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Once-Daily Sustained-Release Matrix Tablets of Losartan potassium: Formulation and In Vitro Evaluation

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Abstract- Objective of the present study was to develop hydrophilic polymer and hydrophobic polymer based matrix Losartan potassium sustained release tablet which can release the drug up to time of 24 hrs in predetermined rate. Formulation of Losartan potassium matrix tablet was prepared by the polymer combination in order to get required theoretical release profile. Influence of hydrophilic and hydrophobic polymer on Losartan potassium was studied. Formulated tablet were also characterized by physical and chemical parameters. In vitro release profile was check for 24 hrs to evaluate the SR matrix tablet of Losartan potassium. 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 hr. Administration of LP in a sustained release dosage would be more desirable for anti-hypertensive effects by maintaining the plasma concentrations of the drug well above the therapeutic concentration. From in vitro dissolution profile, Batch B4 was prepared with blend of HPMC K4M (67.2 mg), HPMC K200M(90mg) and Eudragit RSPO(112.5 mg), where drug release was about 94-98%. Batch B4 showed highest similarity factor values (f_2 = 67.76).
KEYWORDS: Losartan potassium, HPMC K4M, HPMC K200M, Eudragit RSPO, Sustained release, Matrix tablets.

INTRODUCTION

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 hr. To reduce the frequency of administration and to improve patient compliance, a once-daily sustained-release formulation of Losartan potassium is desirable. Drug is freely soluble in water, and hence judicious selection of release-retarding excipients is necessary to achieve a constant in vivo input rate of the drug. Most commonly used method of modulating the drug release is to include it in a matrix system. Because of their flexibility, hydrophilic polymer matrix systems are widely used in oral controlled drug delivery to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance.[2] hence, in present work, an attempt has been made to develop once-daily sustained-release matrix tablets of Losartan potassium using hydrophilic matrix materials such as Hydroxypropylmethylcellulose (HPMC). Drug release for extended duration, particularly for highly water-soluble drugs, using a hydrophilic matrix system is restricted because of rapid diffusion of the dissolved drug through the hydrophilic gel network. For such drugs with high water solubility, hydrophobic polymers are suitable, along with a hydrophilic matrix for developing sustained-release dosage forms. Hydrophobic polymers provide several advantages, ranging from good stability at varying pH values and moisture levels to well-established safe applications. Therefore, in this study, the hydrophobic polymers like Eudragit RSPO were used. Main objective of study is to formulate hydrophilic and hydrophobic matrix systems by polymer material to investigate the effect of both[3].

MATERIALS AND METHODS:

Materials

Losartan potassium, HPMC K4M, HPMC K200M, Eudragit RSPO, MCC, Mg.stearate, Talc, all the ingredients used were of analytical grade.

Methods

Preparation of Tablets

Losartan potassium SR matrix tablets were prepared by direct compression technique .Drug was passed through 40# sieve. HPMC K4M, HPMC K 200M, Eudragit RSPO were passed through 30# sieve. All other ingredients were passed through 40# sieve. All ingredients were

mixed for 15-20 min. After mixing, Mg. stearate (60# sieve), was added to mixer blend and mix again for 3-5 min. Prepared blend was compressed (10/30 diameter, flat punches) using Hydraulic Pellet Press Machine (Type: KP-587, PCI services, Mumbai). Each tablet contains 100 mg of Losartan potassium and other pharmaceuticals ingredients as listed in Table 1.

Table 1: Composition of Sustained release tablets of Losartan potassium *

Ingredients	B1	B2	B3	B4	B5	B6	B7	B8
Losartan potassium	100	100	100	100	100	100	100	100
HPMC K4M	67.5	67.5	67.5	67.5	90	90	90	90
HPMC K200M	45	90	45	90	45	90	45	90
Eudragit RSPO	67.5	67.5	112.5	112.5	67.5	67.5	112.5	112.5
Talc	10.25	10.25	10.25	10.25	10.25	10.25	10.25	10.25
Magnesium stearate	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75
MCC	45	45	45	45	45	45	45	45
Lactose	113	68	68	23	90.5	45.5	45.5	0.5
Total	450	450	450	450	450	450	450	450

**all weights in mg.*

Evaluation of powder

Angel of Repose

Angel of Repose of powder was determined by the funnel method .Accurately weight powder blend were taken in the funnel. Height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend .Powder blend was allowed to flow through the funnel freely on to the surface .Diameter of the powder cone was measured and angel of repose was calculated using the following equation. [4, 5]

$\tan \alpha = h/r$

Bulk density

a) Loose Bulk density(BD): Weigh accurately 25 g of drug , which was previously passed through 20# sieve and transffered in 100 ml graduated cylinder .Carefully level the powder without compacting , and read the unsetteled apparent volume (V_0) .calculate the apparent bulk density in gm/ml by the following formula. [4, 5]

Bulk density = Weigh of powder/ Bulk volume

b) Tapped bulk density (TD): Weigh accurately 25 g of drug, which was previously passed through 20# sieve and transffered in 100 ml graduated cylinder .Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14±2 mm at a nominal rate of 300 drops per minute. Tap the cylinder for 500 times initially and measure the tapped volume (V_1) to the nearest graduated units,repeat the tapping an additional 750 times and measure the tap volume (V_2) to the nearest graduated units. If the difference between the two volumes is less than 2% then final the volume (V_2).Calculate the tapped bulk density in gm/ml by the following formula. [4, 5]

Tapped density = Weigh of powder / Tapped volume

Carr's Index

Compressibility index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down [4, 5]. The formula for Carr's index is as below:

Carr's index (%) = [(TD-BD)*100] / TD

Husner's Ratio

Husner's Ratio is a number that is correlated to the flowability of a powder. [4, 5]

Husner's Ratio = TD / BD

Table 2: Evaluation of physical properties of powder blend of all formulations*

Powder Blend	Angel of Repose	Bulk density	Tapped density	Carr's index(%)	Hausner's ratio
B1	23.22	0.471	0.581	18.93	1.23
B2	21.53	0.437	0.572	23.60	1.31
B3	24.51	0.454	0.584	22.26	1.29
B4	23.56	0.473	0.581	18.59	1.23
B5	24.54	0.494	0.574	13.94	1.16
B6	22.19	0.493	0.573	13.96	1.16
B7	25.43	0.489	0.586	16.55	1.20
B8	24.74	0.485	0.575	15.65	1.19

*all results were average of n=3 observation

Evaluation of Tablets

Thickness

Thickness of the tablets was determined using a vernier caliper (For-bro engineers, Mumbai, India).[6]

Weight Variation Test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Sartorius electronic balance: Model CP-2245, Labtronic), and the test was performed according to the official method.[7]

Drug content uniformity

Drug content was determined by taking an accurately weight amount of powdered Losartan potassium with water and solution was filtered through 45µ membrane. The absorbance was measured at 205nm, using double beam UV visible spectrophotometer.[8]

Hardness

Hardness of the tablets was determined using a hardness testing apparatus (Monseto Type). A tablet hardness of about 5-6 kg/cm^2 is considered adequate for mechanical stability.[9]

Friability

Friability of the tablets was measured in a Roche friabilator (Camp-bell Electronics, Mumbai, India). Tablets of a known weight (W_0) or a sample of tablets are de-dusted 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 weight loss should not be more than 1% w/w.[10]

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

Table 3: Evaluation of various parameters of Tablets of all batches*

*above values shows Mean ± S.D

Batches	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Avg. wt (mg)	Assay (%)
B1	6.2±0.10	3.1±0.15	0.084±0.002	453.2±1.4	99.39±0.52
B2	6.3±0.15	3.0±0.26	0.077±0.002	453.7±2.4	99.76±0.10
B3	6.4±0.15	3.0±0.21	0.085±0.002	455.6±2.7	98.38±0.46
B4	6.4±0.06	3.1±0.15	0.079±0.001	454.1±2.3	99.49±0.16
B5	5.9±0.25	2.9±0.11	0.083±0.002	452.6±1.6	99.72±0.11
B6	6.3±0.20	3.2±0.06	0.081±0.002	454.7±2.2	99.50±0.11
B7	6.4±0.26	2.9±0.06	0.085±0.001	454.4±1.6	98.94±0.44
B8	6.4±0.15	3.1±0.06	0.087±0.002	453.6±2.6	99.49±0.51

***In Vitro* Release Studies**

In vitro dissolution studies were carried out using USP apparatus type II (at 75 rpm. Dissolution medium consisted of 0.1N hydrochloric acid for the first 2 hours and phosphate buffer pH 6.8 from 3 to 24 hours, maintained at 37℃ ± 0.5℃. Drug release at different time intervals was measured by UV-visible spectrophotometer at 205 nm. *In vitro* drug release profile of all batches was compared with market product drug release profile[11]shown in fig.1.

Table 4- Effect of independent variable on dependent variable by 2^3 full factorial design of Losartan potassium Sustained release matrix tablet

	X1	X2	X3	Q1	Q22	T80
B1	67.5	45	67.5	8.8	96.8	16.9
B2	90	45	67.5	7.3	95.2	17.4
B3	67.5	90	67.5	5.4	93.5	18.5
B4	90	90	67.5	4.7	92.6	19.1
B5	67.5	45	112.5	4.7	92.4	18.5
B6	90	45	112.5	4.3	91.4	20.1
B7	67.5	90	112.5	5	92.7	19.1
B8	90	90	112.5	4.9	92.9	19.1

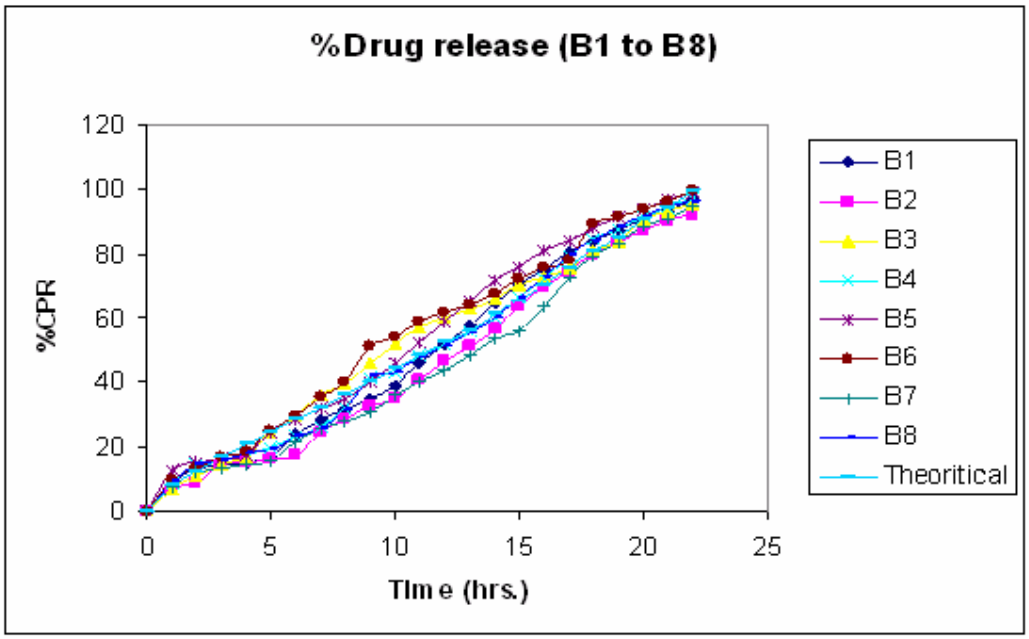

Fig. 1- Cumulative percentage Drug release from batch B1 to B8

Table 5- Summary output of regression analysis for effect of X1 & X2 on Q1

Regression Statistics for Q1		
Multiple R	0.999097391	
R Square	0.998195597	
Adjusted R Square	0.987369181	
Standard Error	0.176776695	
Observations	8	
	Coefficients	***P-value***
b0	32.75	0.046086406
b1	-0.142222222	0.125164162
b2	-0.224444444	0.063794558
b3	-0.221666667	0.061089609
b12	0.00054321	0.271599498
b13	0.000839506	0.182106004
b23	0.001703704	0.046051375

Table 6- Summary output of regression analysis for effect of X1 & X2 on Q22

Regression Statistics for Q22	
Multiple R	0.99926196
R Square	0.998524464
Adjusted R Square	0.989671251
Standard Error	0.176776695
Observations	8

	Coefficients	***P-value***
b0	124.7	0.01212341
b1	-0.175555556	0.101847943
b2	-0.267777778	0.053524185
b3	-0.242777778	0.055805922
b12	0.000938272	0.163817365
b13	0.000839506	0.182106004
b23	0.001901235	0.04128099

5.7 Stability study:

Stability study for tablets were carried out at long term as well as accelerated condition for 1 month as per ICH guidelines Q1 A (R2), Drug products stored at refrigerator condition after packing a tablet in an Aluminium strip.[12]

Table 7- Evaluation of Tablets of Check point batch

Parameters	**Accelerated (25℃ ± 2℃, 60 % ± 5 %RH)**	
	Initial	**After 30 days**
Weight	454.1±2.3mg	456.3±1.2mg
Hardness	6.42±0.12kg/cm^2	6.23±0.42kg/cm^2
Friability	0.079±0.001	0.081±0.001
Thickness	3.1±0.15mm	3.1±0.12mm

Note: all value denote the mean ± SD (n=3)

Table 8- Assay of tablets at Long-term and accelerated stability condition.

Condition	**Accelerated 25℃ ± 2℃, 60 % ± 5 %RH**
Initial	99.45±0.47
30 days	93.93±0.79

Note: all value denote the mean ± SD (n=3)

RESULTS AND DISCUSSION

Losartan potassium 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 hr. Losartan potassium with all evident advantages proved to be a suitable candidate for development of a sustained-release dosage form. In present study, HPMC K4M and HPMC K200M, which were used in hydrophilic matrix drug delivery systems, have been employed to formulate sustained-release tablets of Losartan potassium but alone it was not gives a good result so it was used in combination with hydrophobic polymer like Eudragit RSPO.

Batches of Losartan potassium were prepared according to 2^3 full factorial design by using HPMC K4M, HPMC K 200M Eudragit RSPO. Prepared powder blend of different batches were evaluated. Result showed that powder blend have, Angle of repose range from 21 to 26, Carr's index range from 14 to 24 and Husner's ratio range form 1.16 to 1.31, which indicate good flow property. Hardness, Thickness and Friability was found to be in range of 5.9 to 6.4, 2.9 to 3.2 and 0.077 to 0.087 respectively, which is in acceptable criteria in tablet formulation.

Table 9- *In-Vitro* drug release of Check point batch at Accelerated storage condition

Time (hrs.)	Initial	After 30 Days
0	0.0	0.0
1	9.39±0.07	8.35±0.14
2	14.37±0.47	13.56±0.25
3	15.63±0.52	14.84±0.35
4	18.02±0.19	17.09±0.42
5	19.18±0.15	20.56±0.56
6	23.01±0.09	22.98±0.48
7	25.54±0.13	25.63±0.52
8	31.73±0.42	31.12±0.97
9	41.89±0.36	42.04±0.63
10	43.30±0.23	43.54±0.47
11	47.75±0.47	48.12±1.23
12	51.13±0.68	51.43±0.52
13	55.43±0.49	55.68±0.63
14	59.92±0.86	60.23±0.24
15	66.16±1.20	66.85±0.82
16	72.75±0.12	71.24±0.34
17	79.70±1.08	79.53±0.17
18	84.14±0.15	84.33±0.19
19	88.62±0.56	87.24±0.46
20	91.73±0.45	90.53±0.75
21	94.5±0.65	92.62±1.54
22	96.26±0.75	95.32±0.27
F2	---	**88.67**

Note: all value denote the mean ± SD (n=3)

Result of angle of repose (<30) indicate good flow properties of the powder. This was further supported by lower Carr's index values . Generally, compressibility index values up to 24% result in good to excellent flow properties. Powder density and hardness are often interrelated properties. In addition, powder density may influence compressibility, tablet porosity, dissolution, and other properties. Drug content in the weighed amount of powder of all formulations was found to be uniform. All these results indicate that the powder possessed satisfactory flow properties, compressibility, and drug content. Tablets of different formulations were subjected to various evaluation tests, such as thickness, uniformity of weight, drug content, hardness, friability, and in vitro dissolution. All formulations showed uniform thickness. In a weight variation test, pharmacopoeias limit for the percentage deviation for tablets of more than 450 mg is ±5%. Average percentage deviation of all tablet formulations was found to be within the above limit, and hence all formulations passed the test for uniformity of weight as per official requirements. Good uniformity in drug content was found among different batches of tablets and percentage of drug content was more than 95%.Tablet hardness is not an absolute indicator of strength. Another measure of a tablet's strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable. In present study, percentage friability for all formulations was below 1%, indicating that friability was within the prescribed limits.[15]All tablet formulations showed acceptable Pharmacotechnical properties and complied with the in-house specifications for weight variation, drug content, hardness, and friability.

All Batches were evaluated for the cumulative drug release and similarity factor (f2) value. From in vitro dissolution profile, Batch B4 was prepared with blend of HPMC K4M (67.2 mg), HPMC K200M(90mg) and Eudragit RSPO(112.5 mg), where drug release was about 94-98%. Batch B4 showed highest similarity factor values (f_2 = 67.76).

From table 5 variable X1 , X2 and X3 has p value 0.125 , 0.063 and 0.061 which is greater then 0.05,but the interaction term b23 has p value 0.046 ($p<0.05$).Variable which have p value less then 0.05 ,Significantly affect the release profile. So the term X2X3 (interaction Between HPMC K200M and Eudragit RSPO) Significantly affect the release profile at 1 hr.

From table 6 variable X1 , X2 and X3 has p value 0.101 , 0.053 and 0.055 which is greater then 0.05,but the interaction term b23 has p value 0.041 ($p<0.05$).Variable which have p value less then 0.05 ,Significantly affect the release profile. So the term X2X3 (interaction Between HPMC K200M and Eudragit RSPO) Significantly affect the release profile at 22 hr.

Several concepts are included in the term pharmaceutical stability. Among them, the important one is the stability of the drug in the dosage form. Stability of a pharmaceutical preparation can be defined as the capability of a particular dosage form or drug product in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its shelf life. Stability of a drug in a dosage form at different environmental conditions is important as it determines the expiry date of that particular formulation. Changes in the physical appearance, color, odor, taste, or texture of the formulation indicate the drug instability. Table 7-9 shows the stability studies results of prepared tablet formulation of optimized batch. There were no significant changes in their physical appearance, hardness, friability, assay, weight variation and drug release profile. It was observed that the initial drug content and the drug contents of the samples analysed after 1 month of storage were nearly similar. The release profile also not showed any significant changes indicating that there were no significant changes in the physical as well as chemical characteristics of the formulation.

CONCLUSION

Hydrophilic matrix of HPMC alone could not control the Losartan potassium release effectively for 24 hours. It is evident from the results that a matrix tablet prepared with hydrophilic polymer and hydrophobic polymer is a better system for once-daily sustained release of a highly water-soluble drug like Losartan potassium and developed tablets were stable and retain their pharmaceutical properties and drug shows no degradation over a period of 1 month.

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