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RESEARCH ARTICLE

FORMULATION AND EVALUTION OF SUSTAINED RELEASE TABLET OF LOSARTAN POTASSIUM IP AS A ANTIHYPERTENSIVE DRUG

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ABSTRACT

The main objective behind the ths study Tablets are solid dosage forms containing medicinal substances with or without suitable diluents they are one of the most preferred form of medication both by pharmaceutical manufacturer as well as physicians and patients. They offer safe and convenient ways of active pharmaceutical ingredients (API) administration with excellent physicochemical stability in comparision to some other dosage forms, and also provide means of accurate dosing. In the present study main goal is we made an develop a stable formulation of oral Sustained -release losartan potassium tablets with optimum properties. To achieve this goal, various formulations of losartan potassium tablets were prepared and evaluated with respect to the so various quality parameters are considering while designing tablet as a solid dosage form. To achieve this goal, various formulation of losartan potassium tablets were prepared and evaluated with respect to the so various quality parameters are considering while designing tablet as a solid dosage form both in process parameters for granules (bulk density, tapped density, compressibility index, Hausner's ratio,Angle of repose) and parameters for finished products(weight variation, tablet thickness, friability, hardness, drug content, in vitro dissolution studies).

KEYWORDS: Designing of Tablet, Losartan Potassium IP, Solid dosage form, Sustained Realese,

INTRODUCTION

Tablets are solid dosage forms containing medicinal substances with or without suitable diluents. They are one of the most preferred forms of medication both by pharmaceutical manufacturer as well as physicians and patients. They offer safe and convenient ways of active pharmaceutical ingredients (API) administration with excellent physicochemical stability in comparision to some other dosage forms, and also provide means of accurate dosing. However, the process of manufacturing of tablets is complex. Hence, careful consideration has to be given to select right process and right quality of excipients to ultimately give a robust, high productivity and regulatory complaint product of good quality[1-3]

Losartan potassium, an orally active non-peptide molecule, is chemically described as 2 - butyl - 4 - chloro - 1 - [*p*- (*o* - 1 *H* -tetrazol - 5 - ylphenyl) benzyl] imidazole – 5 - methanol monopotassium salt. Its empirical formula is $C_{22}H_{22}ClKN_6O$[4-6].

The molecular weight of losartan potassium is 461.01. It is freely soluble in water and soluble in alcohols. Losartan potassium is an angiotensin II receptor

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antagonist. It suppresses the effects of angitensin II at its receptors, thereby blocking the renninangiotensin system.6 The rennin-angiotensin system plays a crucial role in the control of blood pressure, and in particular it is felt to play crucial role in hypertension. Losartan has been demonstrated to be superior to previous peptide receptor antagonists and angiotensin converting enzyme (ACE) inhibitors because of its enhanced specificity, selectively, and tolerability. Generally, losartan potassium is employed in the management of essential hypertension with lower incidence of side-effects like cough. It is readily absorbed and undergoes rapid hepatic metabolism to an active metabolite, EXP-3174, via cytochrome P-450 system. Absorption of losartan potassium is not affected by food. Times to achieve the peak concentration are 1 hour for losartan, and 3.5 hours for the active metabolite. The peak effect on blood pressure occurs 6 hours after the dose. Mean elimination half-lives average 2.1 hours for losartan, and 6.3 for EXP-3174; at 24 hours after acute chronic dosing, only the metabolite is still detectable in plasma. EXP-3174 is a non-competitive antagonist of the AT1 receptor, with a potency of 10-40 times that of the parent compound. It is probably for this reason that 63-74% of the peak anti-hypertensive effect is maintained at the 24 hour. Blood pressure effects have been found to more closely parallel levels of the metabolite (EXP-3174) rather than of losartan. The pharmacokinetics of both losartan and its active metabolite are linear, and not affected by repetitive dosing. Although clearance is both by hepatic and renal mechanisms, only hepatic impairment appears to affect plasma half-life[7-12.]

In the present study, we made an develop a stable formulation of oral Sustained -release losartan potassium tablets with optimum properties. To achieve this goal, various formulation of losartan potassium tablets were prepared and evaluated with respect to the so various quality parameters are considering while designing tablet as a solid dosage form both in process parameters for granules (loss on drying, bulk density, tapped density, compressibility index, Hausner's ratio) and parameters for finished products (average weight, weight variation, tablet thickness, friability, hardness, disintegration time, drug content, dissolution studies).

MATERIALS AND METHODS:

Materials

Losartan potassium, HPMC K200M, Eudragit RSPO, MCC, Talc, Eudragit S100, Eudragit L100 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.

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Table 1: Preparation of wet granules of Losartan potassium sustained release

Compositions (mg)	**LP1**	**LP2**	**LP3**	**LP4**	**LP5**	**LP6**	**LP7**	**LP8**	**LP9**
Losartan potassium IP	100	100	100	100	100	100	100	100	100
HPMC K100M	200	200	-	-	150	125	125	200	-
Eudragit RLPO	-	-	200	200	80	75	75	-	200
Eudragit S100	30	-	30	-	-	30	-	15	15
Eudragit L100	-	30	-	30	-	-	30	15	15
MCC	20	20	20	20	20	20	20	20	20
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	8	8	8	8	8	8	8	8	8
di-calcium phosphate	40	40	40	40	40	40	40	40	40
Total	450	450	450	450	450	450	450	450	450

Evaluation of powder

1. 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 (V0) .calculate the apparent bulk density in gm/ml by the following formula[13-14.]

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 (V1) to the nearest graduated units,repeat the tapping an additional 750 times and measure the tap volume (V2) to the nearest graduated units. If the difference between the two volumes is less than 2% then final the volume (V2).Calculate the tapped bulk density in gm/ml by the following formula[13-14.]

Tapped density = Weigh of powder / Tapped volume

2. 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[13-14.] The formula for Carr's index is as below:

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

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3. Husner's Ratio

Husner's Ratio is a number that is correlated to the flowability of a powder[13-14.]

Husner's Ratio = TD / BD

4. 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[13-14.]

$$\tan \theta = h/r$$

Table 2: Pre-compression parameters

Formulaons Code	Bulk density	Tapped density	Carr,s index	Hausner's ratio	Angle of repose
LP1	0.330 ± 0.004	0.384 ±0.008	13.96 ± 1.09	1.16 ± 0.010	28.68 ± 0.651
LP2	0.373 ± 0.003	0.413 ± 0.01	11.19 ± .385	1.10 ±0 .035	28.25 ± 0.645
LP3	0.295 ± 0.023	0.329 ±0.024	10.40 ±0 .770	1.11 ± 0.010	25.55 ± 0.719
LP4	0.318 ±0.010	0.355 ± 0.009	10.48 ± 1.15	1.11 ±0.014	28.40 ± 0.681
LP5	0.339 ± 0.01	0.392 ± 0.013	13.55 ± 0.322	1.15 ± 0.005	28.83 ± 1.04
LP6	0.347 ± 0.005	0.387 ± 0.014	10.20 ± 1.29	1.11 ± 0.016	25.56 ± 1.22
LP7	0.300 ± 0.004	0.323 ± 0.002	7.080 ± 1.21	1.07 ± 0.014	24.67 ± 1.02
LP8	0.369 ± 0.006	0.408 ± 0.007	9.600 ± 0.151	1.10 ± 0.002	29.64 ± 1.05
LP9	0.375 ± 0.005	0.413 ± 0.006	9.161 ± .740	1.10 ± 0.010	24.83 ± 1.30

Mean ± SD *n=3.

Evaluation of Tablets

1. Thickness

Thickness of the tablets was determined using a vernier caliper (For-bro engineers, Mumbai, India)[15.]

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2. 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[15.]

3. 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[15.]

4. Hardness

Hardness of the tablets was determined using a hardness testing apparatus (Monseto Type). A tablet hardness of about 5-6 kg/cm2 is considered adequate for mechanical stability[15.]

5. Friability

Friability of the tablets was measured in a Roche friabilator (Camp-bell Electronics, Mumbai, India). Tablets of 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 equation as below .The weight loss should not be more than 1% w/w[15.]

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

Table 3: Post compression parameters of tablets

Formulations code	Hardness(kg/cm^2)	Thickness (mm)	Drug Content (mg)	Weight variation	Friability (%)
LP1	6.15 ± 0.191	5.19 ± 0.037	90.24 ± 1.235	349.05 ± 4.904	0.23 ± 0.12
LP2	7.17 ± 0.221	5.18 ± 0.054	97.60 ± 1.560	350.84 ± 5.871	0.20 ± 0.09
LP3	7.07 ± 0.150	5.28 ± 0.071	98.52 ± 1.485	351.7 ± 5.939	0.22 ± 0.14
LP4	5.85 ± 0.251	5.88 ± 0.030	99.96 ± 1.864	351.35 ± 3.910	0.31 ± 0.08
LP5	6.52 ± 0.150	5.85 ± 0.068	94.84 ± 1.356	352.35 ± 4.568	0.51 ± 0.08
LP6	6.52 ± 0.125	5.88 ± 0.020	95.08 ± 1.894	350.65 ± 2.033	0.50 ± 0.05
LP7	6.70 ± 0.081	5.88 ± 0.025	97.72 ± 1.756	350.6 ± 2.087	0.51 ± 0.09
LP8	6.27 ± 0.095	5.90 ± 0.012	98.36± 1.764	350.25 ± 1.802	0.49 ± 0.11
LP9	6.50 ± 0.081	5.93 ± 0.018	96.52 ± 1.523	350.65 ± 1.899	0.54 ± 0.12

Mean ± SD, *n=3, ** n=10, ***n=20.

In Vitro Release Studies

Dissolution rate was studied by using USP type-II apparatus (USP XXIII dissolution test apparatus - II paddle model, TDL 084, Electrolab, India) using 200mL of 0.1N HCl for 2 hrs and 900 ml of phosphate buffer pH 6.8 for 22 hrs as dissolution medium. Temperature of the dissolution medium was maintained at 37 ^{o} ± 0.5 ^{o}C. Aliquots of dissolution medium (1 ml) was withdrawn at every 15, 30 min and 1 and 2 hrs interval and replaced with equal volume of fresh medium. The absorbance of filtered solution was measured by UV Spectrophotometrically method at 254 nm and concentration of the drug was determined from standard calibration curve[16].

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Table 4: In-vitro drug dissolution profile for all formulations

Formulation	Time	Cumulative percentage drug
LP1	24	96.65 ± 2.23
LP2	20	96.15 ± 2.79
LP3	20	98.27 ± 2.063
LP4	18	98.27 ± 2.537
LP5	18	99.92 ± 1.402
LP6	24	83.15 ± 0.702
LP7	24	95.67 ± 0.407
LP8	18	97.02 ± 0.426
LP9	24	74.45 ± 0.681

Result and Discussion

The prepared sustained release tablets were evaluated for thickness, weight variation, hardness, friability, drug content, in vitro drug dissolution studies.All the studies were performed in triplicate, and results are expressed as mean ±SD. Batches of Losartan potassium were prepared according to table no. 1 by using HPMC K100M, Eudragit RLPO, Eudragit S100, Eudragit L100, MCC, Magnesium stearate, Talc, di-calcium phosphate in direct compression method. Prepared powder blend of different batches were evaluated. Result showed that powder blend have, Angle of repose range from 24.67 ± 1.02 to 28.83 ± 1.04,Carr's index range from 7.080 ± 1.21 to 13.96 ± 1.09 and Husner's ratio range from1.07 ± 0.014 to 1.16 ± 0.010, which indicate good flow property. Hardness, Thickness and Friability was found to be in range of 5.85 ± 0.251 to7.17 ± 0.221, 5.18 ± 0.054to 5.93 ± 0.018, and 0.20 ± 0.09 to 0.51 ± 0.09 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, drug content & *in-vitro* dissolution studies are shown in table no. 3 & 4. 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 (99.92) for LP5. The tablets were subjected for evaluation of *in-vitro* dissolution studies. It was observed that when HPMC k100M and Eudragit RLPO were used as polymer respectively they shows good dissolution rate sustained for 18 hours.

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