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Research Article

FORMULATION AND EVALUATION OF LOSARTAN POTASSIUM SUSTAINED RELEASE TABLETS

SMITAPADMA MOHANTY[1]*, ASISH DEV[2], S. TRIPATHY[3]

[1]*School of Pharmaceutical Education and Research, Berhampur University, Odisha, [2]Oriental college of pharmacy, Sanpada, Navi Mumbai, [3]Sri Vasavi Institute of Pharmaceutical Sciences Tadepaligudem, AP India. Email: smitapharma@yahoo.com

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ABSTRACT

Losartan potassium is a potent antihypertensive drug which is a highly specific Angiotensin II Type/AT_1 receptor antagonist. It is readily absorbed from the gastro intestinal tract, having oral bioavailability 33% and plasma elimination half life from 1.5 to 2.5 hours. The present study is an attempt to increase therapeutic efficacy, reduce frequency of administration and improve patient compliance of Losartan potassium by developing sustained release tablets. Losartan potassium was formulated as oral sustained release tablets by using HPMC k4M and HPMC k15M. Preformulation studies were carried out to evaluate the parameters like powder flow properties, loss on drying, Drug-excipient compatibility and stress stability. All four formulations showed acceptable IP specifications for weight variation, thickness, hardness and friability. The dissolution studies showed release of drug over a period of 10 hours in zero-order kinetic.

Keywords: Lasartan Pottassium, HPMC K4M, HPMC K15M

INTRODUCTION

Losartan2-n-butyl-4-chloro-5-hydroxymethyl-1-((2?-(1H-tetrazol-5-yl)(biphenyl-4-yl) methyl) imidazole, potassium salt, is a strong antihypertensive agent, non-peptide, and exerts its action by specific blockade of angiotensin II receptors [1-3]. Sustained release dosage forms are designed to complement the pharmaceutical activity of the medicament in order to achieve longer duration of action [4,5]. Sustained release preparations are useful to reduce the dosage frequency to improve patient convenience. Sustained release tablets are easy to fabricate by incorporating drug molecule in a slowly disintegrating and inert porous swellable polymers[6]. This study is intended to prepare sustained release tablets to improve patient compliance and decrease drug load in body. Due to the less plasma half life of Losartan potassium author thought to make a sustained release formulation which releases the drug up to 10 hours following zero order kinetics.

MATERIALS AND METHODS

Losartan potassium was received as a gift sample from Cirix pharmaceuticals Ltd. MCC PH103, lactose monohydrates, crosscarmellose sodium, talc were obtained from Accent microcell, Lactose India Ltd., Rosswell Indusries, Nilakanta mine chemicalsand Anishi drug and chemicals respectively. HPMC k4M, HPMC k15M were obtained from Hyzhou zhynmocong pharma co-China.

Table 1: Composition of different batches of tablets

Name of Ingredients	Quantities in mg			
	F-1	F-2	F-3	F-4
Losartan potassium	100	100	100	100
Lactose IP	90	80	90	80
MCC pH103	60	48	46	48
HPMC k4M	35	55	35	30
HPMC k15M	--	--	12	25
CCS	6	6	6	6
Talc	8	8	8	8
Magnesium stearate	3	3	3	3

Preparation of sustained release tablets

Losartan potassium sustained release tablets (100 mg) were prepared by direct compression method[7]. Pre-lubrication was done by mixing of active ingredients and excipients other than lubricants. They were shifted in sieve # 40 and properly weighed according to Table No. 1. They were properly mixed by rolling in a poly bag. Then it was lubricated by talc and magnesium stearate. Finally tablets were punched by using 8 stations, singles rotary tablet compression machine (kanavat mini22). All tablets were stored in airtight containers at room temperature for further study.

Evaluation of Powder Blends

Angle of repose

Angle of Repose of powder was determined by the funnel method. Accurately weighed 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 angle of repose was calculated using the following equation[8,9].

$$\text{Tan } \alpha = h/r$$

Where, h= height of powder cone; r= radius of powder cone

Bulk density and tapped density

An accurately weighed quantity of the blend **(W)**, was carefully poured into the graduated cylinder and the volume **(V_0)** was measured. Then the graduated cylinder with lid, set into the density determination apparatus (Tapped Density Apparatus, (ElectrolabLTD1020). The density apparatus was set for 1250 taps and after that the volume **(V_f)** was measured which was tapped volume. The bulk density and tapped density were calculated by using the following formulas[8, 9].

Bulk density = W/ V_0

Tapped density = W/ V_f

Compressibility index (CI)/ Carr's index

It was obtained from bulk and tapped densities. It was calculated by using the following formula[8,9].

$$CI = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio

Hausner's ratio is a number that is correlated to the flowability of a powder[8,9]. It is measured by ratio of tapped density to bulk density.

$$\text{Hausner' index} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Table 2: Preformulation studies of powder blends

Parameters	F-1	F-2	F-3	F-4
Loss on drying or water content %w/w	3.52	4.25	4.17	4.38
Angle of repose	24.45	24.53	24.63	22.37
Bulk density gm/ml	0.472	0.526	0.540	0.533
Tapped density gm/ml	0.571	0.642	0.664	0.656
Compressibility index %	17.38	18.07	18.73	18.75
Hausner's ratio	1.21	1.22	1.23	1.23

Evaluation of Tablets

Thickness

Thickness of the tablets was determined using a digital vernier caliper MITUOTYO.

Weight variation Test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance SARTORIUS, Germany, and the test was performed according to the official method[10].

Drug content (assay)

Hardness

Hardness of the tablets was determined using a digital tablet hardness tester (Eruika D 63150).

A tablet hardness of about 8-10 kg/cm^2 is considered adequate for mechanical stability[11].

Friability

Friability of the tablets was measured in a friabilator (Electrolab F-2). 20 tablets were accurately weighed (W0) and placed in friability test apparatus. They were observed for 100 rotations. After 100 rotations they were weighed again (W). The weight loss should not be more than 1% w/w[11].

$$\%\text{Friability} = (W0\text{-}W)/\ W0\ X100$$

***In-Vitro* drug release study**

Dissolution was carried out in USP test apparatus (Electrolab TDT 08L). 900 ml of DM water was taken as dissolution medium. Dissolution was performed at 37 ± 0.5^{0}C with 50 rpm for 10 hours. The sample (5 ml) was withdrawn at specific intervals (0, 1, 2, 4, 6, 8, 10 hours) and replaced with fresh dissolution medium of same quantity. Samples were diluted suitably, filtered 0.45µm filter paper and analysed for drug content at 250 nm[12]

Table 3: Evaluation of various parameters of tablets of all batches

S. No.	Hardness (Kg/cm^2)	Thickness (mm)	Friability (%)	Weight Variation (% w/w)	Drug Content
F-1	8 - 10	3.31 ± 0.1	0.271	300 ± 1.5%	99.32 ± 0.33
F-2	8 - 10	3.28 ± 0.1	0.152	300 ± 1%	98.38 ± 0.42
F-3	8 -10	3.3 ± 0.2	0.259	300 ± 1.5%	99.18 ± 0.68
F-4	8 - 10	3.2 ± 0.2	0.18	300 ± 1%	99.69 ± 0.45

Table 4: Cumulative drug release of all formulations

Time in hrs	% Drug released			
	F-1	F-2	F-3	F-4
0	0	0	0	0
1	86.6088	73.9875	9.27667	9.40767
2	97.5333	92.931	15.0008	17.1743
4	-	-	35.9733	35.0167
6	-	-	87.5708	64.6413
8	-	-	98.3172	73.4742
10	-	-	-	93.7213

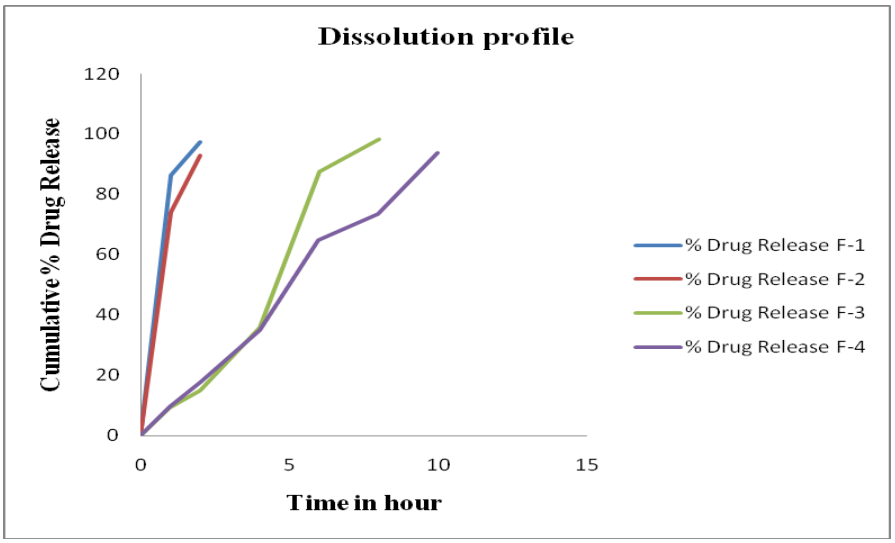

Fig. 1: *In Vitro* Dissolution profile of prepared formulations

Drug content of tablets was determined by HPLC (Shimadzu).

Table 5: Stability data for optimized formulation (F-4)

Condition	Period	Description	Avg. wt.(mg)	Hardness kg/cm²	Moisture	Assay (%)	Impurities (%)
Room temp.	3M	White	300	7.5	4.09	98.2	0.25
40°c ± 2°c/ 75%RH ±5% RH	6M	White	300.4	7.39	4.34	100.4	0.195
30°c ± 2°c/ 65%RH ±5% RH	6M	White	300.6	7.82	4.21	99.83	0.137

Stability studies

The stability study for tablets was carried out at room temperature (for 3 months), 40 ± 2^{0}C (75 ± 5% RH for 6 months) and 30 ± 2^{0}C (60 ± 5% RH for 6 months) by storing the samples in room and stability chamber. No appreciable change in physical characteristics like color, moisture content, dissolution, assay, related substance was observed. The stability studies results are shown in (Table No. 5)

RESULT AND DISCUSSION

Batches of Losartan potassium were prepared according to table no. 1 by using HPMC K4M, HPMC K15M in direct compression method. Prepared powder blend of different batches were evaluated. Result showed that powder blend have, Angle of repose range from 22 to 25, Carr's index range from 17.38 to 18.75 and Husner's ratio range from 1.21 to 1.23, which indicate good flow property. Hardness, Thickness and Friability was found to be in range of 8 to 10, 3.28±0.1 to 3.3± 0.2 and 0.18 to 0.271 respectively, which is an acceptable criteria in tablet formulations. The values of pre-compression parameters evaluated were within prescribed limits and indicated good free flowing property (data in table no. 2). The data obtained from post-compression parameters such as weight variation, hardness, friability, *in-vitro* dissolution studies, drug content are shown in table no. 3. In all the formulations, hardness test indicates good mechanical strength, friability is less than 1% which indicates that tablets had a good mechanical resistance. Drug content was found to be high (99.69) and uniform in all formulations. The tablets were subjected for evaluation of *in-vitro* dissolution studies. Figure No.1 depicts the dissolution behavior of the tablets. It was observed that when HPMC k4M and HPMC k15M were used as polymer in the concentration of 10% and 8.33% respectively dissolution rate sustained for 10 hours.

CONCLUSION

It is evident from the results that sustained release tablets prepared by using hydrophilic polymer of HPMC k4M and HPMC k 15M in concentration of 10 % and 8.33 % respectively is a better system which sustain release of a highly water-soluble drug, Losartan potassium and can be taken once daily. The developed tablets (F-4) were stable and retain their pharmaceutical properties and drug shows no degradation over a period of 6 month.

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