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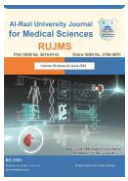

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In vitro Comparative Quality Assessment of Four Brands of Moxifloxacin 400 mg Tablets Marketed in Yemen

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Abstract

Background: 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. **Objective** : The objective of the current study was to characterize the quality control parameters and cost effective analysis of four selected different brands of moxifloxacin 400 mg tablets. **Methods**: All four selected brands were coded as IB*, A, B, and C and the price were noted as YR 5700. ($9.5), 4200 ($7), 2000 ($3.33) and 2000 ($3.33) 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 IB* 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- f2), 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 Yemen. **Results**: The results of the identification tests confirmed that all of the samples contained the active medicinal ingredients that were listed. Weight variation tests revealed that all samples were within the USP standard limits. The active pharmaceutical components quantitative assay revealed that all brands of moxifloxacin tablets were within the label claim limit of 90% to 105 percent. **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, local

Introduction

Moxifloxacin is a fourth-generation fluoroquinolone that has a broad spectrum of antibacterial activity against both gram-negative and gram-positive bacteria. This antibiotic has a large C-7 side chain and a methoxy group on position C-8 (Keating & Scott, 2004). Different strains of bacteria have shown to be sensitive to moxifloxacin 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 [1]. It's a broad-spectrum antibacterial agent that's been synthesized and can be used orally or intravenously. Only the quinolones are direct DNA synthesis inhibitors, and it's an 8-methoxy fluoroquinolone. Moxifloxacin inhibits the replication of DNA by inhibiting two bacterial enzymes, topoisomerase II and IV [2]. Drug binding with these enzymes, obstructs replication of DNA, resulting in death of a cell. Community-acquired pneumonia, skin and skin structure infections, plague, acute bacterial exacerbation of chronic bronchitis, and acute bacterial sinusitis are all conditions for which moxifloxacin is prescribed. The quality of brands in many pharmaceutical marketplaces in developing countries is inadequate. In the vast majority of cases, using low-quality medications raises the chances of treatment failure. 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 Supreme Board of Drugs and Medical Appliances (SBDMA)- Yemen. Moreover, Yemen is also included in those countries who are the largest importer of counterfeit drugs reported in one research study [3]. A number of studies on the physicochemical and pharmaceutical quality evaluation of various marketed brands have been published, indicating the necessity for pharmaceutical equivalency. Moreover, other researchers have compared pharmaceutical quality and pricing discrepancies in various marketed medications. However, no research has been done to compare moxifloxacin brands sold in Yemen. Therefore, the current study was performed to assess cost analysis of moxifloxacin 400 mg tablets of 4 available brands collected from different retail pharmacies located at Sana`a, Yemen. Hardness, friability, weight fluctuation, disintegration, assay, and dissolution tests were evaluated as quality control characteristics according to pharmacopeial standards and non-compendial limits. There is a large variation in the price of international (reference) and other generic drugs marketed in Yemen. 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 quality of items is primarily concerned with brands of the same generic. As a result, generic drugs must be introduced and practiced to address access and affordability of these brands [4].

MATERIAL AND METHODS

Moxifloxacin raw material Denk pharma Germany. Acetonitrile Fisher chemicals U.K. Tribasic sodium phosphate Scharlau Spain. Ortho phosphoric acid Scharlau Spain. Hydrochloric acid Scharlau Spain,. Triethylamine CHES Germany. Sodium hydroxide Scharlau Spain. Sodium acetate Scharlau Spain. Potassium chloride Scharlau Spain. HPLC System WATERS USA. UV Spectrophotometer SP-3000 plus, Optima Tokyo Japan. Balances METTLER TOLEDO USA. Hot plate stirrer Daihan Labtech- Korea. pH meter Metrohm Germany. Water bath Pharma test Germany. Hardness tester, Pharma test Germany. Dissolution tester DT 600, Erweka, Germany. Disintegration tester, Pharma test Germany. Friability tester Pharma test Germany. Filter paper Tested 3bar Germany. Volumetric Flask, Pipit, Beaker, ..etc. Local market, Yemen

Samples Collection

Four different brands of moxifloxacin tablets with labeled strength of 400 mg and registered by SBDMA, Yemen were randomly obtained from registered pharmacy shops in Sana`a, Yemen. All the tests were performed within product expiry dates. The innovator/reference brand was labeled IB*

Quality Control Evaluation of Brands

Non-official quality control tests

Organoleptic test

Organoleptic test (color, taste, shape and odor) was performed visually for the four brands of moxifloxacin 400 mg tablets which used in this study and the results were recorded.

Hardness test

Hardness test for different brands of moxifloxacin 400mg tablets were performed using digital hardness tester for ten tablets from each brand then the average strength per Kg The optimum limit :4-10 kPa.

Friability Test

Twenty tablets were randomly taken from each brand then test for different brands of moxifloxacin 400 mg tablets were performed using friabilators for ten tablets from each brand then the friability percent was calculated as the following equation [5–7]:

$$\% \text{ Friability} = \frac{(\text{Intial weight of 10 tablets} - \text{final weight of 10 tablets})}{\text{Intial weight of20 tablets}} \times 100$$

Acc

Weight Uniformity test

The goal of this test is to ensure that each batch is uniform, which reflects the drug content homogeneity across all formulation batches. The test was carried out according to protocol. Twenty tablets were chosen at random from each moxifloxacin sample. These samples were individually weighed (Wx) and their average weight (Wav.) was calculated using a calibrated analytical balance. Equation 2 was then used to calculate the % deviation from the mean and compare it to the USP limits.

$$\% \text{ of Wt. Variation} = \frac{(W_x - W_{av})}{W_{av}} \times 100\%$$

According to the USP-2015 general standards, the tablet passes the weight variation test if no more than two individual weights differ by more than 5% from the average weight and none by more than 10%.

Disintegration time test

Six tablets from each brand of moxifloxacin were placed in each of the 3 tubes of disintegration apparatus , The tubes were in the beaker containing medium of distilled water and the apparatus was operated for 30 minutes at (37±2)ºC temperature .The instrument operates at 29-30 cycles per minute after that the time for all the tablets has finished disintegration was recorded and the average disintegration time was calculated for each brand. The limit : not more than 30 min [8].

Profile Dissolution test

The profile dissolution test for four brands moxifloxacin 400 mg tablet compared with the original brand were performed in three different medium as the following: Medium: acetate buffer (pH 4.5).

$$f_1 = \frac{\sum_{j=1}^{n} |R_j - T_j|}{\sum_{j=1}^{n} R_j} \times 100$$

$$f_2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{j=1}^{n}(R_j - T_j)^2\right]^{-0.5} \times 100\right\}$$

where n is the number of time points and R_j and T_j are the percentages of reference and test product, respectively, released into the dissolution medium at time j. According to the FDA guidance, dissolution profiles are similar if f_1 values are between 0 and 15 and f_2 values are between 50 and 100.

RESULT AND DISCUSSION

Organoleptic tests

The results of organoleptic (taste, color and odor) and shape were checked visually and presented in tablet (1).

Table 1 : Physical properties for four brands of moxifloxacin tablets:

Brand code	Company	Test	Batch.NO	Manufacturing date	Expiry date	Retail price (YR/5
IB*	Multinational	Conforms	160720	11 / 2019	11 / 2022	7500($9.50)
A	Foreign	Conforms	210420	09 / 2019	09 / 2022	4200
B	Local	Conforms	220420	01 / 2020	01/ 2022	2000
C	Local	Conforms	180419	01 / 2020	01 / 2023	2000

IB*= Innovator brand

Friability test

Table (2) appeared that the friability test, all the four brands of moxifloxacin are within acceptable limit, according to the USP pharmacopeia. limits not more than 1%.

Weight uniformity test

Table (2) had showed that, all the weight of twenty tablets for all the four brands are less than the USP limit 5%. This results of weight uniformity test are acceptable for the four brands **of moxifloxacin film coated tablet** conform according to USP.

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

Brand code	Hardiness (kPa)	Friability (%)	Weight uniformity (mg)	Disintegration time (min)	Assay test (%)
IB*	11.02 ±1.74	0.05	691.5±22.30	1.1	102.09 ± 0.03
A	15.03 ± 0.40	0.17	779.5 ± 9.99	2.1	99.58 ± 0.07
B	13.85 ± 1.14	0.18	687.5±12.51	1.3	100.08 ± 0.05
C	14.48 ± 1.49	0.07	730.0 ±11.69	1.2	99.25 ± 0.19

All values are expressed as mean ± SD

Disintegration test:

From the table (2) are showing the results of the disintegration for the four brands are acceptable with the USP. limits not more than 30 minutes.

Drug Content (Assay)

Table (2) and figure (1) above are showing the average results of assay for the four brands, C, B, A, IB* are 99.25%, 100.08%, 99.57% and 102.085% respectively and these results are within USP acceptable range for moxifloxacin 400 mg tablet (90.0 - 110.0 %).

Dissolution profile test

Table 3 and figure 2 showed the dissolution profile of the innovator alternative (IB*) and (A, B and C) three generic products at acetate buffer medium pH 4.5 as shown in Table 3 and Figure 2 . All brands were release more than 85% within 15 min. and this met

all international guidelines for dissolution profile. By another mean, all moxifloxacin brands (A, B and C) are therapeutic equivalents to IB* and can use interchangeable without farther calculations (FDA, EMA, WHO). The results of this study lie with other previous study include thus mentioned by WHO-IFA about moxifloxacin biowaiver monograph (WHO-IFA). Dissolution profile data analysis moxifloxacin HCl is classified according to BCS (biopharmaceutical classification) as class I group of drugs [9]. The minimum requirements for accepting moxifloxacin immediate release tablet dosage forms are specified by USP moxifloxacin monograph. It states that the amount of not less than 85% (Q) of the labeled amount of moxifloxacin dissolved in 30 min [8]. According to the FDA guidance for industry (Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms, 1997), in the dissolution testing of immediate release solid oral dosage forms, the BCS suggests that for class I and in some cases class III drugs 85% dissolution in acetate buffer pH 4.5 in 15 min insures that the bioavailability comply with requirement of monograph (Guidance for Industry: Immediate Release Solid oral Dosage Forms, 1995). The innovator (IB*) together with three generic products A, B and C are passed the stated limit after 15minutes of dissolution as the average drug dissolution was higher than the 85% required for complying to required bioavailability. In order to compare the dissolution profiles of the studied innovator and generic products, a model independent approach of difference factor (f_1) and similarity factor (f_2) were employed (Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms, 1997). Similarity factor f_2 has been used by FDA and the European medicines evaluation agency (EMEA) to compare the similarity of two or more dissolution profiles. For two dissolution profiles to be considered bioequivalent or similar, difference factor (f_1) should be between 0 and 15 (Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms, 1997). Overall calculation of the difference factor (f_1) and similarity factor (f_2) values for the different generic products under study with respect to innovator (IB*) was not required according to above mentioned FDA Guideline.

Table 3. Dissolution profile of four brands of moxifloxacin 400 mg tablet at different time interval, at pH 4.5.

Brande code	Dissolution Rate at Different Time Interval (Mean) at pH4.5		
	5 min	15 min.	30 min.
IB*	88.66	90.12	95.53
A	63.22	100.34	100.8
B	72.16	102.19	102.80
C	97.13	105.14	115

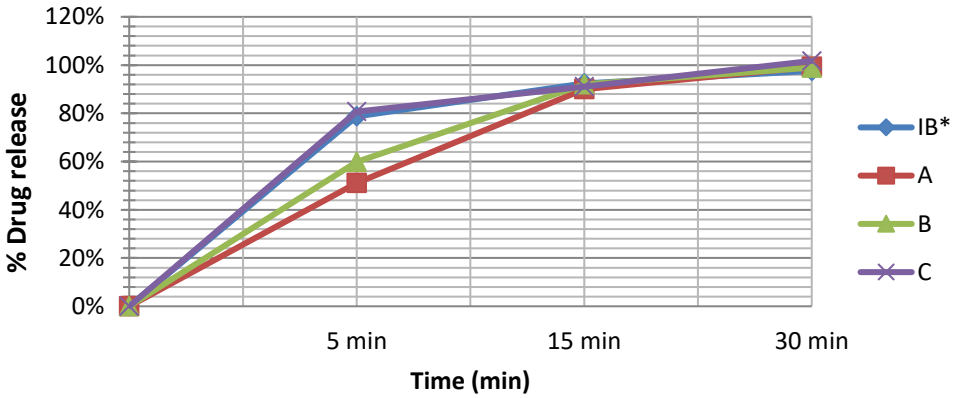

Figure 2 Dissolution rate profile in 900 ml acetate buffer medium pH 4.5 for four generic moxifloxacin 400 mg tablet.

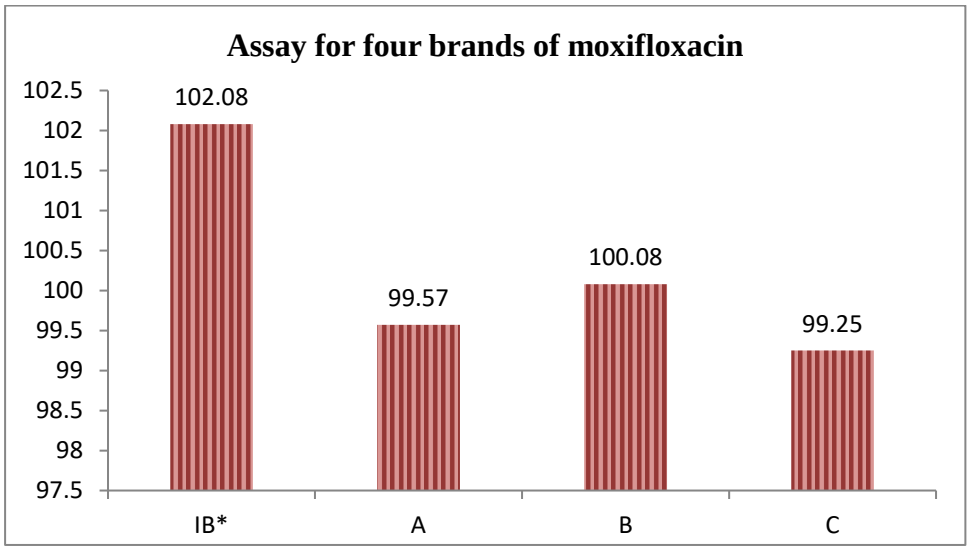

Figure 1 :Results assay % for four brands of moxifloxacin tablets

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