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Research Article

Comparative *In-Vitro* Bioavailability Studies on Different Brands of Levofloxacin Tablets

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Abstract

There are several generics of Levofloxacin tablets available within the drug delivery system in India. The increasing level of use of Levofloxacin tablets in the clinical practice creates the need to monitor and ascertain the quality of the various brands available in the drug market for quality control assessment and for purpose of generic substitution. In this study, the physiochemical properties of various brands of Levofloxacin available in the market were assessed. All the products have satisfactory results in respect of uniformity of weight, hardness test, friability test, thickness, disintegration and dissolution profiles. Every test related to the evaluation of Levofloxacin 250 mg tablets IP was successfully finished according to USP and IP. The important quality characteristics of Levofloxacin 250 mg tablets IP are well defined and controlled. There are no outstanding quality issues that would have a negative impact on the benefit balance. The efficacy of these tablets was well established which lead to patient with microbial contamination to get expected therapeutic effects and minimum side effects. Everything was satisfactory and consistent with that for the cross-reference product. The quality of the products was acceptable. So, this study revealed that collected samples of Levofloxacin 250 mg tablet available in Andhra Pradesh, India manufactured accordingly to cGMP as well as another standard monograph.

Keywords: *Levofloxxacin; Bioavailability; Generic Drugs*

Introduction

Levofloxacin is chemically a chiral fluorinated carboxy quinolone, is the pure (-) - (S) enantiomer of the racemic drug substance Ofloxacin. The chemical name is (-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido [1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate. Levofloxacin fights bacteria in the body. Levofloxacin is used to treat bacterial infections of the skin, sinuses, kidneys, bladder, or prostate. Levofloxacin is also used to treat bacterial infections that cause bronchitis or pneumonia, and to treat people who have been exposed to anthrax or plague [1,2].

This study aimed to compare the *in vitro* equivalence of commonly prescribed brands of Levofloxacin in Chittoor, Andhra Pradesh and to help the healthcare providers select the most economical brand of Levofloxacin having better *in vitro* performance.

Materials and Methods

All chemicals used were of Analytical Grade. The reference sample of Levofloxacin was obtained from Dr. Reddy's Laboratories, Hyderabad as a gift sample. Six different Levofloxacin brands were purchased from retail pharmacies in Chittoor. The samples were checked for their batch number, manufacturing and expiry dates, pack size nd prize per pack. These brands were coded as G-1, G-2, G-3, G-4, G-5 and I-1 for generics and innovative drug respectively. All the samples were of uniform label claim of 250 mg of levofloxacin.

Tests of physiochemical parameters

Hardness Test

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

Friability Test

Friability test is done to check if a tablet abrades during transportation. It is performed by subjecting each brand of tablets in to a uniform tumbling motion for a specified number of times for a specified time, i.e.25 rotation/minute for 4 minutes in Roche Friabilator and the weight loss is determined. 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 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 process was performed by placing six tablets from each brand, one in 6 baskets. Baskets were then immersed in simulated intestinal fluid at 37°C, which was prepared as per the procedure given in IP 1996. The disintegration apparatus was operated for about 30 minutes. The procedure was repeated for each brand of tablets.

Chemical Assay

The chemical assay for each brand was performed using a UV visible spectrophotometer.

Standard Solution

The standard stock solution was prepared by dissolving 100 mg of pure sample of levofloxacin in 100 ml of distilled water to get a concentration of 1mg/ml. An aliquot of 10 ml of standard stock solution was place in a 100 ml volumetric flask and the volume was made up to the mark to get a concentration of 100 µg/ml.

Sample Preparation

Twenty tablets of each brand were weighed separately and the average weight of each was estimated. Tablets were powdered and an amount of powder equivalent to 100 mg of drug Levofloxacin was transferred in to separate 100 ml volumetric flasks. About 20 ml of distilled water was added to each flask and the drug was extracted with intermittent shaking for 15 mins. The volume of all the flasks was made up to the mark with distilled water. All the solutions were filtered using Whatman filter paper and the solutions were labelled appropriately as I-1, G-1 to G- 6.

From these test stock solutions, working solutions were prepared and labelled for further use. Three different dilutions were made at different concentration levels namely 4, 6 and 8 µg/ml for all the brands. Absorbance values were measured at the λ max. The amount of drug present in each tablet is calculated using the following formula:

$$\text{Amount of Levofloxacin (mg)} = \frac{AT \times CS \times DF \times W1}{AS \times W2} \quad \text{eqn (1)}$$

AT = Absorbance of Test solution

AS = Absorbance of Standard solution

CS = Concentration of Standard solution

DF = Dilution factor

W1 = Average Weight in mg

W2 = Weight taken in mg

In vitro Dissolution Test

Dissolution test was carried out by USP paddle apparatus. The *in vitro* dissolution study was carried out using apparatus II (paddle type). About 900 ml of dissolution medium was transferred into the dissolution jars and were placed in the test assembly which was maintained at 370C ± 10C. The medium was allowed to attain the set temperature. The rotations per minute (rpm) were set to 50. The test samples were introduced inside the dissolution jar and the test assembly was brought down to the static position and the medium was stirred at 50 rpm. About 0.5 ml of the samples were withdrawn at various time intervals such as 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55 and 60 minutes using a graduated pipette. The pipette content was transferred immediately to clean and dried 10ml volumetric flasks. The equal volume of fresh dissolution medium was replaced after each sampling and maintained at the correct temperature. The sample withdrawn was diluted to 10ml with respective buffer and the absorbance was measured at 292 nm. The percentage drug release was then determined.

Percentage of drug release (%) = [Amount of drug released (mg/ml)/ drug content in label (mg)] × 100 ------ eqn (2)

Statistical Analysis

Fit Factor

The similarity factor for reference (innovator drug) versus generic drugs were calculated using the following formula and the results are shown below:

$f2 = 50 + \log \{[1+ (1/n) \Sigma t=1 * n (Rt-Tt) 2]-0.5 \times 100\}$

$f1= \{[\Sigma t=1n |Rt-Tt|] / [\Sigma t=1nRt]\} \times 100.$

------ eqn (3)

Where, f2 is the similarity factor and f1 is the dissimilarity factor.

ANOVA

The results of dissolution studies were subjected to comparison using one - way ANOVA.

Results and Discussion

The Hardness was tested using Mosanto Hardness tester. Maximum hardness was observed as 9.8 Kg/cm^2 for brand G-1 and minimum hardness was 5.0 Kg/cm^2 for brand G-4. 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 pass the friability test. The % friability ranges from 0.0 - 0.02%.

The average weights of tablets of six different brands of tablets were found in the range of 0.328 - 0.378 gm. All the film coated tablets passed the weight variation test as the percentage of weight variation was within the USP limits of ± 5% of average weight.

Disintegration test was carried out under USP specifications. The tablets of different brands showed small differences in disintegration time ranges from (08 – 24 mins). Maximum disintegration time was 24 mins of brand I-1 and minimum was 08 mins of brands G-1 and G-3. The disintegration time must be in the range of 30 mins for film coated tablets as mentioned in USP.

The Chemical assay was carried out using UV absorbance method. There was no significant difference in chemical assay of all brands. The results were in the range of 97.3 to 102.51%. Though few variations were observed among the brands, the deviation was found to lie within the limit of 97 - 103%.

The percentage release of all brands of tablets was calculated and shown in the table 6. The maximum average dissolution (98.1%) was observed for I-1 while the minimum average dissolution (90.1%) was shown by G-3. 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 that all the brands are similar in price while having similar physicochemical properties.

The similarity factor for reference (innovator drug) versus generic drugs were calculated. The F2 values ranging from 69.74 to 73.91 shows the similarity between the Innovator and Generic brands. Proves to be Bioequivalent.

The results of dissolution studies were subjected to one way ANOVA. The F ratio value is 0.96376; the p value is 0.437; The result is non - significant at $p < 0.5$. Hence all Generic drugs poses similar bioequivalent properties as that of innovator drug [3-17].

Conclusion

All the selected brands of Levofloxacin 250 mg were physico-chemically equivalent, so if one brand is not available in the market, any of the rest brands can be prescribed by the physician. The results of all the test 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. All brands were therapeutically equivalent. The price of all six brands were found to be same. Hence physician can prescribe any one of the six brands.

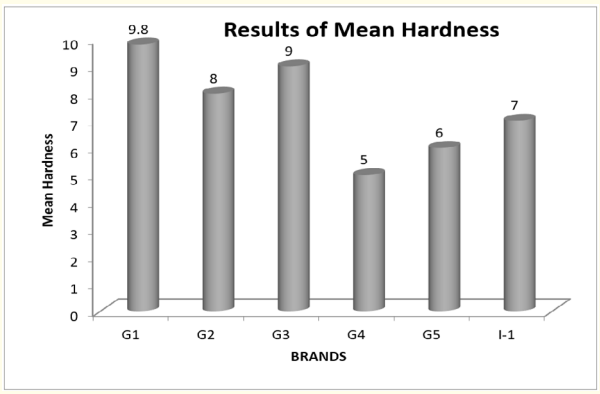

Figure 1: Results of Hardness Test.

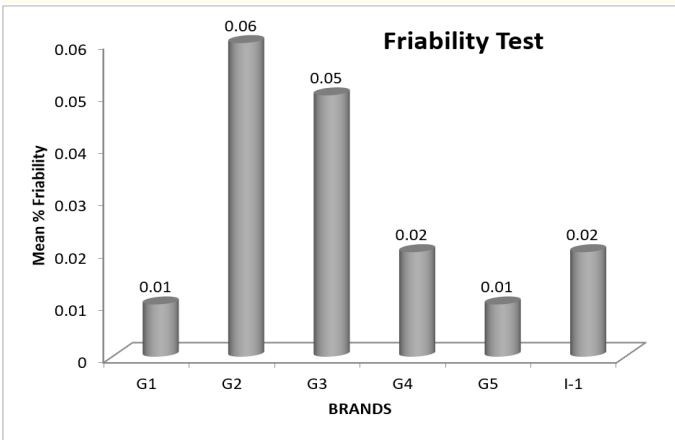

Figure 2: Results of Friability Test.

Figure 3: Results of Weight Variation.

Figure 5: Results of Chemical Assay.

Figure 4: Results of Disintegration time.

Code	G1	G2	G3	G4	G5
F2	36.36	33.59	48.56	23.14	42.45
F1	16.74	17.49	10.40	28.94	13.49

Table 1: Fit factor for all Generic Drugs.

Source	SS	Df	MS	
Between - treatments	1989.456	4	497.364	F = 0.72117
Within - treatments	27586.382	40	689.659	
Total	29575.838	44		

Table 2: Results of ANOVA.

The F ratio value is 0.72117; the p value is 0.582; The result is non - significant at $p < 0.5$

	Levoflox* G-1	Levomac* G-2	Lovolkem* G-3	Leon* G-4	Lek* G-5	Levaquin* I-I
% Purity##	97.30	102.5	100.2	101.4	98.6	99.3
% Recovery##	97.75	100.41	103.12	101.27	98.92	96.75
%Weight variation**	0.328	0.695	0.751	0.351	0.372	0.357
Length(cm)***	1.30	1.80	1.30	1.10	1.00	1.70
Width(cm)***	0.60	0.90	0.20	0.50	0.50	0.80
Thickness(cm)***	0.40	0.50	0.50	0.50	0.50	0.50
% Friability**	0.01	0.06	0.05	0.02	0.01	0.02
Hardness(kg/cm$^{2)}$***	9.8	8	9	5	6	7
Disintegration**** Time (minutes)	8	10	8	9	13	24
Dissolution (% amount of drug elease)#	95.6	98.2	90.1	93.4	94.5	92.5

Table 3: Summary of the results of evaluation parameters.

I-Innovative drug G-Generic drug * Label claim-250 mg

** - Average measurement of 20 tablets; *** - Average measurement of 10 tablets

****- Average measurement of 6 tablets

- Average Measurement of 3 tablets; ## - Average measurement of 6 tablets.

Figure 6: Results of Dissolution Test.

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