0.37±0.00	0.44±0.00	14.94±0.05	22.21±0.84
F9	0.42±0.00	0.50±0.00	16.26±0.05	25.82±0.74
F10	0.42±0.00	0.51±0.00	17.33±0.32	25.68±1.46
F11	0.44±0.00	0.52±0.00	15.17±0.16	26.27±0.81
F12	0.38±0.00	0.45±0.00	15.42±0.12	23.87±1.67
F13	0.40±0.00	0.48±0.00	16.58±0.09	23.49±0.00
F14	0.41±0.00	0.52±0.00	20.25±0.25	23.57±0.87
F15	0.43±0.0	0.56±0.00	23.22±0.22	23.72±0.23
F16	0.46±0.00	0.52±0.00	10.76±0.14	23.34±1.10
F17	0.43±0.00	0.51±0.00	17.23±0.15	25.35±0.73

Table 4: Post-compression parameters of matrix tablets

Formula	Parameters				
	Weight Variation (mg)	Drug Content (mg)	Hardness (kg/cm^2)	Thickness (mm)	% Friability
F1	200±1.048	45.37±0.77	9.33±0.40	4.19±0.02	0.18±0.00
F2	201±1.36	50.04±0.91	8.66±0.40	4.19±0.01	0.25±0.00
F3	199±0.92	48.03±0.16	9±0.00	4.19±0.01	0.39±0.00
F4	201±1.80	48.88±0.29	9.3±0.40	4.19±0.01	0.06±0.00
F5	201±1.07	45.32±0.66	8.66±0.40	4.19±0.00	0.19±0.00
F6	201±1.73	45.34±0.90	9.33±0.40	4.22±0.01	0.17±0.00
F7	201±1.61	46.26±1.00	9.33±0.40	4.20±0.01	0.16±0.00
F8	200±1.36	51.7±0.64	9.33±0.40	4.20±0.01	0.09±0.00
F9	199±1.07	48.8±0.80	8.66±0.40	4.2±0.02	0.15±0.04
F10	200±0.63	45.2±0.25	9.33±0.40	4.20±0.01	0.81±0.02
F11	201±1.62	44.81±0.25	9.33±0.40	4.21±0.00	0.06±0.00
F12	200±1.07	54.17±0.47	9.33±0.40	4.2±0.00	0.11±0.00
F13	199±1.16	47.25±0.87	8.66±0.40	4.21±0.01	0.05±0.00
F14	202±1.58	45.53±0.00	9±0.00	4.20±0.01	0.03±0.00
F15	202±1.46	45.16±0.41	9.33±0.40	4.19±0.01	0.12±0.00
F16	201±1.62	45.5±1.09	8.66±0.40	4.20±0.00	0.08±0.00
F17	199±1.07	47.91±0.31	9.33±0.40	4.20±0.01	0.17±0.00

***In-vitro* release:**

Tablets subjected for dissolution studies shown drug release at 1 hr was ranging between 17.58 ± 2.97 to 32.52 ± 0.30%. As the dissolution studies continued, the release from each dosage form showed an incremental release in sustained manner for a long time suggesting a sustained release pattern (Figure 1, 2 and 3). The release of the drug at 8 hr varied from 72.93 ± 0.58 to 100.71 ± 3.56 % indicating that the overall drug release from the dosage form depends upon the composition of tablet matrix which varies from one formula to another. From this study it may be concluded, that the independent variables included in the study were found to show significant variation for the response variables.

Figure 1: Dissolution profile for matrix tablets of Formulations F1 – F6

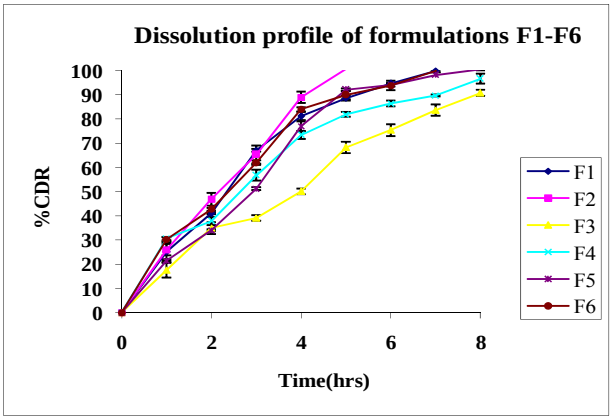


Figure 2: Dissolution profile for matrix tablets of Formulations F7 – F12

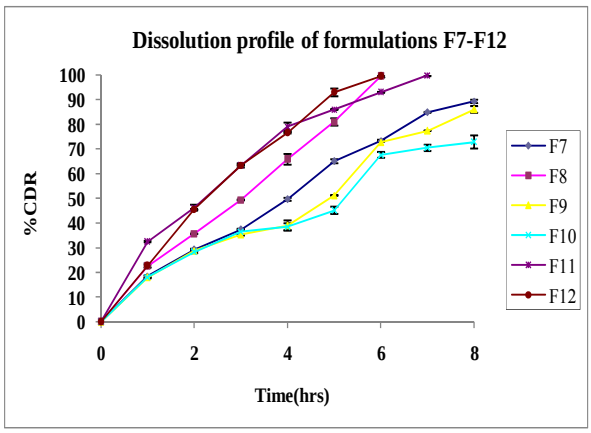
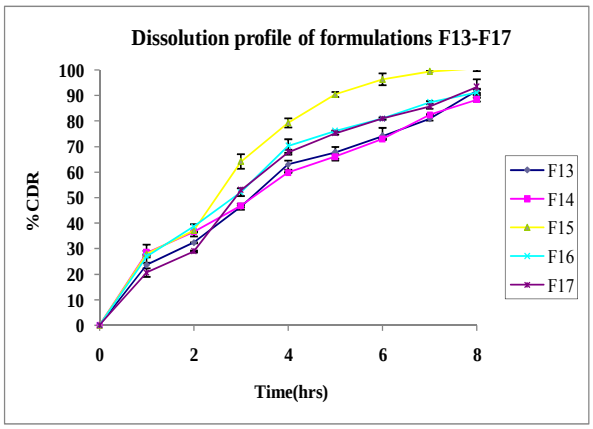


Figure 3: Dissolution profile for matrix tablets of Formulations F13 – F17



Curve fitting analysis:

To study the release kinetics from hydrogel-based matrix tablets, the release data were fitted to the well-known exponential equation (Korsmeyer– Peppas equation) and which is often used to describe the drug release behavior from polymeric systems when the mechanism is not well known or when more than one type of release phenomenon is involved.

Formulations F1, F2, F4, F5, F6, F10, F11, F12, F13, F14, F15, F16 and F17 exhibited anomalous (non Fickian transport) diffusion/polymer relaxation mechanism with a value ranging from 0.59 to 0.78. Whereas in case of formulations F3, F7 and F9 exhibited zero-order release profile as their 'n' values were very close to 0.89. Formulation F8 exhibited an 'n' value 0.96 indicating a super case II transport mechanism.

The results for optimized formulation with n value of 0.8776 confirmed that the formulation followed zero order kinetics indicating Losartan potassium release from controlled drug delivery system were by both diffusion and erosion mechanism.

Optimization:

The optimized formulation (Table 5) was prepared and evaluated for various pre-compression, post-compression parameters and various responses.

Table 5: Optimized formula for matrix tablets

Ingredients	Quantity per tablet (mg)
Losartan potassium	50
Eudragit RSPO	18
Eudragit RLPO	20
HPMC 15cps	59
Ethyl cellulose	3
PVP K-30	5
Aerosil	1
Magnesium Stearate	4
Lactose	40

Pre-compression parameters of optimized formulation having the Angle of repose in the range of 26.21°±1.08 indicating a good flow property and Carr's Index in the range of 14.90±0.09 % indicating compressibility of the granules is passable (Table 6).

Table 6: Pre-compression parameters of Optimized matrix tablets

Parameters	results
Bulk density(g/cc)	0.43±0.00
Tapped density(g/cc)	0.50±0.00
Carr's Index (%)	14.90±0.09
Angle of repose(°)	26.21±1.08

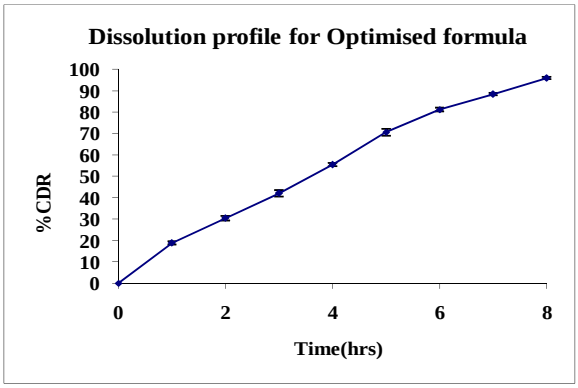
Table 7: Post-compression parameters of Optimized matrix tablets

Parameters	results
Weight variation(mg)	200.8±1.83
Drug content(mg)	52.68± 0.72
Hardness(kg/cm^2)	9.33±0.40
Thickness(mm)	4.20±0.01
% Friability	0.07±0.00

Post-compression parameters of optimized formulation having the weight variation in the range of 200.8±1.83 mg, thickness in the range of 4.20±0.01 mm, hardness in the range of 9.33±0.40 kg/cm^2 and friability 0.07%, which shows all the post-compression parameters, met the test as per official requirements (Table 7).

In case of *in-vitro* dissolution profile the optimized formulation showing drug release at 1 hr was 18.87±0.72, at 4hrs was 55.50±0 and release of the drug at 8 hr was 95.92±0.57 indicating that the overall drug release from the dosage form follows zero order drug release profile (Figure 4).

Figure 4: Dissolution profile for Optimized formula



STABILITY STUDIES:

The optimized formulation was found to be stable in terms of physical appearance, hardness and drug content after 2 months when it is stored under accelerated stability conditions as per ICH guidelines.

CONCLUSION:

The application of experimental design assisted in successfully developing an oral controlled release dosage form for Losartan potassium. Simplex Lattice design was used to study the effect of different formulation variables on the release profile to select optimized formulation by using numerical optimization technique.

Finally it can be concluded that preparation of controlled release drug delivery system is simplified by the use of simple, cost-effective, naturally occurring excipients. This method may be promising in the field of preparation of delayed release dosage form as the drug release profile is complying with USP tolerance.

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