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Research Article

DEVELOPMENT AND OPTIMIZATION OF LOSARTAN POTASSIUM TABLETS

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ABSTRACT

The present investigation highlighted the formulation and optimization of losartan potassium tablets. To achieve this goal, various formulation of losartan potassium tablets were prepared and evaluated with respect to the various quality parameters 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, *in vitro* dissolution studies). On the basis of these parameters, the formula was optimized and compared with the innovator. It was observed that the optimized losartan potassium tablets was pharmaceutically equivalent with the innovator. The stability of optimized tablets at various atmospheric conditions was done and stability parameters were satisfactory.

Key words: Formulation**;** Optimization; Pharmaceutically equivalent; Tablet; Losartan potassium

INTRODUCTION

Tablets are solid dosage forms containing medicinal substances with or without suitable diluents. They are 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. However, the process of manufacturing of tablets is complex. Hence, careful consideration has to be given to select right process, and right excipients to ultimately give a robust, high productivity and regulatory complaint product of good quality.[1]

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.[2-4] Its empirical formula is $C_{22}H_{22}ClKN_6O$ and its structural formula is presented in Figure 1.

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 antagonist.[5] It suppresses the effects of angitensin II at its receptors, thereby blocking the rennin-angiotensin 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.[6] Generally, losartan potassium is employed in the management of essential hypertension with lower incidence of side-effects like cough.[2,7] 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.[8] EXP-3174 is a non-competitive antagonist of the AT_1 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.[9] 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.[10]

In the present study, we made an attempt to develop a stable formulation of oral immediate-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 various quality parameters 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). On the basis of these parameters the formula was optimized and compared with the innovator brand (U.S. market product). Then, the *in-vitro* dissolution profile of optimized losartan potassium tablets was compared the with the innovator in various dissolution medias and evaluated stability parameters at various atmospheric conditions.

MATERIALS AND METHODS

Materials

Losartan potassium was a generous gift from Hetero Lab. Ltd, Hyderabad, India. Microcrystalline cellulose pH 200 (Degussa), Aerosil-200 (Roquette France), sodium starch glycolate (FMC), magnesium stearate (Ferror-Belgium), purified talc, and maize starch were used. Various coating materials: D&C yellow No. aluminum lake, FD&C Blue No. aluminum lake, hypromellose (HPMC-15cps), lactose monohydrate, Polyethylene glycol 6000, and titanium-di-oxide were obtained from Colorcon. All the materials used were of the best quality available.

Preparation of losartan potassium tablets

Various formulation of losartan potassium tablets were prepared by direct compression method.

Formulation F1 to F4

All the ingredients were dispensed as per the batch size. Losartan potassium, maize starch (dried), Avicel pH 200, purified talc, Aerosil 200 were shifted through mesh size (#) 60 separately.

These above ingredients were mixed geometrically ratio and blended for 15 minutes in a cone blender. Then magnesium Stearate were shifted through # 60 and mix with the above blend for further 3 minutes. After that, these above blends were compressed using the tear drop shaped punches (Dimension: 11.65 X 7.1 mm tear drop).

Formulation F5

All the ingredients were dispensed as per the batch size. Losartan potassium, maize starch (dried), Avicel pH 200, purified talc, Aerosil 200 were shifted through mesh size (#) 60 separately.

Losartan potassium was mixed with sodium starch glycolate (SSG), and then with the one half of the Avicel. After that, maize starch was mixed with that blend, and then with another half of the Avicel again. Then, purified talc and Aerosil were mixed to the blend. For each step, the blend was mixed for at least 5 minutes and then remixed for 25 minutes in a cone blender. Magnesium stearate was shifted through # 60 and the above blend was mixed for further 3 minutes. Finnaly, the above blend was compressed using the teardrop shaped punches (Dimension: 11.65 X 7.1 mm tear drop).

Formulation F6 to F8

Core tablets of formulation F6 to F8 were prepared using same methodology of formulation F5. 150 ml of purified water were taken and vortexed with stirring (without drawing air into the liquid). Opadry green powder were steadily added to the vortex, avoiding powder to float on water surface. After all, the opadry green powder has been added and mixed for 45 minutes. The coating solution was passed through muslin cloth. The core tablet using R & D auto coater, with following parameters:

1. Pan rpm: 25
2. Inlet temperature: 60^0C
3. Atomizing pressure: 2.5 Psi
4. Peristallatic pump: 1 rpm
5. Bed temperature: 50-52^0C

Applied solution on tablet coating is given until 2 %, 2.5 % and 3 % weight gain to the tablet. Different formulations of losartan potassium tablets were prepared with their compositions are given in the Table 1.

Evaluation of in process parameters for granules

Various in process parameters for granules like loss on drying, bulk density, tapped density, compressibility index and Hausner's ratio were evaluated. Seive analysis of granules was also done.

Loss on drying was determined at 105°C and measured by an electronic loss on drying measurement apparatus (Sartorius, Germany). Bulk density and tapped density was estimated using Bulk density apparatus (Electro lab, Mumbai, India).

Evaluation of finished products

The finished tablets were tested as per standard procedure for average weight (n = 20), weight variation (n = 20), thickness (n = 20), hardness (n = 6), friability (n = 20) and disintegration time (n = 6).

Average weight and weight variation was estimated using Electronic weighing balance (Mettler Toledo, Switzerland). Thickness of the tablets was measured by Electronic thickness measurement apparatus (Mitutoyo, Japan). Tablet hardness was determined using a Schleuniger tablet hardness tester (Schleuniger, USA). Friability test (n = 20) was conducted using Friability tester USP 23 (Electro lab, Mumbai, India).

Drug content of various losartan potassium tablets was determined by HPLC method using HPLC (Water).

Tablet dissolution was assessed using Automatic tablet dissolution apparatus USP II (Electro lab, Mumbai, India) in 900 ml of dissolution medium. The stirring speed was 50 rpm. Total 6 tablets were taken for test. Temperature was maintained 37°C ± 0.5° C through out the experiment. Dissolution study was carried out for 60 mins. After collection of sample in each interval, dissolution medium was replenished with the same volume of respective medium. Samples were withdrawn at regular intervals and diluted to 100 ml with corresponding medium and analyzed for drug content using HPLC (Water).

Then, *in vitro* tablet dissolution of various formulated losartan potassium tablets were compared with U.S. market product and final formulation was optimized.

Stability studies

Optimized formulation were exposed at room temperature, 40°C / 75 % Relative Humidity, and 30°C / 65 % Relative Humidity for 1 month. The tablets were withdrawn for analysis of following parameters:

1. Average weight
2. Hardness
3. Disintegration time (D. T.)
4. Moisture content
5. Assay

RESULTS

All formulation of losartan potassium tablets were produced using direct compression method. Since the losartan potassium is light sensitive material and has a tendency for moisture absorption, all processing was carried out under controlled humidity conditions and moisture content of the blend to be kept as low as possible.

Evaluation of in process parameters for granules

Various in process parameters for granules like loss on drying, bulk density, tapped density, compressibility index and Hausner's ratio were evaluated. These results were satisfactory are listed in Table 2. Seive analysis of granules was also done and presented in Table 3.

Evaluation of finished products

The finished losartan potassium tablets were evaluated for various physical parameters such as averge weight, weight variation, thickness, hardness, friability and drug content. These results were given in Table 4 & 5.

Table 1: Composition (mg) of various losartan potassium tablets

Name of ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Losartan Potassium	100	100	100	100	100	100	100	100
Maize Starch (dried)	20	20	20	20	20	20	20	20
Avicel pH 200	168	162	154	159	159.2	159.2	159.2	159.2
Purified talc	9	9	9	3	3.2	3.2	3.2	3.2
Aerosil 200	-	6	6	6	4.8	5.6	5.6	5.6
Sodium starch glycolate	-	-	8	9	8	9	9	9
Magnesium stearate	3	3	3	3	4.8	3	3	3

Table 2: Various in process parameters for granules like loss on drying, bulk density, tapped density, compressibility index and Hausner's ratio

Parameters	F1	F2	F3	F4	F5	F6	F7	F8
Loss on drying (% w/w)	2.50	3.50	3.40	3.39	4.37	4.19	4.23	4.35
Bulk density (gm/ml)	0.41	0.55	0.56	0.44	0.56	0.44	0.44	0.44
Tapped density (gm/ml)	0.51	0.67	0.68	0.57	0.67	0.54	0.54	0.54
Compressibility Index (%)	18.56	17.80	20.07	23.75	20.93	23.75	23.75	23.75
Hausner's Ratio	1.22	1.21	1.20	1.31	1.20	1.31	1.31	1.31

Table 3: Sieve analysis data of granules (% Blend retained)

Sieve no.	F1	F2	F3	F4	F5	F6	F7	F8
Sieve No.20	0	0	0	0	0	0	0	0
Sieve No.40	0	1.00	1.00	0	2.50	0	0	0
Sieve No.60	21.25	33.00	39.00	25.00	32.50	27.00	27.00	27.00
Sieve No.80	40.00	46.00	57.00	38.00	47.00	44.00	48.00	48.00
Sieve No.100	57.50	58.00	58.00	56.00	59.00	56.00	59.00	63.00
Receiver	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00

Table 4: Average weight, weight variation, and thickness of finished losartan potassium tablets

Formulation code	Average weight (mg)		Weight variation (%)		Tablet thickness (mm)	
	Core tablets	Coated tablets	Minimum	Maximum	Core tablets	Coated tablets
F1	300.40	-	1.14	1.83	4.36-4.44	-
F2	300.90	-	1.26	1.32	4.40-4.44	-
F3	300.26	-	0.48	0.69	4.34-4.39	-
F4	300.04	-	0.78	0.81	4.72-4.90	-
F5	300.39	-	0.48	0.69	4.35-4.39	-
F6	299.85	305.80	0.98	1.10	4.62-4.69	4.66-4.74
F7	300.10	307.64	0.73	0.93	4.46-4.54	4.58-4.67
F8	299.85	309.20	0.98	1.10	4.58-4.64	4.73-4.83

Table 5: Hardness, friability, and disintegration time of finished losartan potassium tablets

Formulation code	Hardness (N)	Friability* (%)	Disintegration time (min)*		Drug content* (%)
			Core tablets	Coated tablets	
F1	55-70	0.41± 0.06	5.23 ± 0.13	-	98.93 ± 2.23
F2	60-75	0.29 ± 0.03	6.11 ± 0.15	-	99.13 ± 5.17
F3	80-90	0.36 ± 0.04	12.00 ± 0.53	-	99.00 ± 5.43
F4	70-85	0.12 ± 0.02	10.45 ± 0.58	-	99.45 ± 3.53
F5	80-90	0.34 ± 0.05	12.00 ± 0.33	-	98.23 ± 6.38
F6	95-115	0.54 ± 0.13	13.09 ± 0.61	14.33 ± 0.52	98.69 ± 3.69
F7	85-95	0.44 ± 0.05	10.21 ± 0.43	12.32 ± 0.30	99.67 ± 3.94
F8	85-95	0.55 ± 0.09	9.40 ± 0.23	13.41 ± 0.39	99.74 ± 4.22

*Values are mean ± SD, (n = 6).

Table 6: Coparative values of difference factor, f_1 and similarity factor, f_2.

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8
f_1	23.98	19.36	14.72	9.26	9.90	2.96	2.96	1.70
f_2	37.39	42.05	47.71	56.09	55.48	76.67	76.67	85.45

Table 7: Stability study results of optimized formulation (for one month)

Conditions	Avg. wt. (mg)	Hardness (N)	D.T. (min)	Moisture content (%)	Assay (%)
Room temp.	309.2	85-90	12.02 ± 1.12	4.53 ± 0.63	98.03 ± 4.98
40°C/75% RH	309.0	90-95	12.56 ± 0.91	4.32 ± 0.92	96.34 ± 6.32
30°C/65% RH	309.2	75-85	11.07 ± 0.71	4.65 ± 0.34	98.03 ± 4.33

The *in vitro* dissolution studies in water (as release medium) were conducted for all the tablet formulations and compared with a innovator brand (U.S. market product tablet of losartan potassium, 100 mg). The *in vitro* dissolution profiles all tablet formulations and the innovator brand are presented in Figure 1 & 2.

To compare the dissolution profiles of all the tablet formulations and the innovator brand, a model independent approach of difference factor, f_1 and similarity factor, f_2 was employed (FDA, 1997)[11] with all time points included in the *in vitro* dissolution studies.

Difference factor, f_1 is the percentage difference between two curves at each time point and is a measurement of the relative error between the two curves:[12]

$$f_1 = \{[\sum_{t=1}^{n}|R_t - T_t|]/[\sum_{t=1}^{n}R_t]\} \bullet 100 \quad \text{.....(1)}$$

where, n is the number of time points, R_t is the dissolution value of reference product at time t and T_t is the dissolution value for the test product at time t.

Similarity factor, f_2 is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between these two curves:[12]

$$f_2 = 50 \bullet \log \{[1 + (1/n) \sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} \bullet 100\} \quad \text{.....(2)}$$

Similarity factor, f_2 has been adopted by FDA and the European Agency for the Evaluation of Medicinal Products (EMEA) by the Committee for Proprietary Medicinal Products (CPMP) as a criterion to compare the similarity of two or more dissolution profiles. Similarity factor, f_2 is included by the Centre for Drug Evaluation and Research (CDER) in their guidelines such as guidance on dissolution testing of immediate release solid oral dosage forms[11] and guidance on Waiver of *In Vivo* Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (FDA, 2000).[13] EMEA inclusion can be located in Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (EMEA, 2001).[14] For two dissolution profiles to be considered similar and bioequivalent, f_1

should be between 0 and 15, while f_2 should be between 50 and 100 (FDA, 1997).[11] Comperative values of f_1 and f_2 for all formulations using the model independent approache are presented in Table 6. Therefore, the formulation F8 is more bioequivalent than other formulations as its f_1 and f_2 values are 1.7 and 85.45 respectvely. Initially, we have formulated formulation F1 and we found that drug release was not fatisfactory. Then, we made an attempt to increase the drug release by adding Aerosil in the next formulation (F2). Drug release was not upto the mark and in the next formulation (F3 and F4), we have added the disintegrant, sodium starch glycolate increasingly. But, the drug release from these formulations were not satisfactorily. Again, in formulation F4, the flow property of granules were not good enough. So, in the next formulation (F5), we attempted to increase the magnesium Stearate quantity by decreasing the Aerosil quantity. The f_2 value of formulation F5 (55.48) crossed the 50 mark and to increase that value we have increased the quantity of Aerosil by decreasing magnesium stearate. But, in the formulation F6, we found increased the hardness (95-115 N) which may result capping problem. So, in the formulation F7 & F8, we made an attempt to decrease the hardness to 85-95 N. In the formulation F6, F7 & F8, we have coated the core tablet 2 %, 2.5 % and 3 % respectively, which results good f_1 and f_2 values (1.70 and 85.45 respectvely) in case of 3 % coating (formulation F8). Hence, formulation F8 was selected as a optimized formulation for further studies.

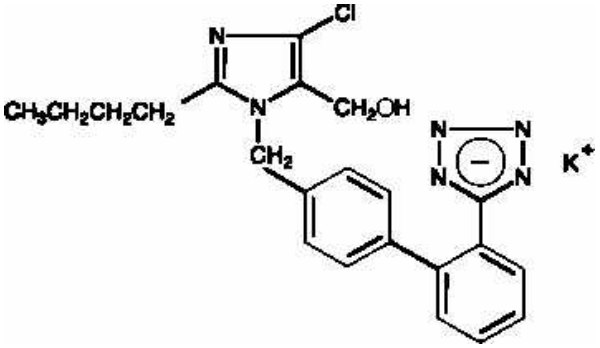

Fig. 1: Structural formula of losartan potassium

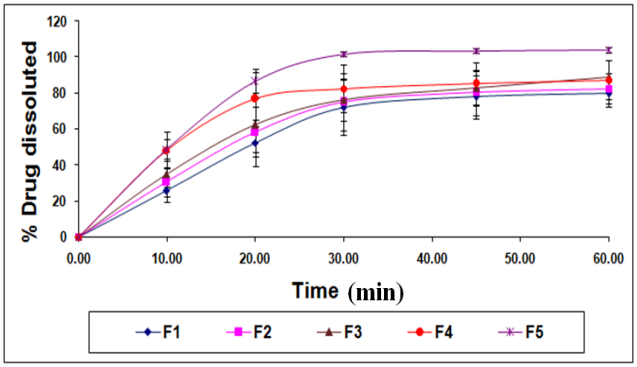

Fig. 2: *In vitro* dissolution profiles (in water) of formulation F1 to F5 (Mean ± SD, n = 6).

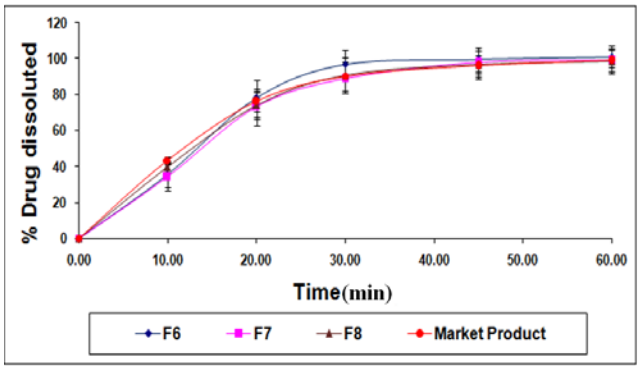

Fig. 3: *In vitro* dissolution profiles (in water) of formulation F6 to F8 and U.S. market product. (Mean ± SD, n = 6).

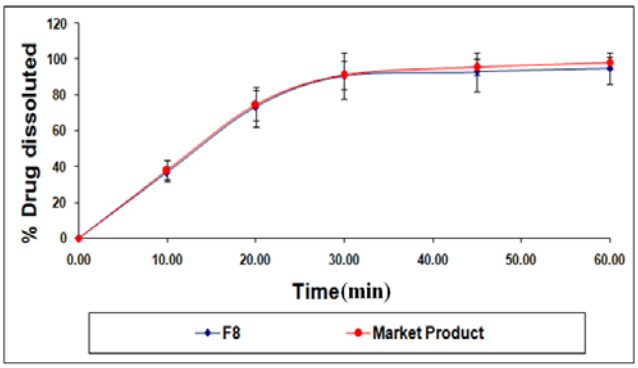

Fig. 4: *In vitro* dissolution profiles (PBS, pH 6.8) of formulation F8 and U.S. market product. (Mean ± SD, n = 6).

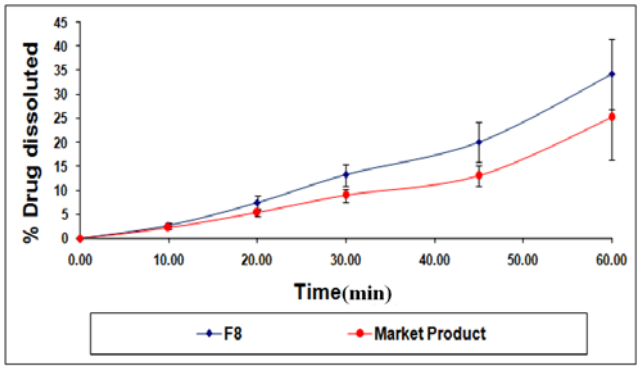

Fig. 5: *In vitro* dissolution profiles (0.1 N HCl, pH 1.2) of formulation F8 and U.S. market product. (Mean ± SD, n = 6).

Finnaly, we have compared *in vitro* dissolution profiles of optimized formulation, optimized losartan potassium tablet (formulation F8) with the innovator tablet (U.S. market product) in different dissolution medias like phosphate buffer saline (PBS), pH 6.8, 0.1 N HCl, pH 1.2. The comparision of *in vitro* drug release from optimized losartan potassium tablet (formulation F8) with the innovator tablet has depicted that the drug release from formulation F8 in 0.1 N HCl, pH 1.2 was faster than the innovator, while the drug release from formulation F8 and the innovator brand in phosphate buffer saline, pH 6.8 was almost similar (Figure 3 & 4). Hence in the acidic environment of stomach, higher amount of losartan potassium from optimized losartan potassium tablet may immediate-release the innovator brand.

Stability studies

Stability studies of the optimized losartan potassium tablet (formulation F8) was carried out at various atmospheric conditions like room temperature, 40°C/75% RH and 30°C/65% RH. Even after the period of one month exposure at various atmospheric conditions different stability parameters like average weight, hardness, dissolution time, moisture content, and drug content (assay) were satisfactory (Table 7). Thus, these results confirmed that the optimized losartan potassium tablet (formulation F8) was stable enough.

CONCLUSION

In conclusion, it could be determined that formulation F8 was the optimized product, which possessed satisfactory quality parameters 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). It was observed that the optimized losartan potassium tablets was pharmaceutically equivalent with the innovator tablet (U.S. market product). Again, the optimized losartan potassium tablet may provide immediate-release of drug than the innovator brand. Even after the period of one month exposure at various atmospheric conditions various stability parameters like average weight, hardness, dissolution time, moisture content, and drug content were satisfactory.

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