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LOSARTAN POTASSIUM ONCE-DAILY SUSTAINED-RELEASE MATRIX TABLETS: FORMULATION AND IN VITRO ASSESSMENT

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ABSTRACT

The goal of the current study was to create a Losartan potassium sustained release tablet based on hydrophilic and hydrophobic polymers that can release the medication up to 24 hours later at a predefined pace. In order to achieve the desired theoretical release profile, a polymer mixture was used in the preparation of the Losartan potassium matrix tablet. The effects of hydrophilic and hydrophobic polymers on potassium losartan were investigated.

The physical and chemical characteristics of the formulated tablet were also noted. To assess the SR matrix tablet of Losartan potassium, the in vitro release profile was monitored for 24 hours.

Angiotensin II type 1 (AT1) receptor antagonist losartan potassium (LP) has powerful and highly selective antihypertensive action.

With an oral bioavailability of roughly 33% and a plasma elimination half-life of 1.5 to 2.5 hours, it is easily absorbed from the digestive tract. For antihypertensive effects, administration of LP in a sustained release dosage would be preferable because it would keep the drug's plasma concentrations much above the therapeutic value. Batch B4 was created using a combination of HPMC K4M (67.2 mg), HPMC K200M (90 mg), and Eudragit RSPO (112.5 mg), with a drug release of between 94 and 98%, according to an in vitro dissolution profile. The highest similarity factor values were displayed by batch B4 (f2 = 67.76).

Keywords: Losartan potassium, HPMC K4M, HPMC K200M, Eudragit RSPO, Sustained release, Matrix tablets.

INTRODUCTION

Angiotensin II type 1 (AT1) receptor antagonist losartan potassium (LP) has powerful and highly selective antihypertensive action. With an oral bioavailability of roughly 33% and a plasma elimination half-life of 1.5 to 2.5 hours, it is easily absorbed from the digestive tract. A once-daily sustained-release version of losartan potassium is preferred to lessen administration frequency and boost patient compliance. Since the medication is widely soluble in water, it is important to choose release-retarding excipients carefully in order to maintain a steady drug input rate in vivo.

The most popular technique for regulating medication release is to include it in a matrix system. Hydrophilic polymer matrix systems are frequently employed in oral controlled drug delivery because of their adaptability, which helps them achieve a desired drug release profile, cost-effectiveness, and widespread regulatory approval. Because of this, an effort has been made in the current work to create once-daily sustained-release matrix tablets containing losartan potassium employing hydrophilic matrix materials such as hydroxypropyl methylcellulose (HPMC).

Because of the quick diffusion of the dissolved drug through the hydrophilic gel network, drug release for an extended period of time utilizing a hydrophilic matrix system is constrained, particularly for highly water-soluble medicines. Considering such medications' considerable water solubility, in order to create sustained-release dosage forms, hydrophobic polymers and a hydrophilic matrix are both appropriate.

Hydrophobic polymers have a number of benefits, including uses that are well-established and safe as well as good stability at various pH and moisture levels. Therefore, hydrophobic polymers like Eudragit RSPO were utilized in this investigation.

The primary goal of the study is to create hydrophilic and hydrophobic matrix systems using polymer materials in order to examine their effects.

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

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Tablets containing losartan potassium SR were created using the direct compression method. 40# sieve was used to filter the drug. Through a 30# sieve, HPMC K4M, HPMC K200M, and Eudragit RSPO were passed. Everything else was put through a 40# sieve. All ingredients were mixed for 15-20 min. Following the initial mixing, Mg. stearate (60# sieve) was added, and the mixer was run again for 3-5 minutes. Compressed using flat punches with a 10/30 diameter and a hydraulic pellet press was the prepared blend (Type: KP-587, PCI services, Mumbai). Losartan potassium, together with the other pharmacological components specified in Table 1, is present in each tablet in an amount of 100 mg.

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	45.5	45.5	0.5
Total	450	450	450	450	450	450	450	450

*All weights in mg.

Evaluation of Powder

Angle of Repose

The funnel method was used to determine the powder's Angle of Repose. Powder blends were measured out precisely and poured into the funnel. The funnel's height was adjusted such that its tip just touched the top of the powder mixture. The powder mixture was permitted to freely flow through the funnel and onto the surface. The powder cone's diameter was measured, and the following equation was used to determine the angle of repose:

$\tan \alpha = h/r$

Bulk Density

a) Loose Bulk Density (BD): Weigh precisely 25 g of medication that has been transferred into a 100 ml graduated cylinder after being passed through a 20# sieve. Without compacting, carefully level the powder, then check the unsettled apparent volume (V0). The formula below can be used to compute the apparent bulk density in gm/ml. 4, 5 Bulk volume/density Equals weight of powder

b) Tapped bulk density (TD): Weigh precisely 25 g of medication that has been transferred into a 100 ml graduated cylinder after being sieved with a 20# mesh size.

Then, using a mechanically tapped density tester that gives a set drop of 142 mm at a nominal rate of 300 drops per minute, mechanically tap the cylinder containing the sample by elevating the cylinder and letting it fall under its own weight.

The cylinder should be tapped 500 times to start, and the tapped volume (V1) should be measured to the nearest graduated units. The tapping should then be repeated 750 times more, and the tapped volume (V2) should be me asured to the same graduated units.

Volume is determined if the difference between the two volumes is less than 2%. (V2). Use the formula below t o determine the tapped bulk density in grams per milliliter.

Tapped density = Weigh of powder / Tapped volume

Carr's Index

Carr's compressibility index was used to calculate the powder blend's compressibility index. Evaluation of a powder's BD, TD, and packing down speed is a straightforward test. The following is the formula for Carr's index:

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

Hausner's Ratio Hausner's Ratio

Is a number that is correlated to the flow ability of a powder.

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Hausner' Ratio = TD / BD

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

Powder Blend	Angle 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 an average of n=3 observation.

Evaluation of Tablets

Thickness

Utilizing vernier callipers, the thickness of the tablets was measured (For-bro engineers, Mumbai, India). Test for Weight Variation 6 Twenty tablets of each formulation were weighed using an electronic scale (Sartorius electronic balance: Model CP-2245, Labtronic) to evaluate weight variance. The test was carried out in accordance with the recommended procedure.

Drug Content Uniformity

Twenty tablets of each formulation were weighed using an electronic scale (Sartorius electronic balance: Model CP-2245, Labtronic) to evaluate weight variance. The test was carried out in accordance with the recommended procedure.

Hardness

By mixing a precisely weighed amount of powdered Losartan potassium with water and filtering the resulting solution via a 45-micron membrane, the drug content was ascertained. Using a twin-beam UV visible spectrophotometer, the absorbance was measured at 205 nm.

Friability

The Friability of the tablets was measured in a Roche friabilator (Camp-bell Electronics, Mumbai, India). Tablets with a known weight (W0) 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 the equation below. The weight loss should not be more than 1% w/w.

%Friability = (W0-W)/ W0 *100

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

Batches	Hardness (kg/cm2)	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

USP equipment type II (operating at 75 rpm) was used for in vitro dissolution investigations.

The dissolution medium was kept at 37°C + 0.5°C and comprised phosphate buffer pH 6.8 for the first three hours and 0.1N hydrochloric acid for the first two hours. The UV-visible spectrophotometer at 205 nm was used to measure the drug release at various time intervals. All batches' in vitro drug release profiles were contrasted with those of the market product.

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Table 4- Effect of the independent variable on a dependent variable by 23 full factorial designs 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

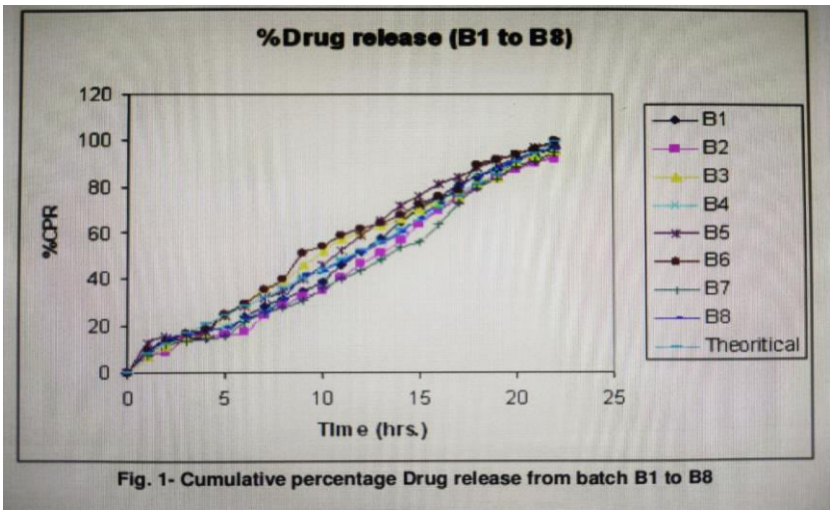

Fig. 1- Cumulative percentage Drug release from batch B1 to B8

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

Regression Statistics for Q1	
Multiple R	**0.99926196**
R Square	0.998524464
Adjusted R Square	0.989671251
Standard Error	0.176776695
Observations	8

Stability Study

According to ICH recommendations, a stability study for tablets was conducted under rapid and long-term conditions for a month. Drug goods packed in an aluminum strip and kept in a refrigerator are the subject of Q1 A (R2).

Table 7- Evaluation of Tablets of Checkpoint batch

Parameters	Accelerated (25°C + 2°C, 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 values denote the mean ± SD (n=3)

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

Condition	Accelerated25°C + 2°C, 60 % + 5 %RH
Initial	99.45±0.47
30 days	93.93±0.79

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

RESULTS AND DISCUSSION

Angiotensin II type 1 (AT1) receptor antagonist losartan potassium has powerful and highly selective antihypertensive action. With an oral bioavailability of about 33% and a plasma elimination half-life of 1.5 to 2.5 hours, it is easily absorbed from the digestive tract. With all of its obvious benefits, losartan potassium has shown to be a good choice for the creation of a sustained-release dosage form. In the current study, sustained-release tablets of losartan potassium were created using HPMC K4M and HPMC K200M, which were used in hydrophilic matrix drug delivery systems. However, used alone, these materials did not produce satisfactory results, so they were combined with hydrophobic polymers such as Eudragit RSPO.

HPMC K4M, HPMC K 200M, and Eudragit RSPO were used to manufacture batches of the potassium salt of losartan in accordance with a 23 complete factorial design. Different batches of prepared powder blends were assessed. The results showed that the powder mix had good flow properties, including an Angle of repose range of 21 to 26, a Carr's index range of 14 to 24, and a Hausner's ratio range of 1.16 to 1.31. In accordance with accepted parameters for tablet formulation, hardness, thickness, and friability were found to be in the range of 5.9 to 6.4, 2.9 to 3.2, and 0.077 to 0.087, respectively.

Table 9- In-Vitro drug release of Checkpoint 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 values denote the mean ± SD (n=3)

The results of the angle of repose (30) show that the powder has good flow characteristics. Lower Carr's index values provided additional evidence in favour of this. Compressibility index values up to 24% often produce satisfactory to exceptional flow characteristics. Hardness and powder density is frequently linked qualities. Additionally, powder density may affect a number of qualities, including compressibility, tablet porosity, dissolving, and others.

All powder formulations' measured drug contents were found to be uniform. All of these findings suggest that the powder has adequate flow characteristics, compressibility, and medication content. Different tablet formulations were tested for things including thickness, weight homogeneity, drug content, hardness, friability, and in vitro dissolution. Each formulation displayed a consistent thickness. The Pharmacopoeia limit for the percentage deviation for tablets containing more than 450 mg in a weight variation test is 5%.

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All tablet formulations passed the test for weight uniformity required by law since the average percentage deviation of all formulations was found to be within the above standard. Between different batches of tablets, there was good consistency in the amount of drug present, and the percentage of drug content was greater than 95%. The hardness of a tablet is not a perfect predictor of strength. Friability is a different indicator of a tablet's durability.

Conventionally compressed tablets are generally regarded as appropriate if they lose less than 1% of their weight. The proportion of friability in the current investigation was less than 1% for all formulations, showing that friability was within the allowed ranges. 15 All tablet formulations met internal standards for weight fluctuation, drug content, hardness, and friability and displayed acceptable pharmacy technical qualities.

CONCLUSION

For 24 hours, the hydrophilic matrix of HPMC alone was unable to effectively restrict the release of losartan potassium. The results clearly show that a matrix tablet made of both hydrophilic and hydrophobic polymers is a better system for the once-daily sustained release of a highly water-soluble medication like losartan potassium. The developed tablets were stable and retained their pharmaceutical properties, and the medication exhibited no degradation over a one-month period.

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