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Post-marketing quality assessment of paracetamol brands in the Libyan market

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Abstract: Paracetamol is one of the most found over-the-counter drugs worldwide. It is widely used as an analgesic and antipyretic drug. Many commercial types of paracetamol tablets are available under different brand names in the Libyan drug market. The present study was conducted to evaluate post-marketing quality parameters for three brands of paracetamol tablets marketed in Libya. All three brands were evaluated for weight variation, hardness, friability, disintegration time and uniformity of content following British pharmacopeia guidelines. The outcomes of this study showed all tested brands complied with the British pharmacopeia specifications for the weight variation test, friability test (0.05%-0.17%), and hardness test (171.3N-197.6 N). In addition, two brands passed the British pharmacopeia requirements for the disintegration time test, whereas one brand exceeded the allowed disintegration time by about five minutes. Furthermore, High-performance liquid chromatography was used to determine paracetamol content. Although the average amount of paracetamol drug available in these brands is not very close to 100%, where one brand achieved the lowest value (438.1 mg), the loaded dose of paracetamol in selected tablets in the three brands was within the British pharmacopeia standard specifications for the uniformity content test. Therefore, it can be concluded that almost all the three tested brands of paracetamol tablets that are available in the Libyan drug market meet the British pharmacopeia specification for quality control analysis.

Introduction

The safety, efficacy and bioavailability of drug products are directly depending on the drug quality. The quality control system for drug production includes starting materials quality control, in-process quality control and finished final drug product quality control as well as, post-marketing quality control assessments. Lack of adequate quality control measures may occasion potential toxicity or treatment failure and drug resistance [1, 2]. The introduction of generic drug products is expected to improve the overall healthcare system, and the World Health Organization (WHO) has continuously recommended the use of generic brands [3]. However, this has been associated with many problems due to the widespread distribution of fake and substandard drug products that are a major cause of morbidity, mortality, and diminished public confidence in drugs and health structures [3, 4]. According to WHO, more than a quarter number of drug products on sale for consumption have been reported as counterfeit products [5]. In Tanzania, 12.0% of marketed antimalarial drug products are reported as of main cause of the failure in the treatment of malaria disease [6]. Hence, post-market evaluations

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can be used to judge the approved drug products for their safety, efficacy and quality. Fake drugs are becoming a big public health problem as either they lose adequate efficacy or they have toxicity [7, 8]. The prevalence of fake drugs is higher in countries with weak regulations, enforcement, and insufficiency of supply of basic drugs, also, unregulated drug markets and unreasonable drug prices [9]. Paracetamol is a widely used analgesic and antipyretic drug all over the world. Long-term application and/or overdoses of paracetamol may cause potentially fatal liver damage and/or renal functioning disorder [10]. Successful therapeutic efficiency of oral solid dosage forms, including tablets, depends mainly on the quality of a series of parameters, such as weight variation, hardness, friability, disintegration time, and dissolution rate, which are affected by drug properties, manufacturing methods and utilized excipients. Paracetamol tablet products of different manufacturers and/or sources are expected to measure varying quality parameters, however, within permitted limits to be considered successful products. The quality of pharmaceutical dosage forms has become a global concern, recently, as counterfeit drugs are increasingly detected, and this concern has led to the necessity to evaluate the drug dosage forms available in the market. This evaluation process is known as post-marketing quality control studies [11]. To date, several post-marketing *in vitro* quality control studies have been conducted to evaluate the physiochemical properties of solid dosage forms [12, 13]. Islam et al. [14] analyzed four brands of paracetamol tablets by different physicochemical quality control parameters. All the brand samples passed the weight variation, hardiness, friability, and disintegration rate tests and they satisfy the specification limits. However, one brand sample fails the dissolution test, as well as, another brand sample fails the uniformity drug content test. The results show that most of the brand samples satisfy the specifications for all quality control parameters with low standard deviations. Alsaifi and Alyahawi [15] evaluated the quality of four brands of paracetamol tablets marketed in the Yemeni market. The findings showed all brands of paracetamol comply with British Pharmacopeia/United States Pharmacopeia (BP/USP) specifications for *in vitro* quality control tests, except the hardness test, which is referred to as a non-official test. The study concluded that the overall quality of all tested brands of paracetamol was acceptable. Furthermore, Sahle and others [16] conducted an exclusively experimental study that used BP/USP to evaluate the *in vitro* quality of paracetamol marketed in the Somali region of Ethiopia. The outcomes showed all of the brands were within the specification for the weight variation test. Nevertheless, from the illegal import brands, two for friability, one for disintegration and all for a percentage of drug content failed to satisfy the standards. The study has concluded that the quality of illegal paracetamol was below the standard in contrast to that legal paracetamol. There are some post-marketing quality control studies of paracetamol tablets that have been conducted in Libya. Khreit and others [17] tested ten brands of paracetamol that conformed to the USP/BP specifications. All the brands had shown their weight variation, hardness and friability measures satisfied with the range specified by USP/BP limitations, in despite some apparent minor differences among them. The paracetamol content test, which was carried out using HPLC showed seven brands complied with the specification of BP within the range of 90%-110% stated content. Three brands failed the content of the active ingredient test and did not comply with specifications. Rwaiha et al. [18] carried out post-marketing *in-vitro* studies for five brands of paracetamol marketed in Libya. Excluding one brand which was failed the friability test by 20.0% deviations more than the desired limit (1.0%), the study exhibited almost all of the selected brands of paracetamol assessed met the BP specifications for quality control analysis. This study aimed to evaluate the legally registered paracetamol tablets in the Libyan market. These brands were selected based on the differences in their manufacturing sources, their fast distribution and acceptability by the consumers, as well as, their significant price differences.

Materials and methods

This study focused on evaluating various quality control parameters for three brands of paracetamol that are the most available products in government and private pharmacies. These quality control parameters include

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weight uniformity, hardness, friability, disintegration time and active ingredient content. Paracetamol 500 mg tablets of legally registered brands namely A, B, and C, were selected and coded, respectively. Paracetamol reference standard powder was obtained from Sigma Aldrich. Electronic analytical balance (ADAM AFP 110 L, India), tablet friability tester (ERWEKA GmbH, Germany), TBH 125 tablet hardness tester (ERWEKA GmbH, Germany), disintegration tester ZT 220 Series, (ERWEKA GmbH, Germany) and HPLC 1260 Infinity Binary LC instrument (Agilent Technologies, Germany) were used to measure general and specific tests for quality of paracetamol tablets in compliance with British pharmacopeia (BP) specifications.

Weight variation test: For each brand, 20 tablets were selected at random, de-dusted and weighed individually using the electronic analytical balance. The average weight and deviations from that mean weight were calculated.

Friability test: This test was carried out by selecting 20 tablets randomly from each brand, de-dusted and weighed using the electronic analytical balance. Then, these tablets were placed in the drum of the friability tester and then operated at 25 rpm for four minutes (100 times rotation). Finally, the tablets were de-dusted and re-weighed. The difference in the two weights was used to calculate the friability value that was expressed in percentage.

Hardness test: 10 tablets were selected at random to carry out this test. Each tablet was placed vertically on the TBH hardness tester. The load was then applied along the radial axis of the measuring tablet. The load or weight required for breaking the tablet was recorded. It was also done for all the selected brands of paracetamol tablets.

Disintegration time test: A disintegration tester ZT 220 Series was used to determine the required time for the tablet to disintegrate. The beaker of the disintegration tester was filled with 900 ml of deionized water at 37.0 ± 2.0^{0}C. Afterward, 6 tablets were placed into the basket rack assembly and connected to the disintegration device. Finally, the disintegration time was recorded for the tablets.

Uniformity of content test: This test is based on the assay of the individual contents of the active ingredients of several single-dose units. This assay was performed in compliance with BP to assess the percentage content of paracetamol using the HPLC method. A standard stock solution of paracetamol (250 mg/L) was prepared using the mobile phase. A series of working standard solutions in a range of (10-100 mg/L) were prepared by dilution from the stock solution. Three sample solutions for the selected brands of paracetamol were prepared as well. The HPLC experimental measurement procedure was conducted under the specific conditions given in **Table 1**. A 10 µl aliquot of each solution was injected into the column in three replicates and the chromatograms were recorded. Thereafter, a calibration curve was constructed by plotting the mean peak area versus the concentration of paracetamol. The unknown concentration for the three paracetamol brands was calculated from the regression equation derived from the calibration graph.

Table 1: The HPLC experimental conditions

Parameter	Specific condition
Column	Zorbax C18 (4.6x150 mm), 5.0 µm
Wavelength	243 nm
Mobile phase	Methanol: water (40:60)
Injection volume	20 µL
Flow rate	1.0 mL/min
Temperature	Ambient

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Results

In this study, standard methods and procedures following the BP were used to conduct each test. Thus, a total of three paracetamol brands legally registered and marketed in the Libyan drug market were assessed for weight variation, friability, hardness, disintegration time and content uniformity. All of the brands of paracetamol investigated were within their shelf lives and immediate-release dosage forms with a label strength of 500 mg. The results of the weight variation test for all the brands revealed values that complied with BP specifications as none of the brands deviated by up to ±5.0% from the mean value as shown in **Table 2**. On the other hand, **Table 3** describes the results of hardness and friability tests. All the brands passed the non-official hardness test according to BP, as none of the obtained values exceeds 400 N. The friability test revealed values that complied with BP friability specifications as the percent friability for all assessed paracetamol tablets was less than 1.0%. This indicated that all the tablets of each brand were mechanically stable. Furthermore, the results of this study showed that all the brands have passed the disintegration time test according to BP, except brand B which has left core mass after 15 min of treatment within the disintegration apparatus, and it showed a disintegration time value of 19.5 min (**Table 3**).

In **Figure 1**, The HPLC method for quantitative analysis of paracetamol content in all brands has been used. The HPLC assay for paracetamol content analysis showed a well-defined chromatographic separation within a run time of six min. It exhibited a retention time of paracetamol at 2.62 min ±0.04 % (RSD), as well as, a standard paracetamol linear calibration curve with a linearity relationship in the range of 10-100 mg/L, a regression equation is Y=84.943X and a correlation coefficient (r) of 0. 999. The outcomes of the uniformity of drug content tests showed all the assessed paracetamol brands complied with the BP standard specifications for the uniformity content test as displayed in **Table 4**.

Table 2: Weight variation tests of different paracetamol brands

Brand code	Average weight in mg, n=20	Permissible weight variation range (mg) based on BP (±5%)	Real measured weight variation range (mg)	Percentage of deviation range
A	676.99	710.84-643.14	687.10-664.50	(1.49%) - (-1.85%)
B	643.59	675.76-611.42	664.20-626.90	(3.20%) - (-2.59%)
C	602.28	632.39-572.16	625.52-585.22	(3.85%) - (-2.83%)

Table 3: Hardness and friability tests of different paracetamol brands

Brand code	Hardness tests (Newton) n=10	*Friability tests*		
		Weight before The test (g) n=10	Weight after the The test (g) n=10	Percentage of Weight loss
A	171.3	6.7566	7.4480	0.17%
B	197.6	6.4892	6.4856	0.05%
C	194.5	6.0277	6.0184	0.15%

Table 4: Disintegration time and uniformity of drug content tests of different paracetamol brands

Brand code	Disintegration Time (min)	*Uniformity of drug content*		
		Branded paracetamol	Real measured paracetamol amount/tab (mg)	Percentage of drug content amount/tab (mg)
A	3.4	500	473.2	94.6%
B	19.5	500	450.9	90.1%
C	1.5	500	438.1	87.6%

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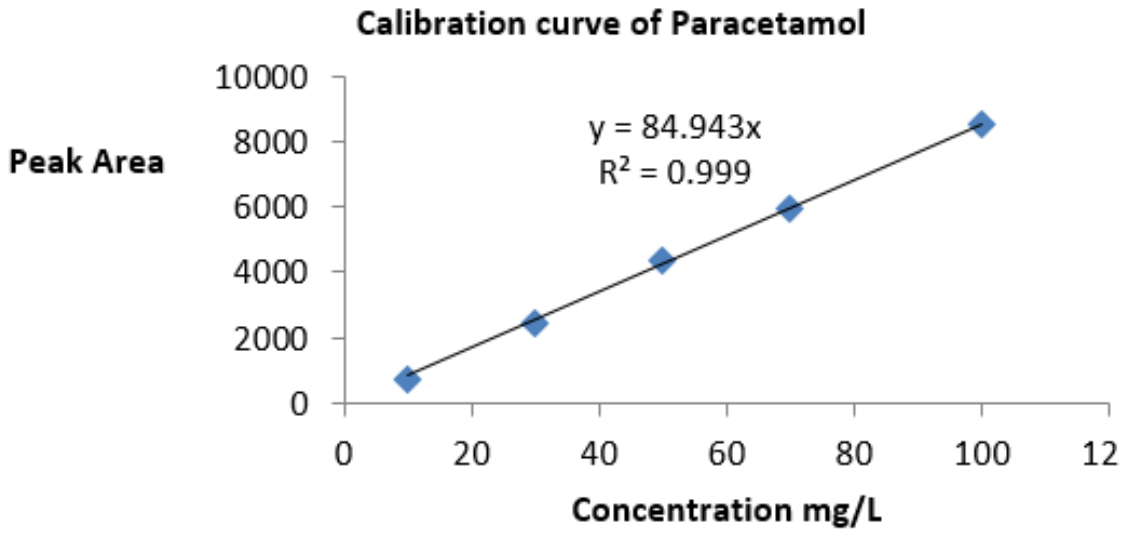

Figure 1: Calibration curve of paracetamol standard obtained using HPLC

Discussion

All the brands of paracetamol tablets investigated in the present study were within their shelf lives and immediate release dosage forms with label strength of 500 mg. The different quality parameters of different brands of paracetamol were evaluated. The physical appearance of the various examined brands of paracetamol tablets was satisfied with BP specifications. Tablet weight is mainly affected during the compression process by factors such as machine speed, head pressure, and the tablet powder or granulate density and particle size distribution. Therefore, uniformity of weight is an in-process test parameter which used to show the content uniformity of drugs. In this study, all of the examined brands of paracetamol tablets did not deviate more than 5.0% of their average and this complies with the BP specification for the weight uniformity test. In addition, the friability test is used to evaluate how well the tablets stand up to coating, packing, shipping and other processing. According to BP specification, no tablet should show any type of break or crack and the total weight loss should not be more than one percent. In this study, all the brands of paracetamol tablets complied with the specifications set by BP, and their percentage loss of mass was less than 1.0%. Moreover, sufficient tablet hardness is essential and conducted to assess the ability of tablets to withstand mechanically. Hardness test values were within the limit of less than 400 N. Furthermore, a disintegration time test is performed to estimate the time required to disintegrate the tablet in a gastric environment. According to BP specifications, conventional uncoated tablets were expected to disintegrate within 15 min. The findings show only two brands of paracetamol tablets complied with the disintegration time test, where one brand achieved the shortest time (1.5 min). While one brand exceeded the allowed disintegration time by about 5 minutes. Additionally, the current study displays the results of the test for the percentage of drug content which is based on the assay of the individual content of active ingredients of several single-dose units. BP specifies the brand passes the test if 9 of the 10 tablets contain not less than 85.0% and not more than 115.0% of the labelled drug content and the 10^{th} tablet may not contain less than 75.0% and more than 125.0% of the labelled content. Although the outcomes of this study of drug assay of three different brands of paracetamol showed that the average amount of paracetamol drug available in all these brands is not very close to 100%, where one brand achieved the lowest value (438.1 mg), the loaded dose of paracetamol in selected tablets in all three brands was within the BP standard specifications for the uniformity content test. Thus, the outcomes of this study were comparable to the results observed from the previous quality assessment studies of paracetamol tablets [17 and 18], and this proves the reliable results of the current study.

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Conclusion: Despite one brand that failed the disintegration time test and exceeded the allowed BP limit test by about 5 minutes, the overall quality evaluation results of the three brands of paracetamol assessed in the Libyan market were verified with BP quality requirements. The results obtained from the present study were similar to the outcomes observed from the previous quality assessment studies of paracetamol tablets. Thus, this supports that paracetamol brands in Libya showed reliable quality standards.

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Ethical issues: Including plagiarism, informed consent, data fabrication or falsification, and double publication or submission were completely observed by the authors.
Data availability statement: The raw data that support the findings of this article are available from the corresponding author upon reasonable request.

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