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Monitoring tests of metformin tablets 500 mg produced by different companies and available at local pharmacies in Misurata city

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Abstract: The widespread use of metformin tablets as an oral hypoglycemic agent from patients suffering from type II diabetes mellites, led to the presence of different brands on pharmaceutical market, with different quality and efficacy. Evaluation tests like weight test, solubility test using HCl acid, Friability test and hardness test were selected to test the quality of four famous brands (A، B، C، D) of metformin tablets with a strength of 500 mg in the local market in Misurata city. The results revealed that, most of metformin tablets brands within the limits of the American Pharmacopoeia USP in all tests, while some other comply partially with the American Pharmacopoeia USP specification.
Keywords: metformin - diabetes - tablets.

اختبارات رقابية لشركات مختلفة من أقراص الميتفورمين بقوة 500 مليجرام

المتواجدة في الصيدليات المحلية في مدينة مصراتة

هند إسماعيل، ريتاج أبوبريدعة، عبدالله عاشور

الملخص

إن الاستخدام الواسع لأقراص الميتفورمين كخافض فموي لمستوى السكر من النوع الثاني في الدم، أدى إلى وجود علامات تجارية مختلفة على نطاق واسع، مما يسبب في اختلاف جودتها وفاعليتها، صممت هذه الدراسة لتقييم جودة أقراص الميتفورمين المتواجدة في السوق المحلي لمدينة مصراتة باستخدام بعض الاختبارات الدستورية مثل اختبار الوزن، اختبار الذوبانية باستخدام حمض HCl اختبار الهشاشة، اختبار الصلابة.

تم اختيار 4 علامات تجارية شهيرة (A، B، C، D) من أقراص الميتفورمين التقليدية بقوة 500 مليجرام المتواجدة في السوق المحلي لمدينة مصراتة لمقارنة الجودة حيث أظهرت النتائج أن مواصفات معظم أقراص هيدروكلوريد الميتفورمين تقع ضمن حدود دستور الأدوية الأمريكي، وكانت ثلاث علامات تجارية بينما تجاوزت علامة تجارية واحدة الحد الرسمي للوزن المسموح به بنسب صغيرة.

الكلمات المفتاحية: الميتفورمين، السكري، أقراص

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Introduction

Diabetes mellitus is defined as a chronic disease resulting from genetic and environmental factors that cause an increase in the level of glucose in the blood, due to the absolute or partial deficiency of insulin secreted by the pancreas, which leads to disorders or defects in the metabolism process of carbohydrates, fats, and proteins. It is considered one of the chronic diseases that need long-term use for treatment and is accompanied by a change in the concentration of antioxidants and multiple pathological deviations. It is divided into two types: type I diabetes and type II diabetes [1].

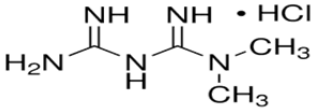
Metformin is one of the drugs that are widely used for type II diabetics. In addition to stimulating the pancreas and increasing the effectiveness of insulin, it reduces appetite. Therefore, they benefit patients with obesity more than others. Metformin has multiple side effects, as they cause digestive disorders and weight loss. It can causes severe hypoglycemia [2].

Metformin of the biguanide class taken orally, is also used to treat polycystic ovary syndrome. It is not recommended in treatment of gestational diabetes; due to safety concerns [3]. It has been tried in other diseases in which insulin resistance plays an important role [4]. Metformin was first described in the scientific literature in 1922, by Emil Fernier & Jims Bail, as a product in the synthesis of (N,N-dimethylguanidine) [5].

French physician Jean Stairen began studying human subjects in the fifties of the last century. It was introduced as a drug in France in 1957 and the United States in 1995 [6-7].

It is included in the World Health Organization's List of Essential Medicines [8]. Metformin is the most commonly used oral diabetes drug and is available as a generic medicine in 2018 [9]. It was the fourth most commonly prescribed drug in the United States, with more than 83 million prescriptions. There are many chemical and physical properties of metformin hydrochloride, and the following table shows the most important [10].

Table (1): Shows some chemical and physical properties of metformin.

Trade Name	Metformine
Chemical name	1,1-Di methyl biguanide Hydrochloride, Metformin
Molecular form	$NH_2C(=NH)NHC(=NH)N(CH_3)_2 \cdot HCl$
Chemical formula	$C_4H_{11}N_5$
Structural formula	
Molar mass	129.16 g/mol
Molecular weight	165.62
Bioavailability	%60 –50
The appearance	Solid

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The use of metformin tablets led to the existence of different brands, which made them differ in their quality and conformity to the specifications and standards of pharmacopoeia.

Materials and Methods

Four different brands of metformin hydrochloride tablets were obtained from the Pharmacy of Misurata city.

Table (2): Information on metformin samples used in the experiments.

Brands	Name	Produced company	Country of manufacture
A	Metformin 500 mg	BROSTOL	Britain
B	Metformin 500 mg	MENARINI	Italia
C	Metformin 500 mg	MYLAN	France
D	Metformin 500 mg	CRESCENT	Britain

1- Materials and tools used

• hydrochloric acid HCl (concentration of 0.1 µl manufactured by Merck K Gas, Germany).
• Electronic Balance with three decimal numbers.
• Roche Friabilato Machine (manufactured by J ingtuoyq Chinese company).
• YD-01 Machine digital tablet hardness measuring device (Manufactured by J ingtuoyq company in China).
• 5 pcs 50ml conical flasks, 10 mL graduated flask.

2- Methods Used

Weight variation test: The purpose of this test is to verify the uniformity of each batch which ultimately reflect the drug content uniformity in all the formulation batches. The test was performed as per the official procedure, 20 tablets were randomly selected and weighed individually and also average weight was calculated. The difference between

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average and individual weight was calculated, further % weight variation was calculated and compare with the USP Limits [11].

Friability test: This test is usually performed to check possible wear and tear loss in the tablet during the transportation and this is closely related to tablet hardness. It is usually performed in the Roche Friabilator. Randomly 5 tablets were selected and their initial weight (W1) was recorded and after that these weighed 5 tablets were placed in the friabilator then it was operated for four minutes at 25 rpm speed and 100 revolutions, the tablets were weighed again (W2) [12], and the percent loss (Friability) was then calculated by using following formula [13].

$$\textbf{Friability}\ (\%) = \frac{(w1-w2)}{w1} * 100$$

The official permissible limit for friability is 1%.

Where :

W1: The first weight of metformin tablets before fragility testing.

W2: The second weight of metformin tablets after fragility test

Dissolution test: The dissolution test is known as the test closest to the bioavailability of the drug inside the human body, so this test is done to ensure the proper pattern of drug action as well as its effectiveness inside the body and the time of its disintegration and decomposition in the body. This test was carried out by measuring 10 ml of HCl (with a concentration of 0.1 µl, which is the pH of stomach acid) per 50 ml flask, and 5 tablets of each brand were randomly selected, and each tablet was placed separately in the acid; At

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a spin speed of 100 revolutions per minute, its dissolution rate and dissolution time were monitored [14].

Hardness Test: This test is usually done to check the strength of the tablet and its resistance to breaking, and this is closely related to the hardness of the tablet. One tablet at a time inside the device, and then apply pressure by rotating the knurled knot, just enough to hold the tablet in place, then the pressure is increased as uniformly as possible until the tablet breaks, after which the required pressure that the tablet needed to break is read [15] .

Result & Discussion

The types of tested tablets (Table 2) were obtained from private pharmacies in the city of Misurata, which were subjected to several pharmaceutical tests in order to ensure their safety and compliance with the specifications of the US Pharmacopoeia of 2014 [11], these tests included Uniformity of weight, solubility, hardness test, brittleness test.

Through Figure (1) and Table (3), the percentage of metformin tablets weights present in the local market of Misurata city ranges between +5 to -6.5%, the highest percentage was for brand A, where it was +5% to +2.4%, and the lowest percentage for brand D -6.5% to -4%.

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Table (3): The weights of metformin tablets for the four brands

TAB	Brand A%	Brand B%	Brand C%	Brand D %
1	+5	1.4 -	+2.6	5.5-
2	+4.3	1.7-	+3.3	4.8-
3	+4.4	0.8-	+3	6.5-
4	+2.4	0.8-	+3.3	4-
5	+2.4	1.6-	+2.5	5.8-

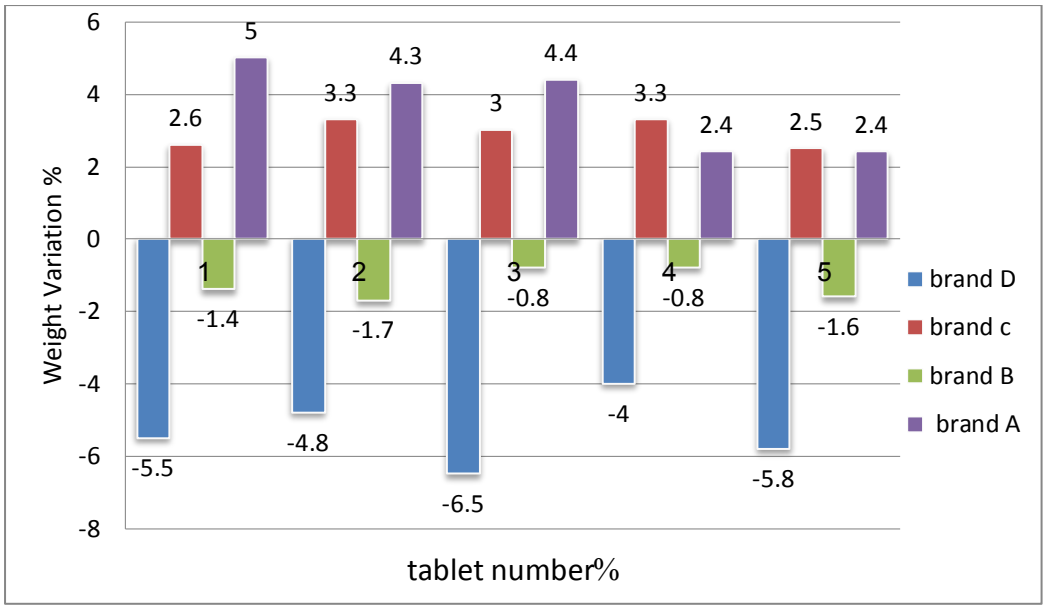

Figure (1): The average weights of metformin tablets for the brands used in this test.

We note that the weights of metformin tablets available in the local market (brands A - B - C) were within the limits of the Pharmacopoeia, as it was stated in the constitution that the official limit for the weights of the solid oral tablets coated with a thin film is equal to ±5% of the average deviation of the total weight of the tablets used, which is (561mg), and the results of this test are similar to the results of the study conducted in the West Indies (Trinidad and Tobago) for the year 2016 with the difference in the resulting weights as shown in Table (4), so the brand D differed from the limits stipulated in the

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Pharmacopoeia, This difference in weight may be due to differences in packaging materials as well as storage conditions and production and expiry dates [3].

Table (4): Weights of metformin tablets in the West Indies (Trinidad and Tobago) for the year 2016.

TAB	Brand A	Brand B	Brand C	Brand D
1	+0.03	+1.1	3.4 -	+1.5
2	1.5-	1.3-	0.1 -	1.9 -
3	+0.8	0.8-	+3.2	+0.1
4	+0.01	1.4-	0.7 -	+0.2
5	+0.1	+0.6	+2.5	+0.1

According to Table (5) and Figure (2), the fragility rate of metformin tablets used in this test ranged between (0.03-0.41%), brand D recorded the largest fragility rate estimated at (0.41%), while brand B had the lowest percentage. It is estimated at (0.03%), while brand A and brand C had medium fragility rates.

Table (5): The resulting values of fragility test for the four companies of metformin hydrochloride tablets.

TAB	Brand A	Brand B	Brand C	Brand D
Friability test	%0.30	%0.03	%0.10	%0.41

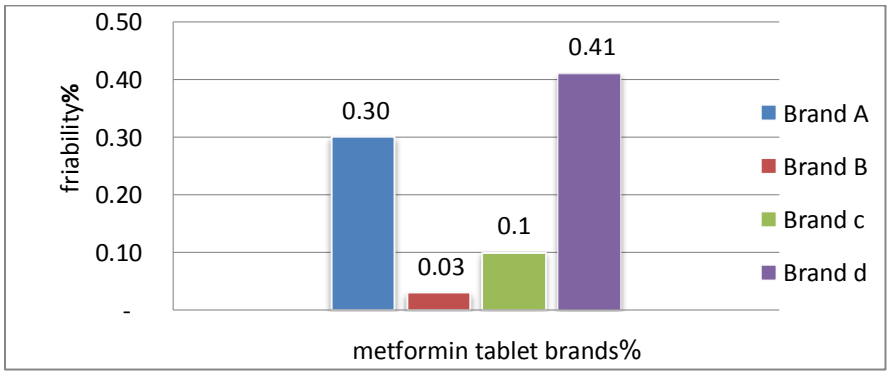

Figure (2): The percentage of fragility of metformin tablets.

When comparing these results with the results of the study conducted in the West Indies (Trinidad and Tobago) [13] as shown in Table (6) and the results of the study conducted in the State of Nigeria [16] as shown in Table (7), we find that they are all within the allowable limit in the US Pharmacopoeia of 2014 and it is less than 1% for film-coated oral tablets [11], with different values resulting due to the difference in environmental factors.

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Table (6): The values obtained for the fragility test of the four companies of metformin hydrochloride tablets in the West Indies (Trinidad and Tobago).

TAB	Brand A	Brand B	Brand C	Brand D
Friability test	%0.30	%0.02	%0.03	%0.41

Table (7): shows the resulting fragility test values for the four metformin hydrochloride tablet companies in Nigeria.

TAB	Brand A	Brand B	Brand C	Brand D
Friability test	%0.40	%0.44	%0.01	%0.40

Through the results obtained for this test in Table (8) and Figure (3): we notice the fluctuation of the resulting values in the studied samples between 8-13 minutes approximately, where the longest melting time was in favor of brand A with a time of (12.625) minutes, and the shortest melting time was in favor of Brand D with a time (8.842).

Table (8): The average dissolution time of the four companies for metformin hydrochloride tablets.

TAB	Brand A	Brand B	Brand C	Brand D
Time in minutes	12.625	9.342	12.432	8.842

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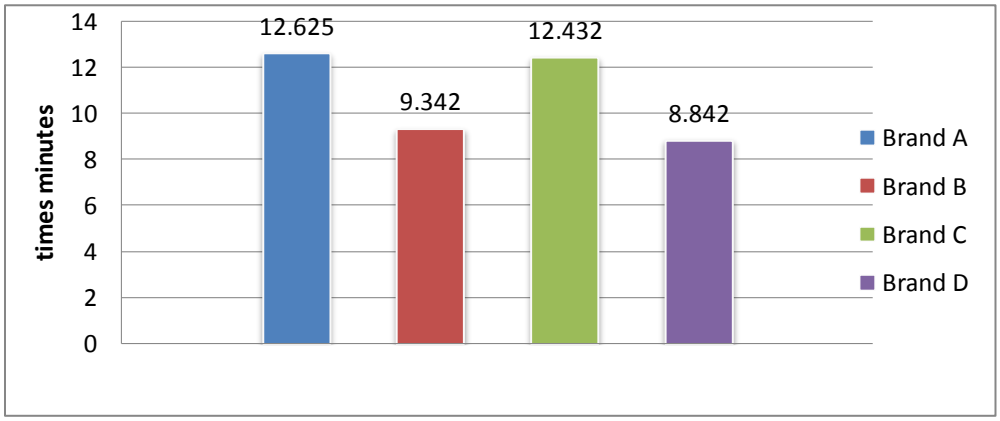

Figure (3): The average dissolution time of the four companies of metformin hydrochloride tablets

Whereas, brand D had the lowest solubility time, and therefore its effect inside the body is faster than other brands, followed by brand B with an average solubility time of 9.34 minutes, while brand A recorded the highest solubility time estimated at 12.62 minutes, which makes its effect inside the body less rapid than other brands.

The Table (9) and Figure (4): the percentage of hardness for the studied samples ranged between 10-18%, so the highest percentage was brand A, where the hardness of the tablet was 18.31%, and the hardness results showed that brand B and C had a good hardness ratio; Brand D had the lowest hardness percentage of 10.54%.

Table (9): The results obtained for the hardness test of the four companies of metformin hydrochloride tablets

TAB	Brand A%	Brand B%	Brand C%	Brand D%
Hardness Test	18.316	12.02	15.86	10.54

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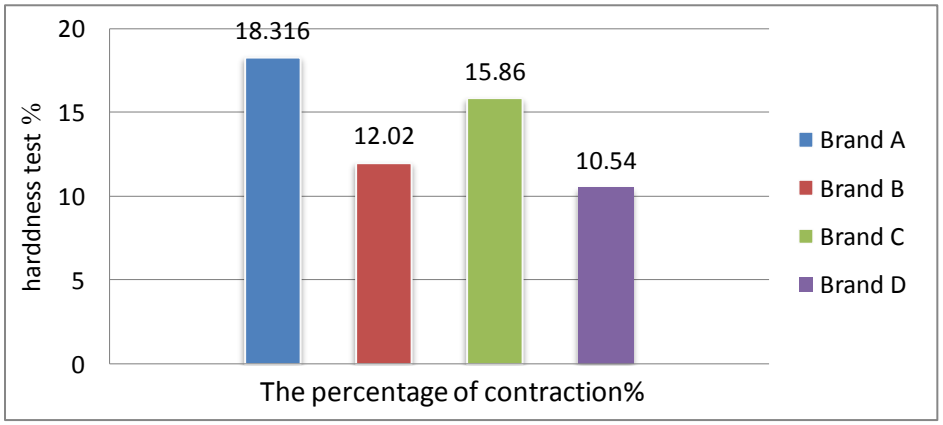

Figure (4): The percentage of hardness test for the four brands of metformin hydrochloride tablets.

The brand A had the highest percentage of hardness, and therefore this brand possesses tablets of good strength, while the brand B and C were medium percentage marks, and when comparing the results of this test with the specifications of the American Pharmacopoeia of 2014 [11], we find that they are within the permissible limits, Where the specifications require that the hardness percentage not exceed 20% for the film-coated discs, and the results of this test agreed with the study conducted in Nigeria for the year 2012 [16] as shown in Table (9), with the difference in the resulting values due to the difference in some physical factors such as date of production and humidity.

Table (9): The results obtained for the hardness test of the four companies of metformin hydrochloride tablets in Nigeria.

TAB	Brand A	Brand B	Brand C	Brand D
Hardness Test	%10.55	%18.74	%8.38	%13.83

Conclusion:

The obtained results showed that some of the metformin hydrochloride tablets located in the Misurata city conform to the standards of the American Pharmacopoeia of 2014, and therefore are of good quality and are able to withstand transportation and movement, while some brands differ from the standards stipulated in the Pharmacopoeia, and the reason may be due to the coating materials.

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