Research Article

Comparative *in-vitro* Bioavailability Studies on Different Brands of Losartan Potassium Tablet and its Pharmacoeconomics Study

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ABSTRACT

Losartan potassium is a non-peptide angiotensin II receptor antagonist used in the treatment of hypertension. It exhibits highly variable and low oral bioavailability approximately 33%. Losartan is, therefore, considered a class III in the Bio-pharmaceutics Classification System, because it has high solubility and low permeability. The objective of this study was to evaluate the suitable brand of Losartan potassium tablet having better dissolution profile, to evaluate study of physicochemical equivalence of different brands as well as to determine that which brand is economically as well as therapeutically effective for the patient of hypertension. Six brands (five national and one multinational brand) of Losartan potassium 50mg were collected randomly from different pharmacies. Six selected brands were coded as F1, F2, F3, F4, F5 and F6. The different brands were evaluated for hardness, friability, weight variation, disintegration, chemical assay and dissolution tests. Different brands were found within in the limits for friability and disintegration time tests. All the coated tablets passed the weight variation test as the percentage of weight variation was within USP limits of ± 7.5% of the average weight. The chemical assay test of all the tablets showed that none had potency less than the required specifications of USP. In comparison, F5 and F6 brands showed better results in terms of compliance with USP results limits for different physico-chemical tests. The results of all the tests performed show that GMP and cGMP guidelines have been followed during manufacturing. This study proved the physicochemical equivalent of the six different brands. So if one brand is not available in the market then any of the other three brands can be taken in place of that unavailable brand according to the economic conditions of the patients.

Keywords: Losartan potassium, In-Vitro Dissolution, Disintegration Time, Physicochemical Equivalency.

INTRODUCTION

Hypertension is the most common cardiovascular disease. The prevalence of hypertension increases with advancing age; for example, about 50% of people between the ages of 60 and 69 years old have hypertension, and the prevalence is further increased beyond age 70.

Elevated arterial pressure causes pathological changes in the vasculature and hypertrophy of the left ventricle. As a consequence, hypertension is the principal cause of stroke, is a major risk factor for coronary artery disease and its attendant complications myocardial infarction and sudden cardiac death, and is a major contributor to cardiac failure, renal insufficiency, and dissecting aneurysm of the aorta. Hypertension is defined as a sustained increase in blood pressure ≥140/90 mm Hg, a criterion where the risk of hypertension-related cardiovascular disease is high enough to merit medical attention[1].

Losartan is a non-peptide angiotensin II receptor antagonist with high affinity and selectivity for the AT_1 receptor[2-7]. Losartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by inhibiting the binding of angiotensin II to the AT_1 receptor[2,5,8].

AT_1 receptor blockade results in an increase in plasma renin activity (PRA) followed by increases in plasma angiotensin II concentration.

Peak plasma levels of losartan and EXP 3174 occur approximately 1 to 3 hours after oral administration, respectively, and the plasma half-lives are 2.5 and 6 to 9 hours, respectively. Both losartan and its active metabolite are ≥ 99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 liters. Approximately 14% of an oral dose of losartan is converted to the 5-carboxylic acid metabolite EXP 3174, which is more potent than losartan as an AT_1-receptor antagonist. The metabolism of losartan to EXP 3174 and to inactive metabolites is mediated by CYP2C9 and CYP3A4. The plasma clearances of losartan and EXP 3174 (600 and 50 ml/min, respectively) are due to renal clearance (75 and 25 ml/min, respectively) and hepatic clearance (metabolism and biliary excretion). The plasma clearance of losartan and EXP 3174 is affected by hepatic but not renal insufficiency[9].

The usual daily dose given orally in children ≥6 years of age initially, 0.7 mg/kg (up to 50mg) once daily (maximum dosage of 1.4 mg/kg or 100 mg daily). In adults initially, 50mg once daily in adults without intravascular volume depletion. In adults with depletion of intravascular volume, the usual initial dosage is 25 mg once daily. 25–100mg daily, given in 1 dose or 2 divided doses; no additional therapeutic benefit with higher dosages. If

effectiveness diminishes toward the end of the dosing interval in patients treated once daily, consider increasing dosage or administering drug in 2 divided doses. Maximum 1.4 mg/kg or 100 mg daily[10,11].

The dissolution profile of all selected brands is in the range of standard limits so after its pharmacoeconomics evaluation it is recommended that anyone of the selected brands can use according to the financial status of the patients. All brands are therapeutically equivalent so patients can use any brand alternatively according to his economic conditions. However, out of these six brands F5 showed better dissolution profile and is comparatively of low cost.

This study was aimed to compare the *in vitro* equivalence of commonly prescribed brands of losartan potassium in Pakistan and to help healthcare providers select the most economical brand of losartan potassium having better *in vitro* performance.

MATERIALS AND METHODS

Chemical

The standard Losartan potassium powder was gifted by Pearl Pharmaceutical Islamabad, Pakistan. Distilled water used for dilution was of analytical reagent grade.

Sampling

To study the *in vitro* drug release five national and one multinational brands of losartan potassium were collected randomly from different pharmacies. The samples were checked for their batch number, manufacturing and expiry dates, pack size and price per pack. These samples were randomly coded as F1, F2, F3, F4, F5, and F6 the reference brand and stored properly. All the collected samples have labeled active ingredient Losartan potassium 50mg and were packaged in blister packing.

Tests of Physicochemical Parameter

Hardness test

Five tablets from each brand were selected randomly and subjected to hardness test by using Monsanto hardness tester.

Friability test

Friability test has been performed on tablets of each brand of losartan potassium and subjecting to a uniform tumbling motion for a specified period of time i.e. 25 rotation/minute for 4 minutes in model No. FOD-02 Roche friabilitor and the weight loss is determined. Friability test is done to check if a tablet abrades during transportation by taking initial and final weight and determining the weight loss. The tablets from each brand were re-dusted and re-weighed. According to the USP, the tablets should not lose more than 1% of their total weight.

Weight variation test

Twenty tablets from each brand were weighed on electronic balance and the average weight was calculated. Each tablet was then weighed individually and maximum and minimum values for the weight of the tablet were noted.

Disintegration test

The disintegration test was carried out in accordance to USP specifications by using Disintegration Tester. Six tablets from each brand were subjected to disintegration test. One tablet was placed in each of the six tubes of the basket. Then disks were added to each tube of the basket. The time taken for the entire tablet to disintegrate completely was recorded in minutes. Water was used as a medium and test was performed at 50 RPM for 30mins at 37°C.

Chemical assay

The chemical assay of film coated tablets of each brand was carried out according to USP by using 0.1 N NaOH by using a UV spectrophotometer (Model No. 1700, Shimadzu, Japan).

Standard preparation

About 50mg of reference working standard of losartan potassium was weighed accurately on electronic balance and transferred into a 100 ml volumetric flask. The volume was made up to the mark and mixed. 1 ml of the first dilution was taken into another 25 ml volumetric flask and volume was made up to the mark.

Sample preparation

20 tablets were weighed on electronic balance and average weight of the tablet was calculated. Tablets were grinded to a fine powder. Powder equivalent to about 50 mg of losartan potassium was weighed accurately and transferred into a 100 ml volumetric flask. 1ml of the filtrate was taken into another 25 ml volumetric flask and volume was made up to the mark.

Procedure of assay

Both standard preparation and sample preparation were scanned between 196–226 nm and the absorbance was taken at the maximum wavelength (λ_{max}) at 224 nm using distilled water as blank solution.

% of Losartan potassium = (Absorbance of sample/Absorbance of standard) x 100

In-vitro Dissolution Test

The in vitro dissolution test of film coated tablets of each brand was carried out according to USP. The dissolution test was conducted using USP type II apparatus (PharmaTest Germany type PTWS3) at 37±0.5°C and 50 rpm with six sections assembly according to the USP 30 procedure. Dissolution media used was distilled water. The medium was maintained at 37 ± 0.5°C. Samples were assayed by a validated UV method (Model No. 1700,

Shimadzu, Japan). The concentration of each sample was determined from a calibration curve obtained from pure samples of losartan potassium.

Parameters of dissolution test

Medium: Distilled water maintained at 37±0.5 °C

Volume: 900 ml

Apparatus: 2 (Paddle type)

Speed: 50 RPM

Time: 30 minutes

Limits: Not less than 80% (Q) of the labeled amount of losartan potassium is dissolved in 30 minutes.

Procedure of dissolution test

Six tablets were taken and one tablet was placed in each of the six baskets. Dissolution test was carried out according to above mentioned parameters. After completion of 30 minutes, the dissolved amount losartan potassium was determined by employing UV absorption at the wavelength of maximum absorbance (λ_{max}) at about 256 nm on the filtered portion of solution under test suitably diluted with the dissolution medium to a concentration of 0.01 mg/ml in comparison with reference working standard solution having a concentration of 0.01 mg/ml in the same medium using distilled water as blank solution.

% of losartan potassium = (Absorbance of sample/Absorbance of standard) x 100

Statistical analysis

The data of dissolution test was evaluated statistically by analysis of variance (ANOVA) and comparison among mean dissolution data was made by Least significant difference (LSD) test.

RESULTS AND DISCUSSION

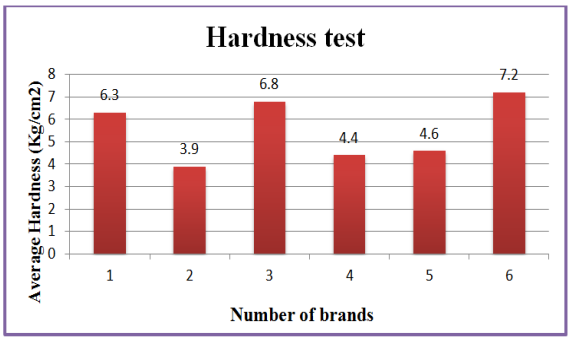

Figure 1: Hardness Test

The average hardness of tablets was determined by using Monsanto hardness tester. The hardness of all brands ranges from (3.9-7.2 Kg/cm^2). Maximum hardness was observed 7.2 Kg/cm^2 for brand F6 and minimum hardness was 3.9 Kg/cm^2 for brand F2. The tablets of different brands possessed good mechanical strength with sufficient hardness. The hardness of all brands was found to be within limits (<10 Kg/cm^2).

According to the USP, the tablets should not lose more than 1% of their total weight. All the brands were passed the friability test. The % friability ranges from (0.0-0.2%).

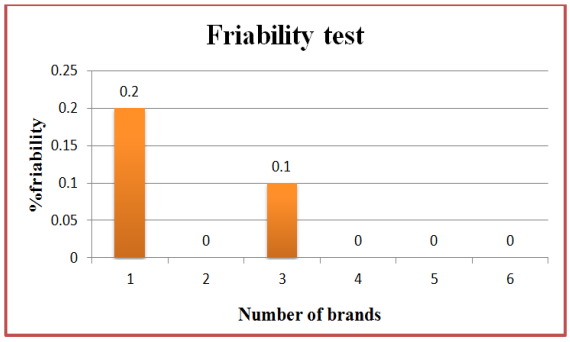

Figure 2: Friability Test

The average weights of tablets of six different brands of losartan potassium were found in the range of (132.5-200.5mg). All the film coated tablets passed the weight variation test as the percentage of weight variation was within USP limits of ± 7.5% of the average weight.

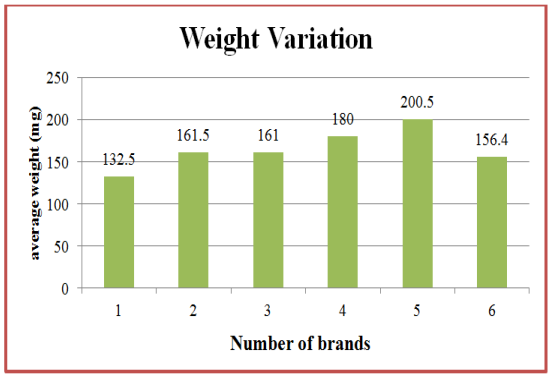

Figure 3: Weight variation Test

Disintegration test was carried out under USP specifications. The tablets of different brands showed small differences in disintegration time ranges from (10-14mins). Maximum D- time was 14mins of brands F3 and F5, and minimum was 10mins of brands F4 and F6. The D time must be in the range of 30mins for film coated tablets as mentioned in USP.

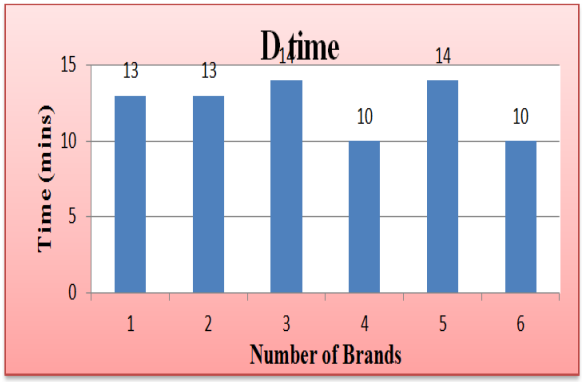

Figure 4: Disintegration time Test

The chemical assay of tablets was carried out in accordance with USP 30. 0.1N NaOH was used as a solvent. There was no considerable difference in chemical assay of six brands. The results of chemical assay were in the range of 94.66% (F6) to 108.23% (F3). The brands showed variation in the percentage of assay but lie in the standard limits (>75%) so the test was passed for all brands.

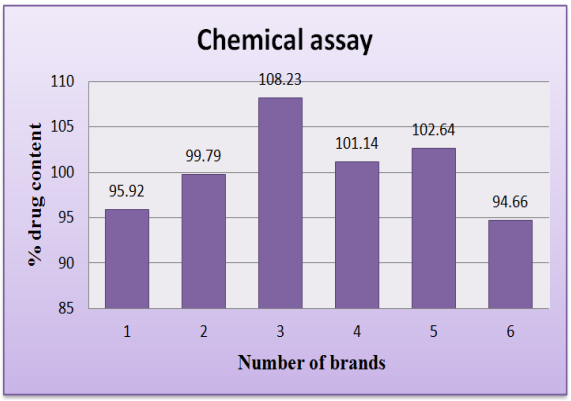

Figure 5: Chemical Assay

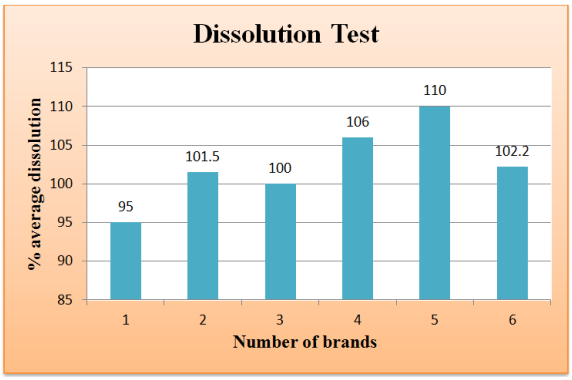

Figure 6: Dissolution Test

The *in vitro* dissolution test was carried out in accordance with USP 30 by using PharmaTest Germany type PTWS3 and UV apparatus of Shimadzu Pharma Spec 1700. The maximum average dissolution (110.0%) was observed for F5 while the minimum average dissolution (95.0%) was shown by F1. It has been reported that dissolution rate has a direct effect on the bioavailability profile of tablet dosage forms because it can be used to determine the pattern of drug release *in vivo*.

Price variation of all the brands was checked and compared indicating a fact that all the local brands are less in price as compare to brand leader (F6) while having similar physicochemical property. Local brands took less time to dissolve and having all other parameters similar to brand leader, but having low prices than F6, indicating the fact that they are physicochemical equivalent with brand leader which having a cost of Rs. 440/20 tablets.

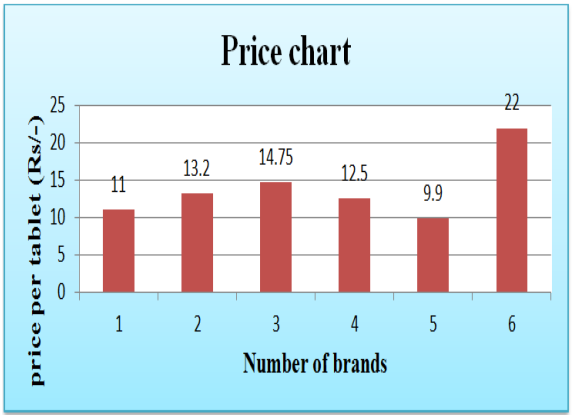

Figure 7: Price comparison

The tablet is called as ideal when it shows the high value of hardness, low disintegration time and readily dissolve. In comparison, F6 brand met the ideal conditions having maximum hardness 7.2 kg/cm^2, disintegration time 10 mins and % dissolution 102.2%. It showed that the drug was prepared according to the GMP and cGMP. It also showed that the concentration of different formulation components was added in reasonable amount. The brand F1 did not meet the ideal conditions as it has maximum hardness 6.3 kg/cm^2 but disintegration time is high as compared to other brands and dissolution rate is lowest 95%.

Table 1: Different brands of Losartan Potassium tablets

Sr#	Brands	Batch #	Mfg date	Expiry date	Pack size	Price/pack(Rs/-)
1	F1	2v	02/14	02/17	2x10	220
2	F2	FK156	10/14	09/16	1x10	132
3	F3	T2770	08/14	08/16	2x10	295
4	F4	H8775	09/14	09/16	2x10	250
5	F5	032	08/14	08/16	2x10	198
6	F6	A4465	09/14	09/16	1x10	220

Table 2: Complete Evaluation of all selected Brands

S. No	Parameters	F1	F2	F3	F4	F5	F6
1	Hardness (Kg/cm2)	6.3	3.9	6.8	4.4	4.6	7.2
2	% Friability	0.2	0.0	0.1	0.0	0.0	0.0
3	Weight variation (± %)	132.5±7.5	161.5±7.5	161±7.5	180±7.5	200.5±7.5	156.5±7.5
4	Disintegration (min)	13	13	14	10	14	10
5	Chemical assay (%)	95.92	99.79	108.23	101.14	102.64	94.66
6	Dissolution (%)	94.6	101.7	100.8	107.17	110.4	102.3
7	Price/tab (Rs/-)	11.00	13.20	14.75	12.50	09.90	22.00
8	Price/20units (Rs/-)	220	264	295	250	198	440

CONCLUSION

All the selected brands of losartan potassium 50mg were physico-chemically equivalent so if one brand is not available in market, anyone of the rest of the brands can be prescribed by the physician.

The results of all the tests performed showed that GMP and cGMP guidelines have been followed during manufacturing. The dissolution profile of all selected brands was in the range of standard limits so after its pharmacoeconomics evaluation it is recommended that anyone of the selected brands can be used according to the financial status of the patients. All brands were therapeutically equivalent so patients can use any brand alternatively according to his economic conditions. However, out of these six brands F5 and F6 showed better dissolution profile and F5 is comparatively of low cost 198 Rs./- 20tablets.

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