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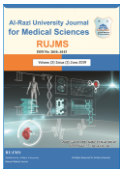

Comparative Study of in vitro Quality Specifications of Yemeni Brand of Glimepiride Tablets Versus Foreign Brands Marketed in Yemen

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Abstract

Background: *Generic drug products are increasing in the market nowadays making it possible for people to select a particular generic drug from several equivalent products. Local pharmaceutical industry in Yemen has provided many Generic medicines to the Yemeni drug market. These medicines are cheaper alternatives to the high cost brands. Unfortunately, there is a wrong belief that generic medicines are inferior in quality compared to the original brands.* ***Aim****: To assess the quality specifications of a Yemeni brand of Glimepiride 2-mg tablets versus 2 foreign brands marketed in Yemen including one Arabian Brand and one innovator European brand.* ***Methods****: The quality physical specifications including tablet thickness, hardness, friability, and disintegration and weight variations were investigated for each of the three tested brands. In addition, the drug content and dissolution behavior of drug in those brands were also evaluated.* ***Results:*** *The results of quality specification testing of tablet thickness, friability, disintegration, weight variations and drug content of the three tested brands were within the accepted limits. With respect to other tests, the original and the Yemeni brands showed hardness within acceptable limit and also showed good dissolution similarity. However, the Arabian brand demonstrated high harness out of accepted limit and also showed dissolution dissimilarity with the original brand.* ***Conclusion:*** *The Yemeni brand of Glimepiride investigated in this study has equivalent quality specifications as that of the original brand*

Keywords: Quality; specifications; Glimepiride; Yemeni

Introduction

Internationally the use of generic drugs is increasing due to rising cost of the original brands. Major savings in health care expenditure is possible by using generic drugs as they are usually cheaper than the innovator brands. However, physicians have doubt on the quality of generic drugs. Generic medicines are widely believed as inferior in their therapeutic efficacy and quality to branded product even though they are produced under good manufacturing practices[1, 2,3]. In 2011, the international diabetes federation (IDF) estimated 366.2 million adult population with diabetes, which is estimated to grow by 51% to 551.8 million by 2030[4]. As a result, the use of antidiabetic agents has increased in the past two decades[5] Glimepiride is a sulfonylurea approved by FDA since 1995 as oral hypoglycemic. It is widely used as mono-therapy or in combination with insulin for diabetes mellitus type II[6]. Compared to other sulfonylureas, glimepiride was as effective in lowering glucose levels as glibenclamide and glipizide, but

glimepiride was associated with a reduced likelihood of side effects of hypoglycemia and a smaller increase in fasting insulin[7].

Bioequivalence studies between generic brands of Glimepiride and the original brand have been conducted using human volunteers and showed optimum equivalency between the two brands[8]. The drug absorption after oral administration is almost complete [8,9]. However, the drug is insoluble in water1 and thus its dissolution is the rate-limiting step in its bioavailability. Factors related to drug formulation including the types of excipients added, drug particle size can greatly influence dissolution behavior of drugs[10].

Aim of the study

To compare the in vitro quality specifications of a Yemeni brand of Glimepiride tablets to those of 2 foreign brands including one Arabian and one innovator European brand

Subject and Methods

Materials: Three brands of Glimepiride 2-mg tablets including a Yemeni brand (Glimaryl ®, YEPC; Yemeni Egyptian Pharm. Co.), an Arabian brand and innovator European brand (Amaryl ®, Sanofi Aventis, Italy) were investigated in this study. A reference standard of the drug was a gift form Shafaco Phar. Co, Yemen. All other materials used in this study were at least of analytical grade.

Instrumentation: Tablet Thickness tester (Digital Caliper®, Germany), hardness tester (Erweka® Gmbh Heusentamm , TB24, Germany), electric blalance Mettler® pm 480 deltarange , Swizerland), disintegration tester (Tianjin-Guoming- PT3, China), friability tester (Digital Friability Test Apparatus Sr:1009564, Germany), dissolution apparatus (Erweka® DT6, Germany), HPLC equipment (SHIMADZU® Lc-solution , Japan) and UV spectroscopy (V-630 , Germany) were used in this study.

Experimental analysis

Tablet thickness[11]***:*** Tablet thickness (mm) was measured for 10 tablets of each brand using an electric Digital Caliper. The ideal size is within a ± 5 % of a standard value**.**

Weight variation: Twenty tablet ware weighed individually. The average was calculated and individual tablet weight was compared to the average[1]. The tablet pass the U.S.P. test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times of the percentage limit. (Not more than ± 10%).

Friability[12]**:** The friability test was performed for 20 tablets at 25 rpm for 4 minutes using friability tester. The tablets were initially weight before testing and then reweighed after removal of fines and the percentage of weight loss was calculated. The accepted limit is weight loss of not more than 1%.

Hardness[13]**:** Tit was tested using hardness tester. Ten tablets of each brand were investigated and the average hardness was calculated. Accepted limit is a range between 40- 80 N.

Disintegration[1]***:*** The disintegration time of 6 tablets of each brand were investigated using disintegration tester. The test was carried out in 900 ml distilled water at 37± 1 ^{o}C. The accepted limit is all 6 tablets passing the mesh within not more than 30 minutes.

Drug content [1]***:*** It was tested by HPLC system stated in USP[1] compromising a stationary column (C18; 4.6 mm x 5 cm); mobile phase (acetonitrile and water 9: 1); flow rate 1.5 ml/min,

injection size 20 µl and UV detector at 228 nm. The accepted limit of drug content is 90-110%.

Dissolution: Standard 2-mg Glimepiride was investigated initially. Then, 6 tablets of each brand were tested. In both tests, the standard or tablet was added to 900 ml of dissolution media (pH 7.8 phosphate buffer) in USP dissolution apparatus II and stirred at a speed of 75 rpm at 37±0.5˚C. 10ml aliquots were withdrawn at 10, 20, 30, 45, minutes and replaced by 10ml of fresh dissolution medium. The collected samples were analyzed by UV spectroscopy after suitable dilution at 228 nm against the blank[1]. The amount dissolved % was calculated by comparison the sample absorbance with standard one. The average % dissolved of each brand tablets was calculated. The accepted limit was to dissolve not less than 80 % in 45 min. The average % dissolved was then constructed against time (in vitro release profile).

The dissolution similarity factor between each 2 brands was calculated as follows[13]

$$f_2 = 50 \cdot \log \{[1 + (1/n)\Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \cdot 100\}$$

Where f_2 = Similarity factor, n = number of time points, R_t = % drug dissolved (reference product), Tt = % drug dissolved (test product).
If $f_2 > 50$, the profiles were considered similar.

Results

Table 1 shows the results of quality specifications of tablet thickness, weight variation, friability, hardness and disintegration time, of the three tested brands. With exception of hardness, the three brands showed results within the accepted limits. Regarding hardness, the Yemeni and innovator brands showed hardness of (58.7 ± 17.8 N) and (78 ±10.5 N) , respectively which were within accepted limits (40-80 N), while the Arabian brand hardness was 104 ± 7.4 N, out of accepted limit.

Table 1: Drug content and physical specifications of quality of the three investigated brands of Glimepiride tablets

Test	Accepted limit	Amaryl® (Innovator brand)	Arabian ®	Glimaryl ® (Yemeni brand)
Drug content (%)	90-110	98.74± 2.5	102.66 ±4.3	105.83 ± 1.6
Thickness (mm)	± 5 %	2.85 ± 1.8	3.2 ± 0	2.8 ± 0
Weight variation (%)	± 10 %	0.168 ± 1.37	0.157 ±0.85	0.163 ± 0.94
Friability (%)	Not more than 1 %	0.23	0.12	0.1
Hardness (N)	40- 80 N	58.7 ± 17.8	104 ± 7.4	78 ±10.5
Disintegration (min.)	Not more than 30 min.	15 ± 0.6	27 ± 1.4	20 ± 1.3

Concerning drug content, the content was calculated by comparison of the peak area of HPLC peak obtained with sample to that obtained with standard solution of the drug, Figure1. The innovator, Arabian and Yemeni brands showed content of 98.74 ± 2.5 %, 102.66 ± 4.3 %, and 105.83 ± 1.6 %, respectively, and all were within accepted limits (90-110%). A dramatic difference between the three brands was demonstrated in dissolution test, Figure 2. The Arabian brand failed to dissolve of not less than 80 % in 45 min. In contrast, the two other brands passed that pharmacopeial specification. Moreover, the Yemeni and innovator brands showed similarity factor f2 of > 50 indicating good similarity in dissolution profiles between the two brands. In the contrary, the Arabian brand compared with the innovator brand showed f_2 of 36 indicating dissimilarity of dissolution between the two brands

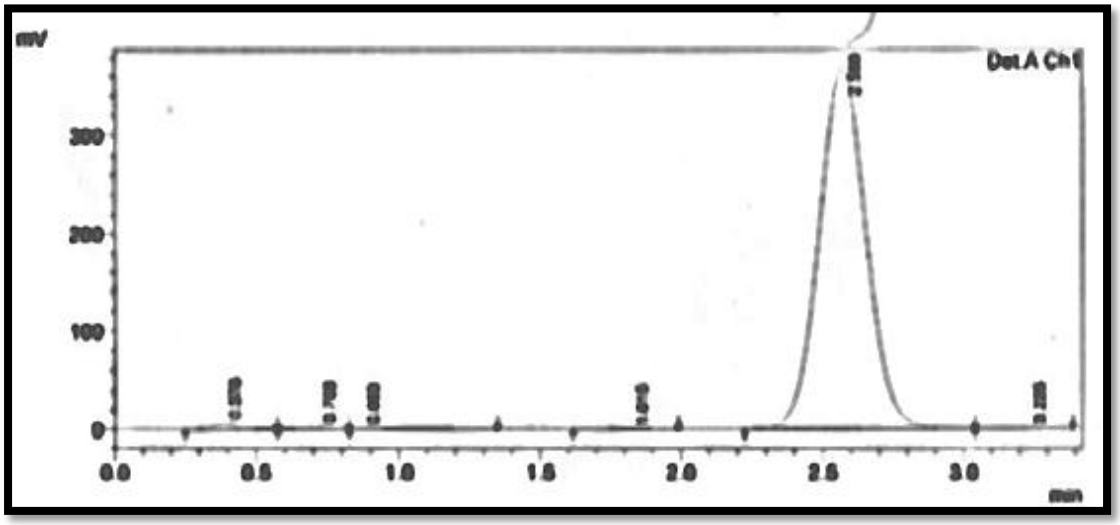

Figure 1: HPLC chromatogram of a standard solution Glimepiride

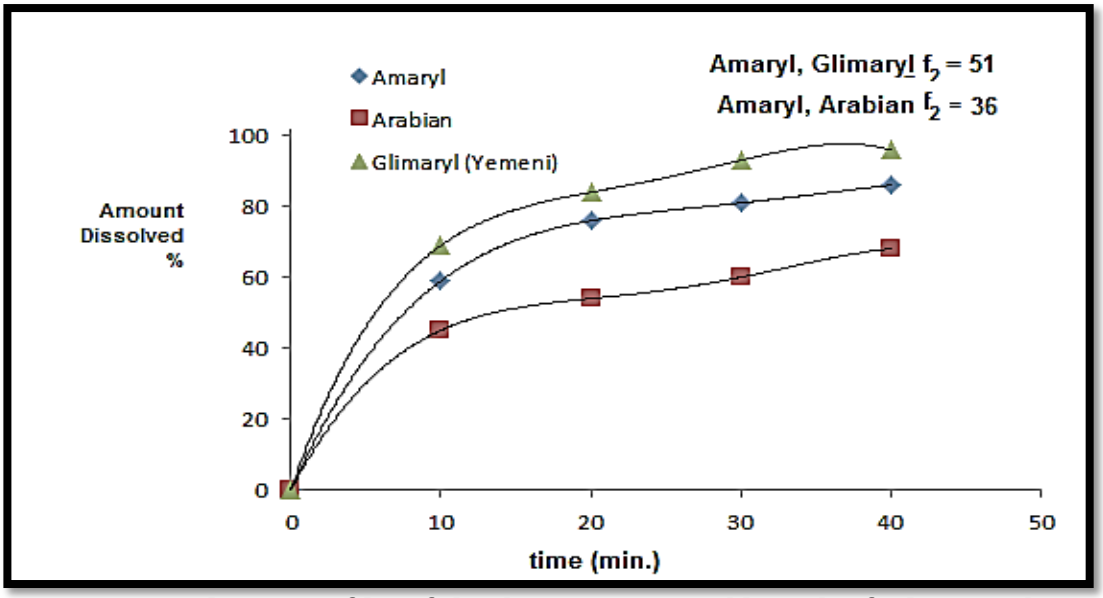

Figure 2: Dissolution profiles of the three investigated brands of Glimepiride 2-mg tablets.

f_2 : similarity factor ; $f_2 > 50$: similar dissolution profile.

Discussion

In vitro physical, drug content and dissolution tests are employed to evaluate the quality specification of tablet dosage forms. If tablets of two or more brands show results within accepted limits, these brands would have optimum quality and hence are equivalent in their therapeutic values[14]. In the present study, the Yemeni brand of Glimepiride was found to have equivalent quality specifications to those of the innovator European brand. This finding support the use of Yemeni brand as cheaper alternative to the European brand. Although, bioequivalence study between the two brands are still to be conducted. In the opposite way, the Arabian brand showed inferior quality specifications in particular in hardness and dissolution. The higher unaccepted hardness and lower dissolution could be attributed to manufacturing / formulation defects in particular higher concentration of binder, improper compression force or other reason[10].

Conclusion

Glimaryl® a Yemeni brand of Glimepiride 2mg-tablet has equivalent in vitro quality specifications to that of amaryl® the European innovator brand. Moreover, the specifications of the Yemeni brand is superior to that of an Arabian brand

Recommendations

The study recommends to perform bioequivalence study between Glimaryl® and Amaryl ® in order to ensure equivalence between the two brands. The study also recommends the supreme board of drugs and medical appliances (SBDMA) in Yemen to periodically assess the quality specifications of drug products in Yemen in order to save Yemeni patients from products with inferior quality.

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