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Research Article

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Impact of the Libyan Conflict on Quality of Medicines Available in the Local Market

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ABSTRACT

Libyan health authorities have no longer effectively controlled their strategy since the beginning of the Libyan armed uprising in 2011. This lack of planning has led to the illegal trafficking of counterfeit medicines, food, etc., into the country without being subjected to the authority control. This work aims to study the effect of the Libyan post-conflict on the quality of medicines marketed in Libya. Two commonly used medicines for the management of hypertension were picked up from the Libyan market, and studied to assess their quality attributes. Various brands of atenolol, a β-blocker, and furosemide, a diuretic, were studied for their physical and chemical properties according to British Pharmacopoeia 2015. The results of this study showed that all the tested products from the Libyan market were conformed to standards. This indicates that the Libyan pharmaceutical market for drugs imported through authorized distributors has not been affected by the instability conditions in Libya since the conflict being started.

Keywords: Atenolol; Furosemide; Quality control; Libyan conflict; Counterfeit; Illegal drugs

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INTRODUCTION

Wars and conflicts are always having a negative impact on health sector, particularly medicine supply chain, hospitals and primary health care centers. Such services have an impact on the quality and safety of medicines and directly influence the life of habitants, in addition to other basic services, such as education, electricity, water and sewage [1]. The Libyan conflict of 2011 has had different impacts on the health services. Medicine importing, storage, distribution, and availability have all been badly affected during and after the armed uprising of 2011. The Libyan civil conflict following the 2011 uprising has influenced the quality of health in country that in many aspects, has led to a loss of full control over frontiers, and other different gates of importing various products to the country without being subjected to inspection and control by the Libyan pharmaceutical authorities.

In 2015, The World Health Organization (WHO) reported that the country public sector services particularly, health services that were already weak and suffering from several deficiencies, have not properly recovered [2]. Moreover, the WHO stated that there were severe shortages of essential drugs, particularly medicines for chronic diseases such as hypertension and diabetes. This is attributed to the lack of security or interruptions to supplies and deliveries.

Libya has also suffered from the loss of electricity for long periods, which last for up to 15 hours per day. Many pharmacies, drug warehouses, hospitals and clinics do not have generators or fuel for generators, which led to improper storage conditions, particularly in summer where temperature and humidity are quite high.

Libya relies entirely on imports in supplying its pharmaceutical needs. The National Centre for Food and Drug Control is devoted to handle and release pharmaceutical consignments. The center also is suffering in different aspects such as instability, improper management, conflict of interest, lack of trained and skilled personnel, both before and after uprising time. It also lacks essential resources to ensure the quality of imported medicines. As well as other resons related to pharmaceutical authority that have not registered drug items since long time ago.

The increase in consumption of generic drugs in the last decades has an effect on the quality of these drugs.

Drugs for chronic diseases have been target for counterfeiting in developing countries. For instance, a study reported 30%-100% of chronic drug samples failed pharmacopeial tests [3,4]. Since the cardiovascular diseases (CVDs) in general and hypertension in particular are among the leading causes of death worldwide [5]. Hypertensive patients are at a high risk to develop many cardiovascular events such as myocardial infarction, stroke, heart failure, renal failure, and sudden death [6]. However, these complications can be minimized if a proper therapy of hypertension is guaranteed, managed and controlled [7]. Therefore, two cardiovascular drugs were selected to test their quality in order to study the effect of post-war conflicts on the quality of medicines marketed in Libya. Different brands of atenolol and furosemide tablets were studied. These drugs are among the most commonly clinically used medicines for the management of hypertension, and have frequently been employed as first line drugs in control of hypertension [8]. They are also classified by the WHO among the essential drugs [9].

MATERIALS AND METHODS

Materials

All chemicals used in this work were of analytical grade. Methanol was purchased from Merck (Germany). Sodium hydroxide was purchased from Honeywell Riedel-de Haën (Germany). All solutions prepared by using ultrapure MilliQ-water Millipore (USA) and filtered with a 0.2 µm membrane filter syringe from Whatman (Germany). Different brands of atenolol tablets denoted OA for original atenolol brand, and GA1, GA2, GA3, and GA4 for generic atenolol drugs. For furosemide tablets, the drugs denoted OF for original furosemide brand and GF1, GF2, and GF3 for generic furosemide drugs. All the drugs were procured from local pharmacies in Tripoli. Absorbance was measured using UV/Visible spectrophotometer, Varian Cary 1E (USA). The Friabilitor and disintegration test apparatus were from Erweka (Germany).

Methods

All the tests carried out in this study were according to British Pharmacopoeia (BP) 2015 [10]. The analysis of all the drugs involved both physical and chemical quality control. Physical testing included friability, disintegration and uniformity of weight. Chemical testing involved identification and assay of active ingredient.

Friability

Twenty tablets were from each brands were weighed (w1) and put in the friabilator that was adjusted at 25 rpm for 4 min. Then tablets were re-weighed after cleaning them from broken pieces (w2). To determine the percentage of

friability (% F), the following formula was used (%F=[(w1−w2)/w1] x 100). To pass the test, the drug must have % F ≤ 1% [10].

Disintegration

Six tablets were individually placed inside the basket of disintegration test apparatus; the media temperature were maintained at 37ºC±2ºC. If there is no cracking of coat, continue the test by replacing the medium with 0.1M hydrochloric acid. The test needs to be run for 15 min [10].

Uniformity of Weight

Twenty tablets were weighed individually using digital analytical balance, and the average weight was calculated to determine the percentage deviation of each individual tablet from the average. The tablet passes the test if no more than two tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit, which is 10% for tablets contain 80 mg or less of active ingredients [10].

Identification

The assay identification tests were carried out to confirm the presence of active ingredients.

Identification of atenolol

The light absorption in the range 230 to 350 nm of the solution obtained in the assay exhibits maxima at 275 nm and 282 nm [10].

Identification of furosemide

The light absorption in the range 220 to 320 nm of the final solution obtained in the assay exhibits two maxima, at 228 nm and 271 nm.

Assay

The assay tests were carried out to determine the percentage content of the active ingredients.

Assay of atenolol tablets

Powder 20 tablets. Transfer the powder to a 500 mL flask using 300 mL of methanol, heat the resulting suspension to 60° and shake for 15 minutes. Cool, dilute to 500 mL with methanol, filter through a fine glass micro-fiber filter paper (Whatman GF/C is suitable) and dilute a suitable volume of the filtrate with sufficient methanol to produce a solution containing 0.01% w/v of Atenolol. Measure the absorbance of the resulting solution at the maximum at 275 nm. Calculate the content of $C_{14}H_{22}N_2O_3$ taking 53.7 as the value of A (1%, 1 cm) at the maximum at 275 nm [10].

Assay of furosemide tablets

Twenty tablets from each brand were weighed and crushed uniformly with the help of a mortar and pestle. 300 mL of 0.1M of sodium hydroxide was added to a powder containing 0.2 g of furosemide with shaking for 10 minutes. The solution was diluted with wit 0.1M of sodium hydroxide to 500 mL and filtrate. 5 mL of the filtrate was diluted to 250 mL wit 0.1M of sodium hydroxide. The absorbance of the final solution measured at 271nm. The percentage of content was calculated for each brand on the basis of absorbance of 580 for a 1% furosemide solution [10].

RESULTS

Atenolol Results

The quality assessment results for different atenolol tablet products are given in Tables 1-3. All the products met the pharmacopeial standards [10]. The maximum percentage of friability was accounted for OA with 0.215%, while GA1 had the lowest percentage of friability of 0.022%. The average disintegration time for all the products was below 2 min, where OA had the lowest time; however, GA3 has the highest time. All products have showed uniformity in weight according to the BP 2015 Tests. The average weight per tablet was within the pharmacopeial limits. GA1 had the highest average weight per tablet, whereas GA4 had the lowest average weight per tablet. Based on the results of one-way ANOVA analysis that was carried out using Excel, no significant difference ($p < 0.005$) in all of the physical tests among the different atenolol tablet products (Table 1).

Table 1. Results of friability test for different atenolol tablet products

Product	Weight of 20 tablets (g) (before test)	Weight of 20 tablets (g) (after test)	Differences in weight (g)	% Friability (% of weight loss)	No. of tablets with % friability of ≥ 1%
OA	4.182	4.173	0.009	0.215	None
GA1	4.481	4.480	0.001	0.022	None
GA2	4.235	4.234	0.001	0.024	None
GA3	4.091	4.087	0.004	0.098	None
GA4	4.055	4.054	0.001	0.025	None

Table 2. Results of disintegration test for different atenolol tablet products

Product	Average disintegration time (min)	No. of tablets with disintegration time > 30 min
OA	1.079 ± 0.473	None
GA1	1.278 ± 0.960	None
GA2	1.611 ± 0.365	None
GA3	1.978 ± 0.684	None
GA4	1.917 ± 0.386	None

Table 3. Results of uniformity of weight test for different atenolol tablet products

Product	Weight of 20 tablets (g)	Average weight/tablet (g)	No. of tablets with weight variation of ≥ 10%
OA	4.182	0.209 ± 0.002	None
GA1	4.481	0.224 ± 0.003	None
GA2	4.235	0.212 ± 0.002	None
GA3	4.091	0.205 ± 0.002	None
GA4	4.055	0.203 ± 0.002	None

For identification test, the light absorption in the range 230 to 350 nm of all products exhibited two maxima which were at 275 nm and 282 nm, that confirms the identity of atenolol in all the tablets. The average percentage contents of atenolol per tablet in each product are shown in Table 4. All the products met the BP 2015 requirements where the percentage content must be between 92.5% and 107.5%. ANOVA analysis showed no significant difference in the percentage content results among the different atenolol tablet products (Tables 2-4).

Table 4. Average percentage content of atenolol for different atenolol tablet products

Product	Reported % Content	% Content range
OA	106.9 ± 0.4	106.5-107.3
GA1	101.5 ± 0.5	101.0-102.0
GA2	103.2 ± 0.0	103.2
GA3	105.9 ± 1.1	104.8-107.0
GA4	105.1 ± 0.3	105.1-105.4

Furosemide Results

The quality assessment results for the different furosemide tablet products tested are given in Tables 5-7. All products met the pharmacopeial standards [10].

The maximum percentage of friability was accounted for GF2 with 0.29%, while OF had the lowest percentage of friability of 0.088%. The average disintegration time for all tested products was below 3 min, where OF had the highest disintegration time; however GF2 has the lowest time. All tested products showed uniformity in weight. The average weight per tablet was within the pharmacopeial limits [10]. GF3 had the highest average weight per tablet, whereas GF1 had the lowest average weight per tablet. Based on the results of one-way ANOVA analysis that was carried out using Excel, no significant difference ($p < 0.005$) in all of the physical tests among the different furosemide tablet products.

For the identification test, the light absorption in the range 220 to 320 nm of all products exhibited two maxima at 228 nm and 271 nm, which confirms the identity of furosemide in all tested tablets. The average percentage contents of furosemide per tablet in each product are shown in Table 8. All tested products met the BP 2015 requirements where the percentage content must be between 92.5% and 107.5%. ANOVA analysis showed no significant difference in all of the percentage content results among the different furosemide tablets.

Table 5. Results of friability test for different furosemide tablet products

Product	Weight of 20 tablets (g) (before test)	Weight of 20 tablets (g) (after test)	Differences in weight (g)	% Friability (% of weight loss)	No. of tablets with % friability of ≥ 1%
OF	3.1738 g	3.1710 g	0.0028 g	0.088%	None
GF1	3.1855 g	3.1770 g	0.0085	0.27%	None
GF2	3.2019 g	3.1927 g	0.0092 g	0.29%	None
GF3	3.3038 g	3.2971 g	0.0067 g	0.20%	None

Table 6. Results of disintegration test for different furosemide tablet products

Product	Average disintegration time (min)	No. of tablets with disintegration time > 30 min
OF	2.321 ± 0.427	None
GF1	1.389 ± 1.136	None
GF2	0.417 ± 0.097	None
GF3	0.578 ± 0.242	None

Table 7. Results of uniformity of weight test for different furosemide tablet products

Product	Weight of 20 tablets (g)	Average weight/tablet (g)	No. of tablets with weight variation of ≥ 10%
OF	3.177	0.159 ± 0.002	None
GF1	3.169	0.158 ± 0.004	None
GF2	3.188	0.159 ± 0.001	None
GF3	3.291	0.165 ± 0.002	None

Table 8. Average percentage content of furosemide for different furosemide tablet products

Product	Reported % Content	% Content range
OF	97.9 ± 0.1	97.8-98.0
GF1	96.2 ± 0.2	96.0-96.4
GF2	97.8 ± 0.0	97.8
GF3	97.5 ± 0.3	97.2-97.8

DISCUSSION

Product GA1 showed more weight variations, whereas GA4 had the least variations in weight compared to other atenolol tablet products. Since none of the studied atenolol brands deviated from the mean weight by more than 7.5%. The results of the weight uniformity are satisfactory. The significance of this test is to indicate that all tested tablets of each batch are within the appropriate weight range [10]. The disintegration test measures the time needed for the tablets to disintegrate into small particles [10].

All examined atenolol tablets of different brands passed the BP 2015 disintegration test and totally disintegrated in less than 30 minutes, whereas GA1 has the lowest disintegration time. In friability test, GA1 has less percentage in friability, which is 0.02%, while OA has the highest percentage compared to all brands, which is 0.23%. The compendia standards stipulate that the loss in the tablet weight should not exceed 1% of the original tablet's weight after applying the friability test. The results showed that all the tested products of atenolol passed this test by having the values of friability almost close to 0%. According to the official standards of the BP 2015, the percentage of content for atenolol should lie within 92.5–107.5% of the labeled amount. All tested products gave values within the indicated range where they are assumed satisfactory. The significance of this test is to ensure that all the tablets will deliver the same amount of the drug in the body, and hence, producing similar and reproducible bioavailability [10].

For furosemide tablets, OF had the lowest percentage of friability which is 0.088%. GF2, on the other hand, has the highest % friability compared to all brands which is 0.29%.

GF3 showed more weight variation than the other brands, whereas GF2 had the least variation in weight compared to other brands. All tested products gave percentage of content values within the indicated range where they are satisfactory [10].

The results of this study indicate that the Libyan pharmaceutical market for drugs that are imported through authorized distributors has not been affected by the instability conditions in Libya, since the uprising of 2011. This conforms to previous reports which indicated the all the legally imported drugs in Libya met the specifications [11,12].

CONCLUSION

The results of this study showed that all tested products collected from the Libyan market are conformed to BP 2015 monographs. Future studies are recommended to focus on drugs that are illegally imported and marketed which are suspected that have not been tested or controlled by the National Centre for Food and Drug Control.

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CONFLICT OF INTEREST

Authors do not have personal and/or financial conflict of interest.

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