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SHORT COMMUNICATION article

Post-market *in-vitro* comparative studies of different brands of metformin tablets available in Libya

Mohamed I. Daghman [*], **Ali M. Rafieda**, **Osama M. Serrar**, and **Fatema M. Al Hedad**

Faculty of Pharmacy, Misurata University, Misurata, Libya
[*] Author to whom correspondence should be addressed

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Abstract: Metformin hydrochloride is the first-line anti-diabetic drug used to treat type 2 diabetes mellites and helps to control blood sugar levels. Various brands of metformin are available in the Libyan market which makes it challenging to select, an effective and economical one. This study aimed to compare different brands of metformin available in the Misurata and evaluate the quality parameter according to the British Pharmacopoeia. Six brands of metformin tablets (850 mg) were taken from the market and assessed. To achieve this purpose five tests were done on each brand, the uniformity of weight test shows the average weight and 5.0% deviation, the friability test gives how much the tablet can stand attrition, the disintegration time test shows the time taken by the tablet to disintegrate, dissolution test to confirm the rate of drug release, weight variation and friability test of all brands was within the specified limit. Disintegration time for all the brands was within 30 minutes. All six brands of metformin hydrochloride tablets fulfilled the *in-vitro* dissolution rate test specification not less than 80% of the drug is released within 45 minutes. Using Ultraviolet-visible (UV) spectroscopy, UV analysis of different samples shows that the percentage content of active ingredients of five brands of metformin hydrochloride tablets was within the monograph specification (95%-105%) of drug content but one brand failed this test. The study indicated that strict quality control of imported drugs should enforced to ensure effective and safe medicines in the Libyan market.

Introduction

The growth in pharmaceutical industries led to an increase in the number of pharmaceutical products (branded and generic) in markets [1]. Drugs with more than three generic products require analysis for their biopharmaceutical and chemical equivalency. The Food and Drug Administration (FDA) considers a pharmaceutical product equivalent to another if it contains the same active ingredient(s) of the same dosage form and route of administration and is identical in strength or concentration. Drug products are considered therapeutically equivalent only when pharmaceutically equivalent [2]. To ensure the safety and reliability of any pharmaceutical dosage form in terms of quality, pharmaceutical companies should maintain the Pharmacopeial

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standards as prescribed by pharmaceutical regulatory authorities during the manufacturing of the drugs [1]. In the pharmaceutical industry, the total quality of the product must be ensured to prevent the kind of product that does not comply with the specifications laid down by the Pharmacopoeias [3]. Quality is a broad term that includes the suitability of drugs and products for their utilization which is decided by their efficiency and safety, according to label claim, or as promoted or publicized, their conformity specifications about identity, purity, and other characteristics, quality gives importance to test the product for defects and reporting the same to the management according to the international standard of organization quality control is the operational techniques and activities that are used to fulfill requirements for quality [4].

To ensure the requisite quality, drug manufacturers are required to test their products during and after manufacturing at various intervals during the shelf life of the product [5]. Also, drug stability is an essential parameter that has to be evaluated carefully to ensure drug efficacy and improve safety because many drugs are vulnerable to degradation during packing, shipping, and storage. Parameters like color shape, weight variation, hardness, friability, disintegration time, dissolution, and uniformity of content were tested [6]. For ease of identification, many pharmaceutical tablets use color and it is also for consumer acceptance. It must be uniform within a single tablet, from tablet to tablet, and from batch to batch the shape and color of the tablet should be according to the need of the dose requirement and can be dimensionally described monitored, and controlled it is determined by the tooling during the compression processes [4]. Friability is the test for a tablet to see whether the tablet is stable to abrasion or not, and show how much the tablet can withstand attrition it is tested by using a Roche friabilator, and a 1.0% maximum loss in the weight after friability test is allowed. The uniformity of weight test is performed to check that the manufactured tablets have a uniform weight, as per British Pharmacopoeia (BP) [7], following the limit for the tablets shown in **Table 1**.

Table 1: Limitation of weight

Average mass (mg) (BP)	Percentage deviation
80 mg or less	10.0%
More than 80 mg or less than 250 mg	7.5%
250 mg or more	5.0%

The uniformity of content test provides the information on how much is practically available in the given dosage form and after comparing it with the theoretical value, a result about the efficacy can be given. A disintegration test is performed to see how much time a tablet takes to break down into small particles as this is the first step before the drug dissolution in the body, the condition of this test should be the same as in the body as this is part of *in-vivo*, *in-vitro* correlation [6]. Dissolution testing of drug products plays a vital role as a quality control tool in assessing batch-to-batch consistency of drug release from a dosage form. It also functions as a qualitative and quantitative tool, which can provide important information about the biological availability of a drug [2]. Metformin hydrochloride (HCl) is the most popular anti-diabetic drug in Libya and all over the world [8]. The use of metformin HCl tablets needs to monitor and ensure the quality of the various brands commercially available in the Libyan market to assess their quality control [9, 10], additionally, if these brands are interchangeable and patients can safely switch from one brand to another or not and which is the best economically. The present study aimed to evaluate and compare different metformin HCl tablet brands applying both official and unofficial methods following the BP. In addition, evaluate the quality of each brand and compare them to BP's standard to ensure a high degree of safety and quality to be used for patients.

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Materials and methods

Sample collection: Six multinational brands of metformin tablets were collected from the community pharmacies in Misurata, Libya. To conduct separate quality control tests, 72 tablets labelled with metformin (850 mg each tablet) were randomly selected in each brand. To complete this study, as indicated in the table brand quality was assessed using performance quality-control tests and confirmed using BP standards.

Visual Inspection: visual parameters such as the shape, size, and color of the different brands of metformin tablets were examined visually [4].

Table 2: Visual parameters

No	Shape	Colour	Texture
B1	Round	White	Smooth
B2	Round	White	Smooth
B3	Round	White	Smooth
B4	Round	White	Smooth
B5	Round	White	Smooth
B6	Round	White	Smooth

Friability testing: Sample tablets (n=20) of each brand were weighed collectively before being placed in the Roche friabilator for the friability test for four minutes. The friabilator was set to 25 *rpm*. The tablets were then removed, dusted off, and weighed once more. The following formula was used to compute the percentage of friability according to Lakmali and others [11].

$$[(Wi - Wf)/Wi] \times 100.$$

Where Wi = Initial weight and Wf = Final weight

Uniformity of weight variation testing: Twenty tablets were randomly selected from each brand and weighed collectively and individually. The average weight of each tablet and percentage deviation were determined for each brand and reported as ±5.0% and ±10.0% of the average values [9]. The tablet for each brand will pass the test if there are no more than two tablets out of an average of ±5.0% or not more than one tablet out of an average of ±10.0% [9]. The percentage deviation was computed using the following equation:

$$= \frac{(individual\ tablet\ weight - Average\ weight\ of\ 20\ tablet)}{Average\ weight\ of\ 20\ tablet} \times 100$$

Disintegration time testing: Samples of six tablets were selected from each brand. Tablets were placed in six tubes of the disintegration test machine and perforated cylindrical plastic discs were put on the top surface of each tablet. The assembly was allowed to move up and down in a beaker containing distilled water at 37.0±0.5°C. The time taken to break each tablet into small particles and pass out through the mesh at the bottom of the tube was recorded as disintegration time for each one of the brands. The BP limit to disintegration time is not more than 15 min for uncounted tablets but for coated tablets as the metformin tablet involved in this study is not more than 60 min [12].

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Uniformity of content testing: The tablet contains a specific amount of active ingredient (drug) with an allowable variable limit. An assay of the tablet ensures the amount of active ingredient which is indicative of its efficacy and stability of the product. 20 tablets were weighed by electrical balance and powdered by mortar and a bastel sample was weighed equivalent to 0.1 g of metformin HCl, and was shaken with 70 ml of water for 15 min and then diluted to 100 ml with water and filtered, from this dilute 10 ml to 100 ml with water and measure absorbance at 232 nm% drug content was calculated taking 798 as the value of 1.0%, 1.0 cm at the maximum at 232 nm [4].

The percentage of drug content calculated as actual concentrations / theoretical concentrations x 100%

Dissolution testing: In-vitro dissolution study of metformin HCl tablets was performed by six tablets of each brand for 42 min under the standardized condition in 900 ml in distilled water at the temperature of 37.0±0.5ºC using dissolution test, pharma test (paddle), and the rotation per minute:100 *rpm* was set, during dissolution test, 10 ml of dissolution sample was withdrawn at 45 min and then filleted and diluted. 232 nm wavelengths were used to detect the drug in a UV-vis spectrophotometer. The concentration of each sample was determined from the point calibration curve, which was obtained from a standard curve of metformin HCl [13].

Results and discussion

The World Health Assembly Resolution of 2001 on the World Health Organization's (WHO) medicines strategy identified the main objectives of WHO medicines strategy: namely to ensure access, ensure quality, safety, and efficacy; and to promote the rational use of drugs [14]. In this study, all the metformin tablets investigated were within their shelf lives and film-coated dosage forms with a label strength of 850 mg. About visual inspection: The tablets looked good and non-sticky. The color and the shape of tablets were analyzed with the naked eye, the observation results showed that, no defects in the uniformity of color or shape within a single tablet, from tablet to tablet, or from batch to batch for all selected brands, the observation results were represented in **Table 3**. Twenty tablets of all selected brands were weighed and placed in Roche friability, the tablets were then removed, dusted off, and weighed once more, the initial weight and the final weight were recorded to calculate the % friability of the tablets, the BP [7] which specifies that the loss of weight not more than 1.0% of their initial weight, in this study all brands meet the specification of BP **(Table 4)**.

Table 3: Visual inspection

Brand No	Shape	Color	Text
B1	✓	✓	✓
B2	✓	✓	✓
B3	✓	✓	✓
B4	✓	✓	✓
B5	✓	✓	✓
B6	✓	✓	✓

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Table 4: Friability test

Brand No	B1	B2	B3	B4	B5	B6
% weight lose	0.535%	0.190%	0.0032%	0.103	0.182	0.0235

This test was performed to evaluate the ability of metformin HCl tablets to withstand various shocks and friction during packaging, handling, and transporting [15]. Although friability is a nonofficial test, it is related to the hardness of the tablet and it is the tendency of tablets to powder, chip, or fragment. It can negatively affect the elegance, appearance, and consumer acceptance of the table, and if this test failed may be due to the use of an insufficient binder or inappropriate compaction force, making the tablets friable but in this study, there is no brand failure of this test [16]. About uniformity of weight variation: The weight uniformity test revealed that all brands conformed to BP, as the percentage weight deviation of tablets of five brans was not greater than 5.0%, but one brand (**B2**) has one tablet greater than 5.0% and still in acceptance limit the average weight of each brand are represented in **Table 5**.

Table 5: Uniformity of weight

Brand No	B1	B2	B3	B4	B5	B6
Range	0.9060±5%	1.0101 ±5%	0.92708±5%	0.94439±5%	0.9147±5%	1.0080±5%

According to BP specification to pass the uniformity of weight, not more than two of the individual weights of the tablets can deviate from the average weight by more than a percentage deviation of ±5.0%, and none should deviate by more than 10.0% [7]. The purpose of this test is to verify the uniformity of each brand which ultimately reflects the drug content uniformity [11]. In **Table 6**, with regards to the disintegration time test, the results of the disintegration test show that the disintegration time of all four different brands of metformin tablets is less than 30 min which is less than the standard disintegration time proves that all these brands of metformin tablets pass the quality control limits as per the Pharmacopoeia. This test is performed to find out the time required for a solid oral dosage form to completely disintegrate in the gastrointestinal tract. The time of disintegration is a measure of the quality of the tablet as it affects the drug release rate [12]. The disintegration of tablets is dependent on the type of formulation excipients and processes used by different manufacturers which consequently influence the bioavailability of the drug [14]. The rate of disintegration is influenced by the rate of influx of water into the tablets which is also dependent on the porosity of the tablet [15, 17].

Table 6: Disintegration time

Brand No	B1	B2	B3	B4	B5	B6
Time	10:25 min	12:50 min	7:13 min	14:38 min	9.26 min	10:13 min

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With regard to uniformity of content, the loaded dose of metformin in selected tablets in five brands was within the BP standard specifications of 95.0% and 105% [7], but **B2** showed a percentage out of the range of drug content, the **B2** failure in the weight uniformity test and we can reject the batch because the uniformity of content results test is official the percentages of content to each brand are represented in **Table 7**. The dosage form having a higher percentage of drugs than it claimed may lead to adverse reactions while lower percentages lead to treatment failure [11].

Table 7: Uniformity of content

Brand No	B1	B2	B3	B4	B5	B6
Percentage of release	101%	94%	97%	99%	103%	101%

Regarding to dissolution test: Six brands were analyzed to investigate the percentage of drug release after 45 min by conducting dissolution by using a dissolution tester (Pharma test) the absorbance of each sample is obtained and the concentration is calculated by using the equation from the calibration curve of standard metformin Y=0.0711X+0.0323 to calculate the percentage of the drug release the results represented in **Table 8**. Dissolution was performed according to the specified standards all results were found within the limits and the highest percentage of drug release was gained by **B1** as shown in **Table 8**. The *in-vitro* dissolution test is an alternative to the bioequivalence test and it is an important quality control parameter [12]. According to BP [7], active pharmaceutical ingredients should be released from the tablet in not less than 70% of the stated amount within 45 min [15]. The difference in the result can be correlated to all factors which affect the dissolution rate from the raw material which can affect solubility and all diluents which were used in the formulation of each brand [12, 16]. The failure of this test may be due to defective formulation, compression pressure used, and binder effect, but in this study, there is no brand failure of this test.

Table 8: Dissolution test

Brand No	B1	B2	B3	B4	B5	B6
Percentage	109.05%	98.19%	107.18%	102.14%	96.50%	108.12%

Conclusion: Six generic brands of metformin HCl tablets have been subjected to analysis according to the monograph of British Pharmacopoeia, the findings have indicated that the five brands within the Pharmacopeia quality specification but one brand failed in the content uniformity test. The quality of medicines must be reevaluated by responsible committees during their shelf life to ensure the safety and effectiveness of consumed drugs by populations.

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Author contribution: MID conceived and designed the study as well as contributed to the data analysis. OMS performed the analysis/interpretation of data. MID drafted the manuscript/revised it for important intellectual context. FMA & AMR collected data. All the authors approved the final version of the manuscript and agreed to be accountable for its contents.
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