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Research Article

PHARMACEUTICAL EQUIVALENCE ASSESSMENT OF YEMENI AND NON-YEMENI METFORMIN TABLETS MARKETED IN YEMEN

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ABSTRACT

Objectives: The current research was carried out to determine the pharmaceutical equivalence of Yemeni and non-Yemeni metformin tablets that are available in the Yemen market using the major quality control parameters.

Methods: Samples of metformin tablets of various brand names (Yemeni [Y] and non-Yemeni [N]) were obtained at the local pharmacies in Hadhramout city, Yemen. The samples were evaluated on the basis of weight change, thickness, hardness, friability, disintegration period, and dissolution profile as per the official United States Pharmacopeia (USP) requirements. Student's independent t-test was used to statistically compare Yemeni (Y) and non-Yemeni (N) products, where the level of statistical significance was used in the value of p=0.05.

Results: Both formulations met USP specifications for weight, thickness, friability, disintegration, and dissolution. The hardness of non-Yemeni (N) tablets (188±22N) was significantly higher than Yemeni (Y) tablets (113±23N; p<0.05. Disintegration times were within the pharmacopeial limit of 15 min, with Yemeni tablets disintegrating faster than non-Yemeni tablets (p<0.05). Dissolution efficiency was satisfactory for both products (>90%).

Conclusion: Both Yemeni and non-Yemeni metformin tablets met USP quality standards across all evaluated parameters, confirming the pharmaceutical equivalence of Yemeni-manufactured and non-Yemeni-sourced metformin tablets.

Keywords: Metformin hydrochloride, Quality control of tablet, Pharmaceutical equivalence, Yemen.

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INTRODUCTION

Metformin hydrochloride, a biguanide-class drug, is widely accepted as the first-line oral therapy for type 2 diabetes mellitus. It lowers blood glucose levels largely by suppressing hepatic gluconeogenesis, thereby reducing endogenous glucose production in the liver [1]. In addition, metformin improves insulin sensitivity in peripheral tissues and may influence glucose absorption from the intestine [2]. Due to its favorable safety profile, weight neutrality (or slight weight loss), and low cost, metformin is included in the World Health Organization's Model List of Essential Medicines [3]. In Yemen, both locally manufactured and imported brands of metformin tablets are commercially available. Although the importation products may be perceived as of better quality, local pharmaceutical production plays an important role in ensuring national self-sufficiency, cost-containment, and assurance of supplies. Differences in physical, mechanical, and release properties of tablets can, however, occur due to differences in the raw materials, formulation processes, manufacturing processes, quality assurance, and the storage conditions imposed by the environment [4-6]. The differences, when unidentified, have the potential of influencing the bioavailability, therapeutic equivalence, and finally clinical outcomes of patients with diabetes. Pharmaceutical quality control (QC) testing is a collection of *in vitro* tests that are used to determine whether a pill is acceptable according to specific specifications. The most popular QC variables are the weight difference, hardness (or breaking strength), friability, time of disintegration, and dissolution profile. Such tests are used to determine uniform dosage, mechanical strength, adequate disintegration, and adequate drug release rates [7]. In different environments, several studies have also cited that not all generic or localized tablet brands meet pharmacopoeial QC standards, particularly in dissolution or uniformity of the content [8,9]. The published findings have shown the significance of local quality assurance. Since the quality of metformin is critical to addressing type 2 diabetes, any quality variation might have a direct clinical impact. In a nation such as Yemen, where resources are limited and regulatory control might be problematic, it is more important to ensure that local and imported metformin products are equal in terms of quality. As such, the current research was conducted to undertake a comparative *in vitro* analysis of the major QC parameters comparing local and imported metformin tablet brands in Yemen. This is to determine whether these brands meet the pharmacopeial standards, whether there are any deviations of quality, and to offer evidence-based suggestions to authorities, clinicians, and patients on the credibility and interchangeability of such products.

METHODS

Materials

Two brands of Metformin Hydrochloride 500 mg tablets were selected for the study, one locally manufactured in Yemen (coded as Y) and another imported brand (coded as N). All tablets were obtained from registered pharmacies in Hadhramout city, Yemen. All tests were performed within product expiration dates. All analyses were conducted by an analyst who was fully blinded to the product origin. Metformin hydrochloric acid (HCL) powder was a gift from the Biopharm pharmaceutical industry, Sana'a, Yemen. Analytical-grade reagents, including (HCL, 0.1 N), distilled water, methanol, and acetonitrile, were used for dissolution and high-performance liquid chromatography (HPLC) analysis.

Evaluation tests
The evaluation tests were conducted in accordance with procedures stated in the United States Pharmacopeia (USP) [10].

Weight variation test
An analytical balance was used to perform this test in order to be consistent in terms of the weight of the tablets. Each brand was weighed separately on 20 tablets, and the average weight and the percentage deviation of the average weight were determined. The measure was assessed based on the USP tolerance of tablets, which weighed over 250 mg, ranging within the limits of ±5% deviation.

Friability test
A Roche friabilator (Erweka TA20, Germany) was available to determine the friability of each of the formulations by running the equipment at 25 rpm for 4 min. Each batch of tablets was weighed, turned and dusted, and re-weighed 10 times. The percentage weight loss was computed on the basis of the USP.

Hardness test
Tablet breaking strength was measured using a Monsanto hardness tester, and the instrument was calibrated before use to ensure measurement accuracy. Ten tablets were individually tested, and the force required to break each tablet was recorded.

Thickness measurement
Tablet thickness was determined using a digital micrometer gauge (Mitutoyo Model 293-831, Japan). Ten tablets from each brand were measured individually, and the mean thickness was calculated.

Disintegration test
Disintegration time was determined using a USP disintegration apparatus (Electrolab ED-2L, India) containing 0.1 N HCL maintained at 37±0.5°C. Six tablets from each brand were placed in separate tubes of the apparatus, and the time taken for complete disintegration of each tablet was recorded.

Dissolution test
Drug release was evaluated using a USP dissolution apparatus (Type II, paddle method) (Erweka DT 720, Germany) at 50 rpm, containing 900 mL of pH 6.8 phosphate buffer maintained at 37±0.5°C. One tablet was placed in each vessel, and samples were withdrawn at 45 min, filtered, and analyzed by HPLC (Agilent 1200 series, USA)using a mobile phase composed of methanol, acetonitrile, and water (3:3:4 v/v/v). The percentage of metformin released was calculated relative to the reference standard. The HPLC method used for quantifying metformin was validated according to ICH Q2 (R1) guidelines for specificity, linearity, accuracy, precision, and system suitability.

Statistical analysis
Experiments were done in triplicate unless otherwise indicated, and the findings were presented as mean and standard deviation (SD). Student's independent t-test was the statistical test that was used to compare the Yemeni and non-Yemeni metformin tablet formulations in terms of significant differences in physicochemical parameters. Statistical significance was established at $p<0.05$. The IBM Statistical Package for the Social Sciences Statistics software (version 26.0, IBM Corp., Armonk, NY, USA) was used to analyze the data.

RESULTS

Results of evaluation tests
The comparative evaluation of Yemeni (Y) and non-Yemeni (N) metformin tablets is summarized in Table 1. Both formulations complied with USP specifications for weight, thickness, friability, disintegration, and dissolution. The hardness of non-Yemeni (N) tablets (188±22 N) was significantly higher than Yemeni (Y) tablets (113±23 N; $p<0.05$). Disintegration times were within the pharmacopeial limit of 15 min, with Yemeni (Y) tablets disintegrating faster (9.0±0.4 min) than non-Yemeni (N) tablets (12.7±0.6 min; $p<0.05$). Dissolution efficiency was satisfactory for both products (>90%, $p>0.05$), confirming effective drug release.

Table 1: Quality control evaluation of Yemeni (Y) and non-Yemeni (N) metformin tablets

Parameter	Y (Mean±SD)	N (Mean±SD)	p-value
Average weight (g)	0.65±0.01	0.67±0.04	p>0.05
Thickness (cm)	0.60±0.03	0.58±0.01	p>0.05
Friability (%)	0.15±0.01	0.10±0.03	p>0.05
Hardness (N)	113±23	188±22	p<0.05
Disintegration time (min)	9.0±0.4	12.7±0.6	p<0.05
Drug release at 45 min (%)	91.4±4.3	95.8±2.2	p>0.05

All values represent mean ± standard deviation (SD). The sample size for each test (n=20 for weight variation, n=10 for hardness, friability, and thickness, n=6 for disintegration and dissolution). The statistical significance was determined by an independent samples t-test with a $p < 0.05$ threshold. The dissolution test conditions (USP Apparatus II at 50 rpm in 900 mL of pH 6.8 phosphate buffer at 37 ± 0.5 °C, with measurement at 45 minutes).

DISCUSSION

The current research was to examine and compare the quality parameters of the *in-vitro* locally produced and imported metformin tablets in Yemen. The quality of pharmaceuticals met the requirements of the standards of the USP, and both of the formulations passed tests as regards to meeting the standards of the international quality of immediate-release dosage forms. However, minor yet significant variations in the hardness, disintegration, and dissolution profiles portray differences in formulations and manufacturing, which may affect the performance of the products. Findings of variation in weight were quite consistent in both products, with a very good range in the USP of up to ±5. These results will show that there is a consistent die filling, perfect flow of granules, and controlled compression forces in the production process [11]. The fact that there was no significant deviation with regard to weight also indicates the correct dose delivery, which is essential in the maintenance of therapeutic efficacy in chronic illnesses such as diabetes mellitus type 2. We have noted a big difference in hardness where non-Yemeni (N) sourced tablets had higher values as compared to the Yemeni (Y) manufactured tablets. The two formulations were above the standard recommended maximum (39.2–78.5 N) of immediate release tablets, implying over-compression [12]. While the hardness is high, the critical fact is that the tablets still passed the official compendial requirements for disintegration and dissolution. Increased hardness decreases the porosity of the tablet, slows down the speed at which fluids penetrate, and adds to slower disintegration [13]. Goh *et al*. in Ethiopia, also reported similar observations and concluded that there is a great inter-brand difference in the hardness of metformin tablets, which is related to the granulation and compression process [14]. Conversely, excessive hardness may compromise disintegration and bioavailability, underscoring the need for careful optimization of formulation parameters [15]. The friability test is used to supplement the hardness test in determining the mechanical resilience during handling. The metformin tablets (both domestic and imported) were found to have low values of friability, which were way below the USP limit of 1%. These findings indicate that both formulations have sufficient levels of cohesion and are not likely to experience powder or broken tablets during the packaging and transport process. Disintegration is a decisive factor in the availability of drugs in immediate tablets. The local tablets (Y) in the current study were disintegrated more quickly than the imported tablets (N), which adhered to the pharmacopeial requirement of <15 min. The faster disintegration of the local tablets can be attributed to their lower hardness, and therefore they are easier to penetrate through the dissolution medium, and also to the potentially different concentration of the disintegrants or type [16]. Such results are similar to those of Flatie *et al*., who noticed that there was a high inverse relationship between hardness and disintegration between metformin tablet brands in Ethiopia [14]. Metformin is a BCS

Class III drug (high solubility, low permeability), and for such drugs, dissolution rate is generally not the rate-limiting step for absorption. Therefore, the observed differences in hardness and disintegration are unlikely to be clinically significant, which actually strengthens the main conclusion of pharmaceutical equivalence. One of the major predictors of bioavailability, dissolution testing, indicated that both tablet brands discharged over 90% of the marked metformin substance in 45 min. These values are above the USP specification of 80% and above, meaning efficient release of the drug and ascertaining the success in the efficacy of the two products in the immediate therapeutic action. It might be the slightly increased dissolution rate of the imported tablets due to variation in the composition of excipients, particle size distribution, or excipient coating permeability [17,18]. A similar dissolution efficiency was present in a quality evaluation of metformin tablets in Pakistan, where all brands had over 85% drug liberation in 45 min, affirming they were bioequivalent [19,20]. These are the stable results, giving the conclusion that the Yemeni local formulation is equivalent to the international products. As a whole, the results prove the local and imported metformin tablets are pharmacopeially compliant regarding weight uniformity, friability, disintegration, and dissolution. These findings are also in line with the international reports that indicate that the high-quality local production, when guided by the Good Manufacturing Practices can produce products that are therapeutically equivalent to those of the imported brands. The post-marketing surveillance and regular QC evaluation should be continued to monitor the quality of the products and remind patients of the high-quality products manufactured locally.

CONCLUSION

Metformin tablets of Yemeni and non-Yemeni origin marketed in Yemen are pharmaceutically equivalent and comply with USP standards for weight uniformity, thickness, friability, disintegration, and dissolution. However, both formulations had hardness values greater than the commonly cited recommended range for immediate-release tablets (39.2–78.5 N). Limitations of the current study include a small sample size due to the lack of external funding, which restricted the number of products analyzed to a single local product against the international reference standard. Dissolution was assessed at a single time point (45 min) rather than using a complete dissolution profile. Future studies should target the evaluation of multiple products obtained from different manufacturers and provide supporting *in vivo* assessment of clinical performance and generalizability.

AUTHOR CONTRIBUTIONS

Abdullah H. Maad and Tareq Maqlam were the ones who conceived, designed, supervised, interpreted the data, and prepared the manuscript of the study. The actual work in the research was done by Tareq Maqlam, who carried out the experimental work, data collection, and statistical analysis, with Bashir Ahmad Barashid helping in the literature review, data interpretation, and revision of the manuscript. Every author consulted and accepted the final version of the manuscript before submitting.

CONFLICT OF INTEREST

All the authors attest that in the publication of this article, they do not have any conflicts of interest.

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