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Pharmaceutical Quality Assessment of Different Brands of Moxifloxacin 400 mg Tablets Available in Pakistan

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Authors' Contributions
1 Conception & Study Design, Data Collection, Data Analysis, Drafting.
2 Conception & Study Design, Data Analysis, Critical Review.
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4 Drafting, Critical Review.
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ABSTRACT

Objective: The objective of the current study was to characterize the quality control parameters and cost effective analysis of five selected different brands of moxifloxacin 400 mg tablets. Moxifloxacin is a fourth generation fluoroquinolone antibiotic, having activity against gram-negative (*Escherichia coli*, *Haemophilus influenza*, *Klebsiella pneumonia*, *Proteus mirabilis* and *Moraxella catarrhalis*) and gram-positive (*Staphylococcus aureus*, *Streptococcus anginosus*, *Enterococcus faecalis*, *Pneumococci*, and *Streptococcus pyogenes*) microorganisms.

Methods: All five selected brands were coded as M-1, M-2, M-3, M-4 and M-5 and the price were noted as PKR 805.82 ($6.03), 375 ($2.81), 475 ($3.56), 300 ($2.25) and 160 ($1.20) per 5 tablets, respectively. By using official and non-official tests, all the brands were evaluated for physical and chemical characteristics such as hardness, weight variation, friability, disintegration, dissolution, content uniformity and assay using already reported HPLC and spectrophotometric methods. The brand M-1 was considered as reference, due to its good physical and chemical properties and its dissolution profile was compared with other brands, using model independent approach (similarity factor- f_2), to compare the dissolution profile of generic drug products with reference. There is a large variation in the price of reference and other generic drugs available in the local market of Pakistan.

Results: The results of physical and chemical tests showed that that all brands of moxifloxacin were within the specified limits. The amount of moxifloxacin in all five brands was within the USP specification of not less than 80% at 45 minutes. Similarly, the values of f_2 for M-2 (77.20), M-3 (69.56), M-4 (76.98) and M-5 (82.17) indicated that all the brands were found to be similar with reference brand.

Conclusion: It was concluded that low cost local brands of moxifloxacin 400 mg tablets can be used as an alternative in case of un-available brands in the market. This study will be helpful to the healthcare practitioners to prescribe other generic brands of moxifloxacin, as the cost is 50% less in comparison with reference which may reduce the medication cost to the patients.

Keywords: Moxifloxacin, efficacy, generic, patient.

INTRODUCTION

Moxifloxacin is a fourth generation fluoroquinolone with extended action against gram negative and gram positive bacteria. This antibacterial have methoxy group on position of C-8 while a massive C-7 side chain [1]. Moxifloxacin has been sensitive against different strains of the microorganisms, like, *Streptococcus constellatus*, *Staphylococcus aureus*, *Pneumococci*, *Enterococci pyogenes*, *Moraxella catarrhalis*, *Proteus mirabilis*, *Escherichia coli*, *Klebsiella pneumonia*, *Haemophilus influenza*, *Peptostreptococcus* species, *Bacteroides fragilis*, *Taiotao micron*, *Clostridium perfringens*, *Chlamydophila* and *Mycoplasma pneumonia* [2]. It is a synthetically prepared, extended spectrum microbial agent for oral and intravenous use. It is an 8-methoxy fluoroquinolone and only the quinolones are the direct DNA synthesis inhibitors [3]. Moxifloxacin inhibits two bacterial enzymes namely, topoisomerase II and IV, thus inhibit DNA replication [4, 5]. Drug binding with these enzymes, obstructs replication of DNA, resulting in death of a cell [6]. Moxifloxacin usually indicated for community acquired pneumonia, skin and skin structure infections, plague, acute bacterial exacerbation of chronic bronchitis and acute bacterial sinusitis. The quality of brands is inadequate in many pharmaceutical markets of under developing countries. In majority cases, the chances of treatment failure increase due to use of poor-quality medicines. However, on the basis of limited information on literature review and clinical trials; different manufacturer has taken marketing authorization of different medicinal products for public use by Drug Regulatory Authority of Pakistan [7, 8].

Moreover, Pakistan is also included in those countries who are the largest importer of counterfeit drugs reported in one research study [8, 9]. A number of research studies were published on physicochemical and pharmaceutical quality evaluation of different marketed brands which indicated the need of pharmaceutical equivalence of drugs. Moreover, different researchers have worked on the comparison of pharmaceutical quality and price variations in different marketed drugs [10-12]. However, no study was conducted on the comparison of moxifloxacin brands marketed in this region.

Therefore, the current study was performed to assess the quality control parameters and to compare the cost analysis of moxifloxacin 400 mg tablets of 5 available brands collected from different retail pharmacies located at Karachi, Pakistan. The quality control parameters were evaluated for hardness, friability, weight variation, disintegration, assay, content uniformity and dissolution tests, as per pharmacopeial specifications and non-compendial limits. There is a large variation in the price of innovator (reference) and other generic drugs available in the local market. This study will be helpful to healthcare practitioner to prescribe other generic brands of moxifloxacin, as the cost of other generic products is 50% less in comparison with other brands. The maintenance of products' quality is mainly concern with brands of same generic. Therefore, access and affordability of these brands need to be resolved by introducing and practicing of generic medicines.

MATERIALS AND METHODS

Moxifloxacin HCl was purchased from local market. Methanol (HPLC Grade) and buffer potassium dihydrogen phosphate (KH_2PO_4) were procured from Merck (Darmstadt, Germany). Tetra butyl ammonium hydrogen sulfate, sodium sulfite anhydrous, ortho-phosphoric acid and hydrochloric acid (HCl) were procured from Sigma Aldrich (USA). Apparatus used were, analytical balance (Mettler Toledo xs105), tablet hardness tester (Pharma tester PTB 311E), friabilator (Erweka, GmbH D-63150, Germany), disintegration tester (Electro Lab ED-2 SAPO), dissolution tester (USP apparatus II Electro Lab TDT 08L), magnetic stirrer (Isolab, Germany), spectrophotometer (Shimadzu UV-1800) and HPLC (LC solution 20A, Shimadzu) with UV visible and PDA detector (SPD-20A; Tokyo, Japan).

Sample Collection

Five different brands of moxifloxacin 400 mg tablets were purchased from different pharmacies located at Karachi, Pakistan. All collected brands were manufactured and marketed by well reputed national and international pharmaceutical companies registered in Pakistan. All brands were coded as M-1, M-2, M-3, M-4 and M-5 and were within the expiry limits throughout the study. The details of collected brands are present in Table **1**.

Table 1. Labeling information of all five brands of moxifloxacin (400 mg) tablets.

Brand code	Manufacturing date	Expiry date	Retail price (PKR/5 tablets)
M-1	1-11-2016	1-10-2020	805.82 ($6.03)
M-2	1-10-2016	1-10-2018	375 ($2.81)
M-3	1-09-2016	1-09-2019	475 ($3.56)
M-4	1-07-2015	1-07-2018	300 ($2.25)
M-5	1-12-2016	1-11-2018	160 ($1.20)

Quality Control Evaluation of Brands

The quantitative evaluation of a physical and chemical characteristics of tablets are important to observe quality of product. For comparative evaluation, five brands of moxifloxacin 400 mg tablets were selected for assessment of quality control parameters such as hardness, friability, weight variation, disintegration, content uniformity, assay, and dissolution tests.

Weight Variation Test

To check uniformity of weight of the brands as per official method, twenty tablets from each brand were selected and weighed using electronic balance (Mettler Toledo xs105) and was noted in milligrams (mg). The tablets were analyzed for their consistency of weight permitted by British Pharmacopeia *i.e*. ±10% for tablets weighing 80 mg or less, ±7.5% for tablet weighing in between 80 mg – 250 mg and ± 5% for tablet weighing more than 250 mg [13].

Tablet Breaking Force Test

The breaking force of tablets is commonly called *hardness* in the pharmaceutical literature; however, this term is misleading, because *hardness* refers to the resistance of a surface to penetration or indentation by a small probe. The term *crushing strength* is also frequently used to describe the resistance of tablets [14]. Thus, the term *breaking force* was used. Mechanical integrity of tablets can be measured by hardness test in terms of confrontation of the tablet into fragments, scratches, or cracking during storage, handling and transportation from one place to another [15]. The hardness of 20 tablets in kilopascal (kPa) were determined using Hardness tester (Pharma tester PTB 311E) and the data was statistically analyzed using control chart.

Friability Test

The friability test was performed to assess the capability of the tablet to resist fragments, scratches, or cracking. Twenty tablets were placed in the Friabilator (Erweka GmbH D-63150, Germany) and subjected to falling shocks for 100 revolution (25 rpm for 4 min). After test, the tablets were reweighed and percentage friability was calculated by the following formula.

$$\text{Friability (\%)} = \frac{(\text{Initial Weight} - \text{Final Weight})}{\text{Initial Weight}} \times 100 \quad \text{---- Eq. 1}$$

The Acceptance criteria: Loss of weight should not be greater than 1% of the total weight [16].

Content Uniformity Test

Ten tablets of each brand were selected randomly and weighed individually using analytical balance, then drug content in each tablet was analyzed individually [17]. The percentage content was calculated by using the below formula:

$$\text{\% Content uniformity} = \frac{\text{\% Assay} \times \text{Individual weight of tablet}}{\text{Average weight of tablets}} \quad \text{---- Eq. 2}$$

Disintegration Test

Six tablets of each brand were selected randomly to evaluate the disintegration time. The tablets were placed in basket rack assembly of the disintegration apparatus. Deionized water was used as a medium maintained at 37 ± 2^{o}C. The time noted at which all six tablets were completely disintegrated. Comparison of time of disintegration of every brand was done with the maximum acceptable limits of Pharmacopoeia [18].

Multiple Point Dissolution Test

The dissolution test was performed to determine the quantity of drug released from tablet. The dissolution test was performed using USP dissolution type II apparatus, filled with 900 mL of 0.1 N HCl medium, maintained at 37 ± 0.5^{o}C and operated at 50 rpm [19]. The samples were collected from each bowl at different time interval of 5, 10, 15, 20 and 30 minutes using syringe and filtered through Whatman filter paper having 0.45 micron pore size. After filtration

and appropriate dilution to 80 µg/mL, the amount of moxifloxacin dissolved was quantified by using UV Spectrophotometer. The concentration of moxifloxacin was assessed in comparison with the reference working standard solution. However, by using the below formula, the percentage of dissolution of moxifloxacin in each tablet was calculated:

$$\% \text{ Assay} = \frac{\text{Area.spl}}{\text{Area.std}} \times \frac{\text{Weight.std}}{50} \times \frac{2}{20} \times \frac{50}{\text{Weight.spl.}} \times \frac{20}{2} \times \frac{\text{Avg.Weight}}{400} \text{ Potency}$$

Where,

Area spl = Area of sample solution

Area std = Average area of standard solution

Weight std = Weight of standard

Weight spl = Weight of sample

Avg. weight = Average weight of the tablets

Release Profile Comparison

The comparison was performed by using DD-solver software (An Add-In Program for Modeling and Comparison of Drug Dissolution Profiles) [20]. The similarity factor (f_2) provides simple interpretation of data to evaluate release profile of different brands as compare to reference. The brand M-1 (innovator) was used as a reference to assess the similarity of different brands in their dissolution pattern. If the values of f_2 are within range of 50 – 100%, it indicates equivalence and if f_2 values are less than 50%, it indicates that there is no similarity between two dissolution profiles, as explained by Zhang Y, and Costa P and Lobo JMS [20, 21].

Statistical Analysis

All experiments were performed in triplicates. The achieved data was analyzed using SPSS and all experimental data was reported as the means ± SD. Furthermore, one way analysis of variance (ANOVA) was utilized to evaluate the variances among the different brands of moxifloxacin tablets.

RESULT AND DISCUSSION

The objective of the current study was to evaluate and compare different brands of moxifloxacin (400 mg) tablets (Registered by Drugs Regulatory Authority of Pakistan – DRAP) by assessing their quality control parameters and pricing. All the collected brands were within their expiry limits during the whole period of this research study.

In 2004, it was reported that about 30% of the world population has not access to life saving medicines, by world health organization [12]. In some Asian and African countries, this number was approximately 50%. Hence, multinational community encourages little bit generic competition and adapting tiered pricing for resolving this problem [22]. Generic manufacturers were not following the good manufacturing practice (GMP) and due to poor regulatory control, low standard drugs are manufactured and widely distributed. These low quality medicines are direct threat to population.

Evaluation of Physicochemical Properties of Brands

Table **1** shows the labeling information of all five brands. Brand M-1 (innovator) of moxifloxacin tablets was considered as reference while, other four brands (M-2 to M-5) were used as test brands to compare their dissolution profile in order to determine similarity factor (f_2). Hardness of all brands was found satisfactory and the values were observed in between 13.99 – 15.10 kilopascal (kPa) as shown in Table **2**. The results of weight variation test of all brands were found within the BP specification of ± 5 % [13] as given in Table **2**. Some authors also reported similar types of findings [23]. The results of friability test of all brands were found as per Pharmacopeial limit of NMT 1%, reflecting through Table **2** [11, 24].

Price Variation Analysis

The price variation of all collected brands of moxifloxacin 400 mg tablets are listed in Table **1**. The result showed that there was a significant difference in the price of five collected brands of moxifloxacin 400 mg (Rs. 160 – 806 or $1.20 - $6.03). The similar price variations were also observed in previous studies performed on marketed brands of other drugs such as amlodipine besylate, cefadroxil monohydrate, ciprofloxacin hydrochloride, levofloxacin and metronidazole [10, 11, 25, 26]. This variation in the price of brands may create doubt in the quality of low cost brands and physician prescribed higher cost brands for better therapeutic results. This doubt in physician mind may cause hindrance in cost effective therapy. However, these huge variations in price also helpful for patients to use low cost brands having same pharmaceutical quality.

Disintegration Test

The time consumed by tablet to disintegrate completely into its fragments is directly affects the overall release of drugs and absorption inside the body. The disintegration test results were found within UPS limits of 30 minutes [18]. The disintegration time was observed in the range of 1.55 – 2.45 minutes (Table **2**). Similar results were also observed in the earlier studies performed on paracetamol, metronidazole, ranitidine and simvastatin marketed brands [11, 27-29].

Chemical Assay and Content Uniformity of Moxifloxacin Tablets

The drug content in a unit dosage form was determined with respect to their label claim of 400 mg (Table **2**). The content uniformity results all brands of moxifloxacin 400 mg tablets were also felt in the range of 98.03 – 106.59%. The assay results were found within the range of 98.29 to 106.26% (Table **2**). The obtained results indicated that all collected brands of moxifloxacin tablets complied the USP specification limits for assay and content uniformity test [30]. Previously, different research scholars also performed assay on various marketed brands of ciprofloxacin, diclofenac sodium, cefadroxil monohydrate and metronidazole, indicating similar type of results [11, 12, 31].

assessment were found in previous studies performed by different researchers on different marketed drugs such as Amlodipine besylate, Cefadroxil monohydrate, Ciprofloxacin hydrochloride, Levofloxacin and Metronidazole [10, 11, 22, 25, 26]. No study reported yet, regarding the comparative brand study of moxifloxacin tablet.

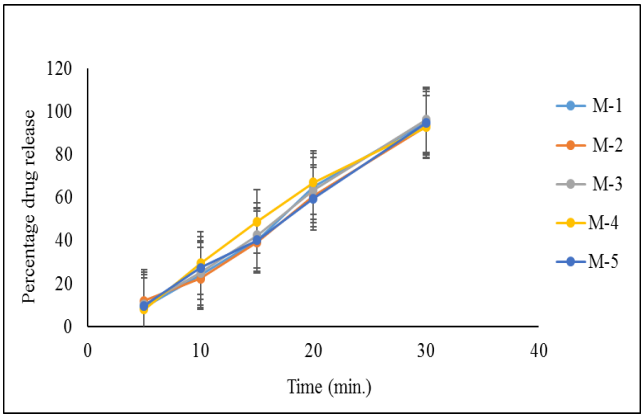

Figure 1. *In vitro* drug release profile of all brands of moxifloxacin 400 mg tablets.

Drug Release Profile Comparison (Similarity Factor f_2 Value)

Similarity factor (f_2) was applied using DD Solver to assess the similarity between dissolution profiles of other brand as compare to reference (M-1). All

Table 2. Physicochemical evaluation of all brands of moxifloxacin 400 mg tablets.

Brand Code	Weight Variation** (mg)	Hardness** (kPa)	Friability** (%)	Disintegration Time*** (min.)	Content Uniformity* (%)	Assay* (%)
M-1	709.34 ± 7.82	14.90 ± 2.20	0.17 ± 0.09	2 .45	106.59 ± 1.21	106.26 ± 0.75
M-2	685.05 ± 6.78	13.99 ± 2.55	0.24 ± 0.11	2.32	103.1 ± 2.06	104.0 ± 0.54
M-3	699.08 ± 7.87	15.10 ± 4.12	0.21 ± 0.21	1.55	105.63 ± 2.11	98.29 ± 1.06
M-4	611.38 ± 6.05	15.05 ± 1.56	0.31 ± 0.36	2.15	98.03 ± 0.19	106.24 ± 1.32
M-5	709.19 ± 7.01	14.89 ± 2.07	0.26 ± 1.21	2.38	98.53 ± 1.02	99.31 ± 0.99

Multiple Point Dissolution Assessment

According to USP guidelines for dissolution, drugs should release not less than 80% of their content with respect to their label claim in a respective fluid medium [19]. The multiple point dissolution assessment results showed that all collected brands of moxifloxacin 400 mg tablets were found within the acceptance range of 93.11 – 96.25% (Table **3** and Figure **1**), indicating that the generics brands were manufactured as per pharmacopeial criteria for dissolution. The similar outcomes of dissolution

observed f_2 values were found within range of 69.56 – 82.17%, which indicated that there were similarity in the release profile of all four brands (M-2 to M-5) of moxifloxacin 400 mg tablets when compared with reference brand as shown in Table **3**. According to the FDA guidelines, if the values of f_2 are within the range of 50 – 100%, it indicates equivalence and if the values are less than 50%, then, there is no similarity between two dissolution profiles [20, 21].

Table 3. Dissolution profile of all brands of moxifloxacin 400 mg tablet at different time interval and similarity factor (f_2).

Brand Code	Dissolution Rate at Different Time Interval (Mean)					USP Limit	Similarity Factor (f_2) Values (%)
	5 min.	10 min.	15 min.	20 min.	30 min.		
M-1	9.03 %	24.06 %	40.23 %	65.21 %	95.11 %	NLT 80% at 45 min	Reference (innovator)
M-2	12.09 %	22.50 %	39.37 %	60.87 %	93.11 %		M-1 & M-2 = 77.20
M-3	10.41 %	25.04 %	42.55 %	63.55 %	96.25 %		M-1 & M-3 = 69.56
M-4	8.09 %	29.56 %	48.98 %	67.09 %	92.81 %		M-1 & M-4 = 76.98
M-5	9.89 %	27.43 %	40.23 %	59.56 %	94.77 %		M-1 & M-5 = 82.17

CONCLUSION

In the present study, the quality parameters of all brands were assessed including weight variation test, disintegration test, dissolution assessment and chemical assay and results were found within the acceptance ranges of USP and BP, with no significant difference in their results. Hence, the outcomes of the study indicated that all brands possess good pharmaceutical qualities. There was a major difference in the price of brands while each brand having same pharmaceutical active ingredient. Therefore, on the basis of results obtained during the present study it can be concluded that low cost brand of moxifloxacin 400 mg tablets can be prescribed and interchanged rather than costly brand.

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