Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 4, Suppl 4, 2012

Research Article

POST MARKET SURVEILLANCE OF DIFFERENT BRANDS OF OFLOXACIN 200 MG TABLETS AVAILABLE IN LOCAL MARKET OF KARACHI (PAKISTAN)

SAMREEN KHALID, [1]SHAHNAZ GAUHAR*, [2]RABIA REHMAN AND [2]SAKINA FATIMA

Department of Pharmaceutics, Faculty of Pharmacy, University of Karachi, Karachi, Pakistan, [1]Department of Pharmaceutics, Rak College of Pharmaceutical Sciences, Rak Medical and Health Sciences University, Ras-Al Khaimah, UAE; [2]Department of Pharmaceutics, Jinnah College of Pharmacy, Jinnah Medical College, Karachi, Pakistan. Email: shahnaz_gauhar@yahoo.com

Received: 02 July 2012, Revised and Accepted: 08 Aug 2012

ABSTRACT

Objective: The aim of present study was to compare the dissolution profiles of ofloxacin (200mg) tablets and examine the feasibility of biowaiver study without performing bioavailability study to achieve the defined quality of the drug. Brands are available in the market at significant price differences, although physicians may have serious concerns as to the efficacy of the different products; they sometimes prescribe economic products due to economic constraints.

Methods: Six brands of ofloxacin 200 mg tablets have been evaluated using some quality control parameters, such as weight variation, hardness, assay, disintegration and dissolution test with the aim to assess its bioequivalence. Dissolution testing was performed according to FDA requirements for all brands for requesting biowaiver. Similarity factor (f2) was used to assess bioequivalent between six formulations.

Results: All brands fulfilled biowaiver requirements at pH 1.2. However, significant variations in dissolution profiles were observed in phosphate buffer (pH 4.5) and in phosphate buffer (pH 6.8). Subsequently the results indicated that 2 of the 6 brands may not be used interchangeably with the chosen 'innovator' brand.

Conclusion: The results suggest that the formulation and/or the manufacturing process affect the dissolution and thus the bioavailability of the drug products. Thus the post-market monitoring is very crucial for effective clinical outcome and this study has emphasized that chemical equivalence does not indicate bioequivalence. The significance of the observed invitro differences must be confirmed by an invivo bioequivalence study.

Keywords: ofloxacin, dissolution testing, quality control parameter, similarity factor f2, Biowaiver Conditions

INTRODUCTION

The quality control of drugs, which is in an international framework not uniformly regulated, and quasi-absence of quality control laboratory raises the problem related to the quality, safety and effectiveness of generics and proprietary drugs in the market. Health professionals are confronted with a wide choice of multi-source generics and trade name, imported and locally produced with unproven effectiveness, safety, quality and bioequivalence.

Pharmacopeial testing confirms these properties according to fixed standards. *In vitro* dissolution testing can also be used in some cases not only to determine the quality of the pharmaceutical products but also to demonstrate bioequivalence to the brand name product.

Due to the importance of ofloxacin as an antibiotic for widely resistant bacteria and the importance of price on a community basis, six running brands of ofloxacin products that are available in local market of Karachi were analyzed.

Ofloxacin is a synthetic chemotherapeutic antibiotic of the fluoroquinolone drug class considered to be a second-generation fluoroquinolone[1,2]. It is a bactericidal and DNA gyrase inhibitor widely prescribed in acute and chronic lower respiratory tract infections and infections of ear and nose [3]. It is a broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative bacteria. It functions by inhibiting DNA gyrase, a type II topoisomerase, and topoisomerase IV [4].

There are multiple sources of ofloxacin brands which are available and majority of them are locally manufactured. Evaluation of the quality, purity, safety and potency of various brands is an important aspect to determine the therapeutic efficacy of these locally manufactured brands. For the health care providers to use these brands interchangeably the bioequivalence of these brands have to be ascertained and there should be continued post market surveillance of brands.

The objective of this study was to investigate the pharmaceutical quality evaluation of different brands of ofloxacin 200 mg tablet and the efficacy and comparison of dissolution profiles of six brands of ofloxacin tablets with innovator ofloxacin under biowaiver conditions.

Dissolution testing is a useful tool for determining batch to batch uniformity and quality control of solid dosage form and it can be used as a surrogate for in-vivo availability. For the quality assessment various physicochemical test were performed which includes weight variation, thickness, hardness, diameter, disintegration, content assay and dissolution.

MATERIALS AND METHODS

Analysis of ofloxacin was carried out on UV -Vis Spectrophotometer (Shimadzu UV 1800, Tokyo Japan), Electronic balance (Mettler Toledo, England), Hardness Tester M.H-1 Galvano Scientific, pH meter (jenway model no 3510), disintegration (Veego SER.No.08/0505 Typ:BTD-2) and Dissolution Appartus (Erweka DT 600).

Reference ofloxacin was kindly gifted sample from Zafa Pharmaceutical (private) Limited. Six ofloxacin brands were obtained from local market of Karachi (Pakistan). Hydrochloric acid (Merck), Potassium Dihydrogen Posphate, Sodium Hydroxide (sigma Aldrich- Germany) and Distilled water were prepared freshly.

Physiochemical Parameters

Any deviation from the physical parameters can lead to marked differences in the dissolution profiles. Assessment of physicochemical parameters which include uniformity of weight, hardness, diameter, thickness, disintegration test and assay content were done according to United State Pharmacopeia (USP-32) and British Pharmacopeia (BP-2007)

Weight variation: Weight variation test were performed on twenty units of each brands and % deviation was calculated. According to USP for tablets weighing less than 130 mg, between 130-325 mg and above than 325 mg deviation limits should be ±10%, ±7.5% and ±5 % respectively [5,16]

Thickness and diameter: Thickness and diameter are important parameter involved in packing because tablets are sealed into grooves of blister. Tests were performed on twenty units of each brand and limits applied for thickness and diameter were ±5% and ±3% 12.5 mm and 15 mm respectively [6]

Hardness: Crushing strength is an important parameter to evaluate the compression forces. If a tablet requires more force to be broken, dissolution profile will be affected. Ten units of each brand were used. Minimum and maximum force needed to break the tablet was determined (British Pharmacopoea-2007)[7].

Disintegration Test: disintegration test was evaluated to measure the time required to break tablets into fragments to increase the surface area which produces higher solubility of the drug [8]. DT was performed on six units of each brand in 0.1 N HCl solutions at 37±0.5ºC [9]

Determination of Content Assay:

Assay for content uniformity was determined according to specifications of USP-32[10]; limits should be within 90-110%

1. Crushed 20 tablets of ofloxacin (of each brand separately).
2. Weighed 50 mg equivalent powder of ofloxacin.
3. Dissolved in 100 ml of 1 M sodium hydroxide and shaken for 3 min, then further diluted up to 200 ml with 1 M sodium hydroxide and allowed to stand for 15 min.
4. 2 ml aliquot of the stock solution was taken and further diluted up to 25 ml with water.
5. The absorbances of the resulting solutions (20 µg/ml) were determined at 294nm.
6. The procedure was repeated for five different brands of ofloxacin tablets used in the present study.

Dissolution Study

The dissolution profile of ofloxacin tablets was evaluated in 900ml of buffer pH 1.2, 4.5 and 6.8 using US Pharmacopoeia dissolution apparatus II (USP-32) [11].

Preparation of Reagents

1) **pH 1.2:** 8.5 ml of HCl and dissolve in 1000 ml of distilled water (USP-23)
2) **pH 4.5:** 6.8 g of Potassium dihydrogen phosphate and dissolve in 1000 ml of distilled water (B.P 2002)
3) **pH 6.8:** Potassium Phosphate, Monobasic, (0.2 M). Dissolve 27.22g of Monobasic Potassium Phosphate (KH2PO4) in water, and dilute with water to 1000 ml.

Take 250 ml of 0.2 M Monobasic potassium phosphate solution and 112 ml of 0.2 M NaoH solution and make up the volume upto 1000 ml with distilled water. (USP 27) [12]

Dissolution Procedure

The temperature and degree of agitation were set at 37°C ± 0.5 and 50 rpm respectively. Samples (10 ml) were collected at predetermined time intervals 5, 10, 15, 30, 45, 60 and 70 minutes and filtered (Millipore) to remove any insoluble excipients.

10ml of fresh medium already equilibrated to 37 °C was replaced into dissolution medium after each sampling in order to maintain sink condition. Six tablets per brand were used for the study.

The filtered samples were analyzed by the Ultra-violet spectrophotometric method (UV) at 294 nm wavelength. The concentration and the percentage release in each time interval was determined.

Standard preparation: dissolve 50 mg of ofloxacin reference powder in 100 ml of mediums (pH = 1.2, 4.5, and 6.8 separately). Dilute 2 ml of stock solution in 100 ml of respective medium to obtain concentration 10 µg/ml

Dissolution Profile Comparison

Differences in the *in vitro* dissolution profiles were assessed using the model-independent approach based on the similarity factor (f_2) as follows (US FDA, 1997)[13]

Similarity factor was calculated by using formula mention below.

$$f_2 = 50 * \log \{[1 + (1/n) \Sigma t=1n (Rt-Tt) 2] -0.5 * 100\}$$

Where Rt and Tt are percent dissolved at each time point for reference and test respectively.

The f_2 is a measurement of the similarity in the percent (%) drug dissolution between the two curves. Values of 50 or above (50–100) ensure similarity of the curves.

RESULTS

The tablets tested were immediate release dosage forms of ofloxacin 200mg that were within their stated expiration date (Table 1).

The percentage price differential of six brands was calculated by using the formula[14]

(Price of innovator – Price of generic) ÷ Price of innovator x 100

Physicochemical tests

All the formulations conformed to USP-32 regulations on Pharmacopoeial tests. The percentage purity of the six brands is shown in Table 2 which is also within the range of 90 – 110% general tolerance level for tablet formulation in USP.

Comparison of Dissolution profiles

Fig. 1-4 and Table-3 represent the dissolution profiles comparison and corresponding data of the six formulations in dissolution medium, pH 1.2, 4.5 and 6.8 Table 3 shows the statistical result for similarity factor, f2 using innovator product flox-1 as the reference.

Table 1: Label information of six different brands of Ofloxacin tablets (200mg)

S. No.	Product code	Batch No.	Mfg Date	Exp. Date	Price/10 units	% price difference with innovator
1	Oflox-1	U040	Nov-09	Oct-12	296.79	innovator
2	Oflox-2	9332	Jan-10	Dec-12	90	69.67
3	Oflox-3	7GBAB	Aug-09	Aug-12	292.56	1.41
4	Oflox-4	59	Nov-09	Nov-12	115	61.25
5	Oflox-5	892	Nov-09	Nov-12	97.5	67.15
6	Oflox-6	8962	Jul-09	Jul-12	115	61.25

Table 2: Physico-chemical Characteristics of six brands of Ofloxacin(200mg) tablets

Brands	Uniformity of weight (mg) ± SD	Thickness (mm) ± SD	Diameter (mm) ± SD	Hardness (kg/cm^2) ± SD	Disintegration (min) ± SD	Assay (%) ± SD
Oflox-1	518.89±8.83	4.24±0.21	13.99±0.7	8.73±0.78	6±1.02	100.08 ± 0.98
Oflox-2	527.35± 8.72	4.36±0.26	14.26±0.69	9.63±0.89	5±0.98	98.96 ±1.31
Oflox-3	375.89 ± 1.38	4.39±0.18	14.02±0.55	10.5 ± 0.56	11.5±0.59	99.60 ± 0.84
Oflox-4	399.03± 4.02	4.19 ±0.21	14.18±0.71	9.16±1.19	7±0.67	99.89 ± 0.56
Oflox-5	392.61 ± 3.99	4.29±0.21	13.71±0.7	5.71±0.97	6±0.58	101.03±1.02
Oflox-6	399.23 ±3.06	5.26±0.26	10.36±0.52	7.96 ±0.99	7±0.69	99.99 ± 0.49

Table 3: Dissolution data of six brands of Ofloxacin (200mg) tablets with f2 comparison

Medium	Time (min)	Oflox-1	Oflox-2	Oflox-3	Oflox-4	Oflox-5	Oflox-6
		% released ± SD	% released ± SD	% released ± SD	% released ± SD	% released ± SD	% released ± SD
pH 1.2	5	18.03±0.88	8.97±1.3	34.54±3.25	49.45±4.74	13.30±2.37	5.21±0.056
	10	33.6±1.53	20.6±2.67	65.53±6.61	76.9±2.74	30.12±4.71	47.80±8.58
	15	45.11±1.4	40.97±3.47	**85.03±2.63**	**85.29±3.63**	46.75±4.88	**85.67±2.7**
	30	87.2±0.74	85.49±2.79	90.18±3.96	91.47±3.38	84.94±3.88	95.03±4.78
	45	96.1±2.8	89.5±1.74	91.22±4.13	92.29±3.1	93.06±2.47	97.56±2.36
	60	99.04±1.54	93.66±2.94	91.05±5.26	93.9±3.91	92.18±1.78	98.53±2.33
	70	100.1±0.98	95.17±2.89	92.48±5.0	95.71±3.44	94.92±1.13	99.08±1.06
F2		**innovator**	**58.46**			**76.97**	
pH 4.5	5	14.33±1.78	22.36±4.30	30.13±2.60	47.29±2.13	4.90±1.28	23.56±2.16
	10	26.06±3.40	43.13±3.25	60.33±2.62	58.22±2.06	11.59±1.97	61.42±2.83
	15	56.08±3.79	61.15±4.7	**85.15±1.62**	59.67±3.27	19.45±2.0	**85.13±2.97**
	30	85.55±5.20	85.67±4.45	86.33±1.35	70.07±2.90	50.08±3.14	92.70±2.99
	45	87.6±4.04	90.47±4.02	89.02±1.78	70.92±2.76	66.20±4.13	94.70±2.93
	60	91.92±2.6	94.27±3.87	90.76±2.74	72.37±2.58	73.72±4.04	97.02±3.50
	70	92.78±3.38	96.61±4.93	92.57±2.78	72.82±2.49	76.87±5.67	97.77±2.46
F2		**innovator**	**56.16**		**35.51**	**32.96**	
pH 6.8	5	16.61±1.97	17.5±2.67	33.56±2.61	25.11±2.47	7.31±2.59	13.4±1.58
	10	30.55±2.36	40.39±2.6	68.65±3.34	45.62±4.08	9.59±2.11	50.32±4.87
	15	58.47±2.16	54.03±2.54	**85.04±2.01**	52.97±5.82	14.03±2.73	69.8±2.31
	30	85.51±1.5	90.95±1.98	98.07±1.49	61.14±3.65	50.98±3.87	92.29±5.79
	45	86.89±1.9	94.15±3.2	99.78±1.07	67.79±3.7	62.90±3.43	97.40±4.65
	60	88.70±1.54	95.51±3.09	100.32±0.4	72.90±3.78	77.78±2.90	99.30±1.22
	70	90.32±1.91	97.27±2.57	100.53±0.49	78.0±2.63	83.6±2.42	99.55±1.21
F2		**innovator**	**63.25**		**43.32**	**30.35**	**50.11**

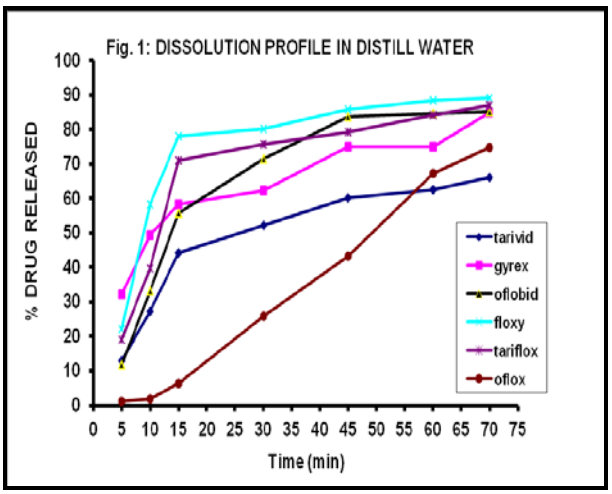

Fig.1: Dissolution compression of six brands in water

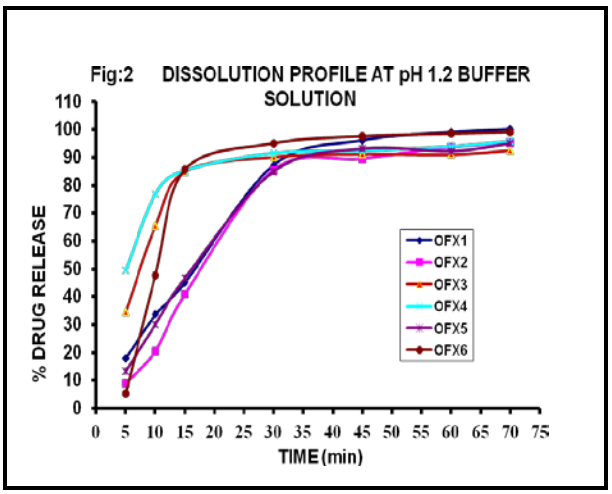

Fig. 2: Dissolution compression of six brands in pH 1.2 buffer

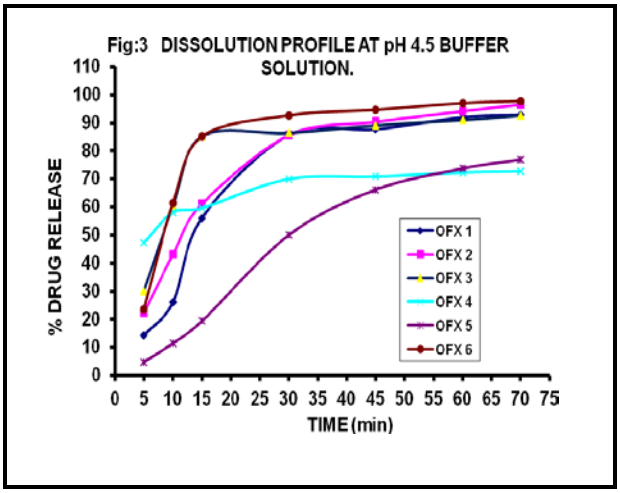

Fig. 3: Dissolution compression of six brands in pH 4.5 buffer

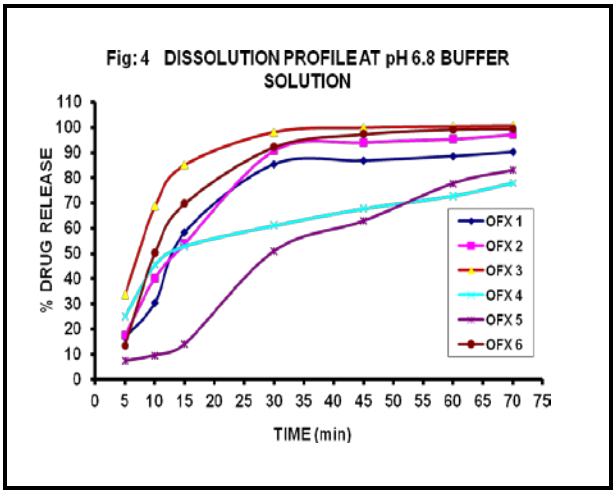

Fig.4: Dissolution compression of six brands in pH 6.8 buffer

Fig. 1-4: Comparison of Dissolution profiles in water, pH 1.2, 4.5 and 6.8 buffer

DISCUSSION

More then 20-25 local and multinational pharmaceutical companies in Karachi are manufacturing ofloxacin tablets, making it difficult for a physician and pharmacist to evaluate which one is better for his patient.

The lowest priced brand among these six is oflx-2 and highest is oflx-1 (Table 1). This fluctuation in the price of same drug makes it difficult for the health care authorities. Whichever the technique or method used for the manufacturing of tablets, it should have active ingredient (ofloxacin) and excipients of the same quality that should comply with the USP / BP specification.

Under these circumstances this fluctuation in the price of different brands is doubtful, making it necessary to conduct bioavailability study. However, it is not only a time consuming but also a very costly procedure.

Similarity factor (f2) is a simple and viable comparison approach to assess bioequivalent between two formulations. The two dissolution profiles to be considered similar and bioequivalent, f1 should be between 0 and 15 while f2 should be between 50 and 100 (FDA, 1997)[13].

So the establishment of Biowaiver study on the basis of BCS classes is a fruitful phenomenon to get at least the idea about the releasing pattern of drug from solid dosage form to the dissolution medium. In vitro dissolution testing is an important tool used for development and approval of generic dosage forms.

According to FDA (2000)[15], a drug product is considered to be very rapidly released if ≥85% of the drug is dissolved in 15minute, which corresponds to gastric emptying half-life ($T_{50\%}$) in fasting conditions.

In case of present study six different brands of Ofloxacin tablets (200mg) immediate release has been studied for their bioequivalence studies. Brands are available in the market at significant price differences, for example, brand Oflox-2 costs 90 rupees that is 3.5 times less than the brand Oflox-1 which cost rupees 296.79. Although physicians may have serious concerns about the efficacy of the different products, they sometimes prescribe economical products due to financial constraints.

The objective of the present study was to compare the quality of locally produced and imported products, including the innovator product (Table 1), available in the Karachi market and to examine the possibility of waiver for in vivo bioequivalence study. Such waivers have the potential to decrease the cost of the product and improve the quality of medicines.

Before testing the brands into different dissolution mediums (pH 1.2, 4.5, 6.8) it was run in distilled water (Fig.1) because under the normal circumstances, the dissolution testing should be conducted at 37°C in distilled water unless otherwise noted.

The FDA recommended dissolution medium for ofloxacin is 0.1N HCl but Fig.1 shows that 4 brands (oflox-3,oflox-2,oflox-6and oflox-4) released more than 85% in water while only 2 brands (oflox-5 and oflox-1) failed to released more than 85% drug in water

Fig. 2 and Table 3 shows the dissolution profiles of tablets in 0.1N HCl (pH 1.2). All products met FDA requirements for requesting BCS – based waiver for in vivo BA/BE studies for solid oral dosage forms, i.e. at least 85% of the drug dissolved in 30 minutes.

Most products may be considered as *very rapidly dissolving* as more than 85% of the labeled amounts of the drug substance dissolves within 15 minutes. Oflox-3, Oflox-4 and Oflox-6 test brand dissolves 85% within 15 min (Table 3). As FDA biowaiver recommendation, the profile comparison with an f2 test is unnecessary in that type of products.

The BCS suggests that for high solubility, high permeability (case 1) drugs and in some instances for high solubility, low permeability (case 3) drugs, 85% dissolution in 0.1N HCl in 15 minutes can ensure that the bioavailability of the drug is not limited by dissolution.

The mean $T_{50\%}$ gastric residence (emptying) time is 15-20 minutes under fasting conditions. Based on this information, a conservative conclusion is that a drug product undergoing 85% dissolution in 15 minutes under mild dissolution test conditions in 0.1N HCl behaves like a solution and generally should not have any bioavailability problems. Significant variations in the ***in vitro*** dissolution profiles were observed when the dissolution media was changed. The dissolution profile of a brand (Oflox-2) with the innovator product Oflox-1 in phosphate buffer (pH 4.5) (Table 3) and in phosphate buffer (pH 6.8) (Table 3) complies with current US FDA (1997) criteria for ***rapidly dissolving*** drug products (no less than 85% dissolved in 30 minutes). No difference was detected in phosphate buffer (pH 4.5) and phosphate buffer (pH 6.8) that indicated these brands can be used interchangeably. Whereas the test brand Oflox-3 and Oflox-6 dissolved 85% within 15 min in pH 4.5, Oflox-3 dissolved 85% within 15min at pH 6.8, Oflox-6 took 30 minutes to dissolve the required amount i.e. 85% (Fig. 3-4).

The brand product Oflox-4 and Oflox-5 (Table 3) dissolved less than 45% (43.32%) and 35% (30.55%) respectively in phosphate buffer (pH 6.8) in 30 minutes compared to about 2-3% for the innovator product. Similarly the brand product Oflox-4 and Oflox-5 (Table 3) also dissolved less in buffer (pH 4.5) that is less than 40% (35.51%) and 35% (32.96%) respectively in 30 minutes compared to about 3% for the innovator product.

These results suggest that the formulation design and/or the manufacturing process affect the dissolution and thus the bioavailability of the drug product so that when properly formulated, Ofloxacin reaches its site of absorption in a solution form.

CONCLUSION

Thus the post-market monitoring is very crucial for effective clinical outcome and this study has emphasized that chemical equivalence does not indicate bioequivalence. Also one brand substituted on assumption of chemical equivalence with another brand may not give the desired onset of action and subsequent therapeutic effectiveness. So for this kind of drug product probably the in-vivo test may be required. As well as the price may not indicate the authenticity and effectiveness of a drug product. The price of brand oflox-1 (innovator) is 29.68 Rs/tablet where as the oflox-2 is sold of 9.0 Rs/tablet and is bioequivalent to innovator, can be used interchangeably

ACKNOWLEDGEMENT

The authors would like to thanks, Department of Pharmaceutics, Faculty of Pharmacy, University of Karachi, for the use of Laboratory Facilities.

REFERENCES

1. Nelson, JM.; Chiller, TM.; Powers, JH.; Angulo, FJ. "Fluoroquinolone-resistant Campylobacter species and the withdrawal of fluoroquinolones from use in poultry: a public health success story". Clin Infect Dis. 2007; 44 (7): 977–80.
2. Kawahara, S. "Chemotherapeutic agents under study". Nippon Rinsho. 1998; 56 (12): 3096–9.
3. Sweetman SC (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version, 35th Ed. 2007.
4. Drlica K, Zhao X. "DNA gyrase, topoisomerase IV, and the 4-quinolones". Microbiol Mol Biol Rev. 1997; 61 (3): 377–92
5. Gennaro, A. R. Remington. The Science and Practice of Pharmacy. 20th edition. Easton Pennsylvania: Mack Publishing Company. 2000; 882-885.
6. Gennaro, A. R. Remington. The Science and Practice of Pharmacy. 19th edition. Easton Pennsylvania: Mack Publishing Company. 1995; 905-918
7. British Pharmacopoeia Volume I &II. British Pharmacopoeia commission. The stationery office limited, London; 2007; 249 – 267.
8. Ziyaur R, Mushir A, Khar RK. Design and Evaluation of bilayer floating tablets of captopril. Acta pharm., 2006; 56: 4957.

9. British Pharmacopoea Appendix: XII, Disintegration of tablets and capsules. Royal Publishers: London. 2002; H A2-53.
10. United States Pharmacopeia and National Formulary USP 32–NF 27. The United States Pharmacopeial Convention, Inc.: Rockville, MD., 2007; 1737.
11. United States Pharmacopeia and National Formulary USP 32–NF 27. The United States Pharmacopeial Convention, Inc.: Rockville, MD., 2007.
12. The United States Pharmacopeia 27. The United States Pharmacopeial Convention, Rockville, MD, USA, 2004; 2011-2012.
13. US FDA, Guidance for Industry: Dissolution testing of immediate-release solid oral dosage forms. Food and Drug Administration, Center for Drug Evaluation and Research (CDER); 1997.
14. Akinleye M Olusola, Oyetunde O Olubukola, Okpara H Emeka and Ayerota E Lilian. Equivalence of Two Generic Brands of Amlodipine Besylate under Biowaiver conditions. Int J Pharm Pharm Sci., 2012; 4 (2): 265-268
15. US Food and Drug Administration, Center for Drug Evaluation and Research Guidance for Industry - Waiver of InVivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, 2000.
16. Raheela Bano1, Shahnaz Gauhar, Syed Baqir Shyum Naqvi and Shoukat Mahmood "Pharmaceutical Evaluation of different brands of Levofloxacin tablets (250mg) available in local market of Karachi (Pakistan)". Int. J Curr Pharm Res., 2011; 3 (1):15-22