

Post-Marketing *In-vitro* Comparative Studies of Different Brands of Paracetamol Tablets Available in Misurata Market, Libya

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ABSTRACT

Post marketing *in-vitro* studying of products is an important to investigate quality of medicines at various intervals time during their shelf life. Paracetamol is a widely used analgesic and antipyretic drug worldwide. The selected five brands of Paracetamol tablets in Misurata market, Libya, were tested for various parameters of quality control tests. 120 tablets for each brand were required to achieve: Uniformity of drug content, weight variation, hardness, friability, disintegration time and dissolution. All brands showed acceptable friability values less than 1% except Aspar® Paracetamol tablets were represent extremely high value around twenty times more than standard level. Uniformity of drug content for all brands claimed that BP standards were values are matches the percentage of loaded drug in the tablets for all brands (around 100% ± 5). Moreover, the release rate of different brands of Paracetamol was satisfactory within 45 minutes, where the highest value was accomplished by Actavis® Paracetamol tablets. According to statistical analysis, there is a significant difference between all brands ($p < 0.05$) However, it can be concluded that almost all of the selected brands of paracetamol that are available in Misurata meet the BP specification for quality control analysis.

INTRODUCTION

Post-marketing Surveillance

Post-market surveillance is an important study for monitoring the safety of health products after being released to the market. It is a tool for tracing adverse reactions produced by Natural Health Products (NHPs), detecting significant causal relationship between a product and disease and informing others regarding product safety^[1]. The history of post-marketing Surveillance had been started in the 1960's, when two significant adverse drug reactions of two medicines were observed in many patients. Firstly, the thalidomide drug, was taken worldwide, it causes a congenital deformity known Phocomelia. Secondly, the Clioquinol drug, it causes optic nerve damage (sub-acute myelo-optic-neuropathy) as adverse effect from the drug^[2]. To ensure quality, efficacy, safety and proper use of drugs, post-marketing surveillance established three systems: ADRs (Adverse Drug Reactions), infections collection and reporting system, reexamination system and reevaluation system. ADRs system are programs for collecting and reporting safety information on drugs such as adverse drug reactions include an adverse drug reaction reporting system undertaken by pharmaceutical companies, the drug and medical device safety information reporting system undertaken by medical personnel, and the WHO International Drug Monitoring Program whereby drug safety information is exchanged among various countries^[3]. The reexamination system is aimed at reconfirmation of the clinical usefulness of drugs by performing Good Post-Marketing Study Practice (GPSP) or Good Vigilance Practice (GVP) as one aspect of post-marketing surveillance (PMS), through collecting information on the efficacy and safety of the drug during a specified period of time after approval. The reevaluation of drugs is a system whereby the efficacy and safety of a drug, which has already been approved, is reconsidered on the basis of the current status of medical and pharmaceutical sciences. This step was intended to assure the quality of generic drugs by confirming their equivalence to the original products^[3]. Collection of information in post-market surveillance is achieved through: passive surveillance, active surveillance, controlled clinical trials and observational studies. Passive Surveillance: Some methods of passive surveillance involve spontaneous reporting or volunteer reporting and mandatory reporting. The most commonly method used for data collection and monitoring of adverse reactions is spontaneous reporting. The early detection of signals of adverse reactions is the main objective of spontaneous reporting^[4]. The active surveillance system

is “regular periodic collection of case reports, of drug events, from health care providers or facilities”^[5]. The main objectives of active surveillance involves collecting adverse reaction reports by focusing on events, settings, or products of benefit, recognize drug safety signal and confirm signals identified through passive surveillance^[6]. The controlled clinical trials are clarifying the mechanism of adverse reactions, examination of post-market safety issues and recognizing the means of prevention^[7]. These trails include treatment and controlled groups which are matched as closely as possible. Randomizations and double-blinding techniques are used for minimizing the biases. The controlled clinical trials are effective method for evaluating a drug's efficacy and safety but there are several rigorous involved with them and the expensive and non-feasibility of these trials^[4]. The observational studies are fewer limitations than clinical trials, but have the potential to determining a drug's beneficial and adverse effects from a sample of real-life patients for a long period of time^[8]. Nevertheless they are high cost, complex to maintain, and it uses still for careful design and analysis^[9].

Post-Marketing Re-evaluation

Post market qualitative and quantitative studies and reevaluations include activities accomplished to obtain more precise data of a product being marketed and available for community use. The facts (qualitative and quantitative) reached as a result of such post market evaluation could be used for product development and enhancements in product quality as per standards. Based on clinical trials and scientific literature, regulatory authorities will liberate market authorization for any product to be available for community use. Consequently, post market assessments and as a result obtained data could be comprehensively used to judge the approved products for their efficacy, quality and safety for end consumers. Therefore, post market qualitative and quantitative evaluations should be a constant activity during the product life cycle^[10]. Post market estimation of a product has been acknowledged to include: Evaluation and investigation of reported product complaints and procedure for manufacture and review of label claim; general public access to data taken and reported to drug regulatory authorities, and in vitro testing of product for complaints to official specifications^[11]. Not all the manufacturers are equally accepted to the consumers. In a general sense most of the consumers choose the popular brands of medicines and not really concerned about the potency and overall quality of the drugs. Nowadays, approximately 90% of drugs that have been intended to produce Systemic effect are administered via oral route. Thus, this fact widely very importance of tablets as a dosage forms. The main objective of an oral compressed tablet that it make available the drug to human body at accurate and defined quantity through gastro-intestinal tract (GIT) in order to gain a therapeutic consequences; accordingly the formulation of a product has a direct influence on the quality parameters: such as uniformity of drug content, disintegration, dissolution, weight variation, hardness and friability. Furthermore, the physiochemical properties of excipients and active pharmaceutical ingredients (API) are important and at the same time the processes of manufacturing. Therefore, in order to maintain a quality consistency in batch to batch production or brand to brand for same drug, quality control parameters are significant to be considered and should be performed for every product through its life cycle. One of the most common approved and available as over the counter drug is Paracetamol tablets with several brands. The therapeutic efficiency of a compressed tablet of Paracetamol relays on minimum of three elements, i.e., content uniformity (the actual label claim), percentage of drug release and its adequate bioavailability^[11]. Medicines that are pharmaceutically and chemically equivalent, and formulated in same dosage forms, for same route of administration must be identical in quality parameters. Hence, the selected five brands of Paracetamol tablets of multinational companies available in Misurata market, Libya, almost anticipated having same quality.

Drug Profile

Paracetamol is an over-the-counter (OTC) non-steroidal anti-inflammatory drug (NSAID) widely used as an analgesic and antipyretic agent worldwide, but it has weak anti-inflammatory effects since it has poor ability to inhibit Cyclooxygenase (COX) in the presence of high concentration of peroxides, as are found at sites of inflammation^[12]. The therapeutic dose of Paracetamol is 0.5-1 g in adult (maximum of 4 g/day) and 10-15 mg/Kg every 4-6 hours in children^[13]. It is available in a tablet, capsule, suspension or solution (liquid), drops, extended-release (Long acting) tablet, orally disintegrating tablet, suppository, intravenous, and intramuscular form^[14]. Paracetamol is generally safe and well tolerated for human use at recommended doses. It also has a low incidence of gastrointestinal side effects at therapeutic doses in contrast to the NSAIDs^[15]. Nonetheless, acute over dosage can cause severe hepatic damage and in rare individuals, a normal dose can do the same. However, the safety and efficacy of a pharmaceutical dosage form can be guaranteed when its quality is reliable. The efficacy of pharmaceutical dosage forms generally depends on their formulation properties, and manufacturing methods, hence it is likely that the quality of dosage form may vary^[16].

Physiochemical Properties

Paracetamol or acetaminophen chemically as shown in **Figure 1** is a 4-hydroxy acetanilide and an active metabolite of phenacetin, a so-called coal tar analgesic which is no longer used for medicinal purpose for its adverse effects. Paracetamol is a white, odorless crystalline powder with a bitter taste, soluble in 70 parts of water (1 in 20 boiling water), 7 parts of alcohol (95%), 13 parts of acetone, 40 parts of glycerol, 9 parts of propylene glycol, 50 parts of chloroform, or 10 parts of methyl alcohol. It is also soluble in solutions of alkali hydroxides. It is insoluble in benzene and ether. A saturated aqueous solution has a pH of about 6 and is stable (half-life over 20 years) but stability decreases in acid or alkaline conditions, the Paracetamol being slowly broken down into acetic acid and p-aminophenol^[17].

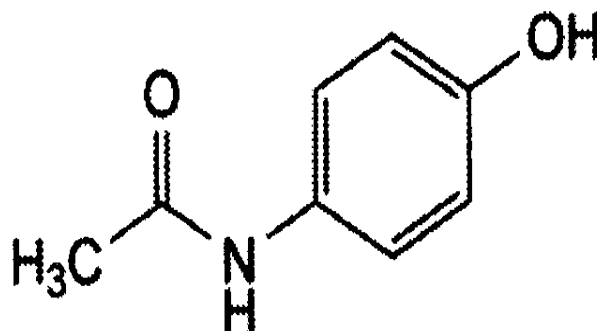


Figure 1. Acetaminophen.

Bioavailability Facts

Paracetamol is well absorbed from the gastrointestinal tract following oral administration and is not subject to significant first-pass metabolism in the liver, with oral bioavailability estimated at between 63–89% in adults^[18,19]. However, drug-food interaction tends to slow the rate of absorption of Paracetamol, while caffeine accelerates absorption. Prokinetic drugs (such as metoclopramide) accelerate gastric emptying, enhancing the rate of absorption, while drugs that decrease the rate of gastric emptying (e.g. morphine) slow absorption, and in some cases prevent attainment of therapeutic plasma levels. Rectal absorption of Paracetamol is slower and less predictable, with bioavailability between 24% and 98%. This variability depends on the size, physical composition and number of suppositories used, and on the rectal pH. Paracetamol is not significantly bound to plasma proteins, and has a volume of distribution of 0.7–1 l. Kg⁻¹. It is non-ionised at physiological pH and freely crosses the placenta and blood brain barrier^[15].

Drug Metabolism and Safety

Metabolism of Paracetamol occurs primarily in the liver, while elimination occurs almost entirely through the kidney. Following absorption of therapeutic doses, approximately 90% is metabolized by glucuronidation and sulphation to form non-toxic metabolites, which are excreted in the urine. A small fraction undergoes oxidation by the cytochrome P450 system to form the highly reactive metabolite N-acetyl-p-benzoquinoneimine (NAPQI). NAPQI reacts with glutathione, forming conjugates that are subsequently excreted in urine^[15]. Hepato-toxicity generally occurs when the glutathione stores fall to less than 30% of the normal^[13]. In case of overdose of Paracetamol, the amount of NAPQI formed is greater than the GSH available such that NAPQI is not conjugated and being an active product, it exerts hepato-toxic effects and also causes renal tubular necrosis by reacting with the nucleophilic aspects of the cells^[20]. Severe hepato-cellular damage and renal tubular necrosis can result from taking 150 mg/Kg (about 5-10 g) in a single dose^[24]. Paracetamol in the dose of 10-15 g can potentially lead to fatal hepato-toxicity^[20]. Clearance is lowest in neonates, with values rising through childhood. Elimination half-life is 2–4 h in normal adults, increasing to 4–5 h in newborns and to 11 h in premature infants. One to four percent is excreted unchanged in the urine, and an increased dose interval of 6–8 h is recommended in patients with severe renal impairment (GFR less than 10 ml. min⁻¹). Kidney is the second target organ of Paracetamol toxicity. It has been revealed that heavy use of Paracetamol (average amount of 300 grams per year or 1 g per day) leads to a condition known as 'Small Indented and Calcified Kidneys' (SICK)^[22]. Hence, renal impairment occurs after acute Paracetamol overdose. Furthermore, renal dysfunction may occur with significant hepatotoxicity or without hepatotoxicity. Renal impairment is more common after sustained repeated excessive dosing. However, there is a dose-dependent relationship between chronic use of Paracetamol and an enhanced risk of end-stage renal disease, as demonstrated by a case-control study involving 1,077 individuals. Injury to other organ such as pancreas is rarely reported^[23]. Additionally, Paracetamol interferes with DNA synthesis and promotes genotoxicity and carcinogenicity^[24].

AIM

The purpose of the study is to ensure the quality and safety of five brands of Paracetamol tablets available in Misurata market, Libya. Additionally, compare them with BP standard specifications and find if there is any significant difference between results.

METHODOLOGY

Five multinational brands of compressed tablets of Paracetamol were purchased and collected from drug store of the agents in Misurata city, Libya. In order to conduct different quality control tests, quantity consist of 120 tablets with same batch number and labelled to contain Paracetamol (500 mg per tablet) were randomly selected in each brand to achieve this study as shown in **Table 1**. Quality of brands were investigated by performance quality control tests (**Table 2**) and confirmed with British pharmacopoeia standards. The same procedure for each test was applied in each brand. The calibration curve was used to determine the concentration/content in all brands

Table 1. The required analysis tests used to evaluate quality of brands.

Type of Test	Key Information that the Test Provides
Weight variation test	Shows the average weight
Disintegration test	Shows the time taken by tablet to disintegrate
Friability test	Shows how much the tablet can withstand attrition
Uniformity of drug content	Studies the drug distribution
Dissolution test	To confirm rate of drug release
Hardness test	It depicts how much the tablet is prone to friability

Precision Test

Three samples of standard solutions representing highest, medium and lowest concentrations in calibration curve were analyzed six times each by using UV/Vis Spectrometer. Standard deviation and coefficient of variation of a series of measurements were calculated to determine variation of obtained results and confirm precision of UV/Vis Spectrometer^[25].

Preparation of Calibration Curve

To prepare standard calibration curve, pure paracetamol was used, where 0.15 g of it was weighed by using an analytical balance and transferred into 200ml volumetric flask. Firstly, 50 ml of 0.1M of sodium hydroxide was added and diluted with 100 ml of purified water and shook for 15 min to dissolve the paracetamol, then the volume was made up to 200 ml with purified water to obtain a stock solution. Calculated volumes of stock solution were pipetted into 100 ml volumetric flasks to prepare the following standard solutions 0.005, 0.01, 0.015, 0.02 and 0.025 mg/ml. One of the standard solution was analyzed by UV/Vis spectrometer to measure and confirm the wavelength (λ_{max}) at which paracetamol absorbs the light by using mixture of sodium hydroxide and purified water as blank. Wavelength was set (257 nm) to analyze and obtain the absorption values for all standard solutions with same blank. A regression equation was obtained from the constructed calibration curve by representing the absorbance versus the concentrations and was used to determine the concentration in all the samples.

Preparation of Buffer Solution

175 ml of 0.2 M NaOH added to 250 ml of 0.2 M dipotassium hydrogen orthophosphate (K_2HPO_4) and diluted to 1000 ml with pure water. Then buffer solution adjusted by using 0.5 HCl to pH 5.8.

Hardness Test

Determination of hardness requiring 20 tablets selected randomly from each brand and are analyzed by using the mentioned hardness tester.

Friability Test

The friability test is closely related to tablet hardness and concentration of binding agent^[23]. According to BP, to achieve friability test number of tablet with unit mass of ≤ 650 mg should be used. Ten tablets were selected randomly, dedusted and weighed. Tablets were placed in the drum of the friability tester and rotated for 4 minutes at speed of 25 rpm/minute. The tablets were removed, re-dedusted and reweighed to find out the percent friability in each brand. The range of weight loss of a tablet must be less than or equal to 1%. However, if more do not reject the tablets as this test is non-official.

Uniformity of Weight Test

The weight uniformity test was conducted to determine the acceptable weight variations of tablets in selected brands. According to the BP in 2013 a total of twenty tablets units should be used for this test. Twenty tablets were weighed individually by using an analytical balance and recorded. The average weights per brand were calculated and reported as $\pm 5\%$ and $\pm 10\%$ of the average values. The tablet for each brand will pass the test if there are no more than 2 tablets out of Average $\pm 5\%$ or not more than one tablet out of Average $\pm 10\%$.

Uniformity Content Test

Ten tablets in each brand were selected randomly, and each individual tablet was weighed by using an analytical balance, powdered by using mortar and pestle, then transferred into 200 ml volumetric flask. 167 ml of 0.1 M of sodium hydroxide was added to dissolve the powder and shook for 15 min, where small volume of it was firstly used to wash the mortar and pestle; thereby the possibility of stocked residues was reduced. Then the volume was made up to 200 ml with purified water. The formed solution was filtered through filter paper (size 125 mm) to remove the precipitants. 0.4 ml from stock solution was pipetted into 100 ml volumetric flask then 10 ml of 0.1 M of sodium hydroxide was added and the volume was made up to 100 ml with purified water. This prepared solution was checked to ensure its light absorption in the range of calibration curve. Samples were analyzed by UV spectroscopy to measure Paracetamol absorption and calculate its concentration using correlation equation from calibration curve. The brand passes the test if 9 of the 10 tablets contain not less than 85% and not more than 115% of the labelled drug content and the 10th tablet may not contain less than 75% and more than 125% of the labelled content. If these conditions are not met, remaining 20 tablets assayed individually and none may fall outside of the 85% to 115% range.

Disintegration Time Test

British pharmacopoeia apparatus A was used, that consists of basket-rack assembly that consists of six open ended transparent tubes. Six tablets in each brand were tested to the disintegrating time, where each tablet was placed in each tube of basket apparatus with mesh size of 2.00 mm. The test was carried out in medium of 800 ml purified water with temperature of $37 \pm 2^\circ\text{C}$. Disintegration time of all tablets was checked visually and recorded. If one or two tablets from the 6 tablets fail disintegrate completely, repeat the same test on another 12 tablets. The test must be repeated on 12 additional tablets ^[15].

Dissolution Test

The dissolution test was conducted by using apparatus II (paddle apparatus) in six replicates for each selected brand, with phosphate buffer solution as dissolution medium (900 ml at $37 \pm 0.5^\circ\text{C}$ for each replicate) of; pH 5.8 ± 0.05 ; RPM for tests was 50. All required parameters were fixed and confirmed with BP specifications. A sample of 5ml of the dissolution medium at 45 minutes was pipetted, filtrated. Then 1 ml of filtrate was diluted with phosphate buffer up to 50 ml by using volumetric flask. The absorbance was measured at 257 nm, after that the concentration was determined by using calibration equation ^[18].

Statistical Analysis

By one-way ANOVA analysis of variance the difference in physicochemical properties was evaluated using Graph Pad Install software. When P is <0.05 the difference were considered significant.

RESULTS

Precision Results

In precision study, the repeatability measurement of UV/Vis spectrometer was investigated and obtained results were showed as limit of mean \pm SD and relative standard deviation (%RSD) for all concentrations as represented in **Table 2**.

Table 2. Represents results of precision studies for UV/Vis spectrophotometer

Variables	0.025 mg/ml	0.015 mg/ml	0.005 mg/ml
Mean \pm SD	0.9904 ± 0.0012	0.5237 ± 0.0001	0.2752 ± 0.0013
% RSD	0.1229	0.0314	0.489

Calibration Curve Results

Figure 2 demonstrates a calibration curve for pure paracetamol from 0.005 mg/ml up to 0.025 mg/ml, against absorbance at a wavelength of 257 nm (λ_{max}). The dilution of tested samples was achieved according to this concentration range of calibration curve.

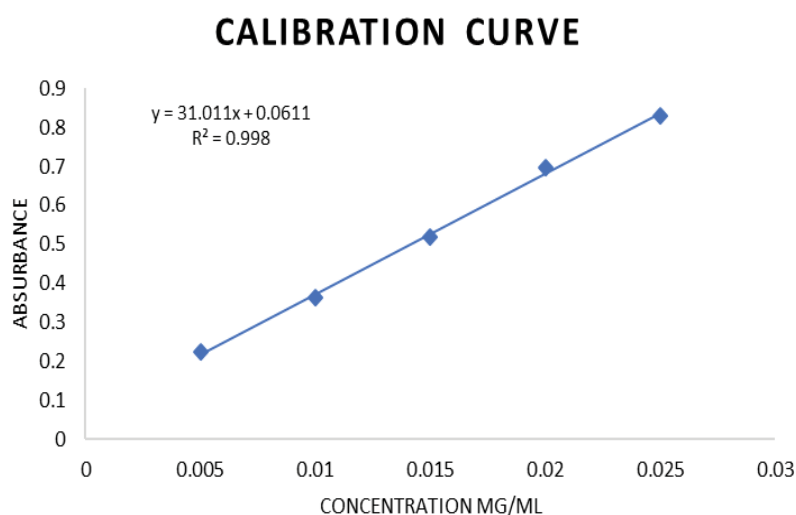


Figure 2. Calibration Curve of pure Paracetamol at wavelength 257 nm.

Drug Content Results

Percentage of drug content for each selected tablets in all brands was calculated and represented as showed in **Table 3**.

Table 3. Clarify uniformity of content.

No.	Uniformity of Drug Content				
	B1	B2	B3	B4	B5
1	98.68%	88.69%	90.11%	94.54%	99.39%

2	102.69%	107.14%	103.45%	101.61%	106.02%
3	100.40%	98.21%	96.54%	97.76%	109.03%
4	101.83%	87.50%	105.32%	103.16%	101.80%
5	97.59%	100.70%	100.81%	107.56%	97.08%
6	105.56%	98.80%	107.66%	100.18%	96.98%
7	101.26%	101.30%	103.56%	100.31%	97.22%
8	92.59%	111.07%	99.53%	100.86%	94.78%
9	92.19%	107.44%	96.13%	96.02%	108.43%
10	107.40%	97.97%	97.71%	98.44%	92.77%
Av	100.02%	99.88%	100.08%	100.04%	100.35%

The loaded dose of Paracetamol in selected tablets in all five brands was within the BP standard specifications. However, Actavis® (B5) showed the highest average percentage of drug content.

Weight Variation Results

Table 4 clarifies weight of 20 selected tablets in each brand and range of weight variations.

Table 4. Illustrates weight variation results of five brands.

No.	B1	B2	B3	B4	B5
1	0.602	0.65	0.546	0.558	0.595
2	0.588	0.658	0.55	0.563	0.603
3	0.594	0.645	0.55	0.559	0.605
4	0.581	0.655	0.544	0.559	0.601
5	0.591	0.656	0.549	0.565	0.602
6	0.602	0.652	0.549	0.56	0.596
7	0.587	0.646	0.548	0.572	0.597
8	0.6	0.648	0.553	0.554	0.592
9	0.59	0.659	0.548	0.566	0.596
10	0.592	0.654	0.549	0.563	0.621
11	0.616	0.647	0.555	0.557	0.593
12	0.599	0.655	0.56	0.56	0.601
13	0.598	0.654	0.554	0.562	0.61
14	0.588	0.651	0.545	0.557	0.594
15	0.592	0.653	0.552	0.56	0.597
16	0.593	0.662	0.547	0.56	0.613
17	0.597	0.659	0.558	0.556	0.591
18	0.593	0.661	0.547	0.555	0.6
19	0.583	0.653	0.557	0.564	0.608
20	0.584	0.654	0.554	0.572	0.62
Average ± 5%	0.6093 ± 5%	0.6538 ± 5%	0.5478 ± 5%	0.5611 ± 5%	0.6017 ± 5%

Weight of tablets in each brand is different compared with others due to the difference in weight of manufactured formulation in each brand. Nevertheless, all tablets were within the range of average ± 5%.

Results of Disintegration, Friability and Hardness Tests

All of these quality tests were performed and obtained results were represented together in **Table 5**.

Table 5. Shows results of disintegration, % friability and hardness tests.

No	Disintegration time test (min)				
	B1	B2	B3	B4	B5
Tablet 1	3.2	4.27	1.48	1.25	5.37
Tablet 2	3.3	5.18	1.51	1.34	6
Tablet 3	3.47	5.44	2.16	1.37	6.36
Tablet 4	3.51	6	2.19	1.4	7.33
Tablet 5	3.55	6.16	2.26	1.48	7.51
Tablet 6	4	6.38	2.58	2.25	8.22
Average	3.5	5.57	2.03	1.51	6.79
% Friability test	0.25%	0.14%	20.23%	0.21%	0.37%
Hardness test (Kg)	11.93	12.46	8.4	8.66	10.53

In disintegration time test, all five brands showed acceptable time, where brand 4 achieved the shortest time (1.51 min). In case of hardness test, all the results are accepted compared with their disintegration time. Despite brand 3 represented accepted hardness and disintegration time values; its friability was too high and out of the limit.

Results of Dissolution Test

Five brands were analyzed to investigate percentage of drug release after 45 minutes by conducting dissolution test and the results represented in **Table 6**.

Table 6. Demonstrates % of drug release from tables during dissolution test.

Variables	B1	B2	B3	B4	B5
% Drug Release (Through 45 min)	87.78%	71.15%	71.77%	95.77%	100.84%
Conventional tablets should not release less than 70% of loaded active ingredients through 45 min					

The required drug release from all tested tablets in all five brands was obtained and conformed to BP specification. The highest percentage of drug release was gained by Actavis® Paracetamol tablets.

DISCUSSION

Precision

Closeness of series measurements obtained by analyzing standard solutions indicates on repeatability of utilized instrument^[26]. According to obtained results in this study as shown in **Table 3**, % RSD for all concentrations were less than 1,26 which confirm by another study was conducted as method development and validation of assay of Paracetamol tablet formulation. Thereby, UV/Vis spectrometer which used in this study is valid and give reliable results^[27].

Calibration Curve

The response of the drug was found to be linear in the investigation concentration range and the linear regression equation was $y = 31.011x + 0.0611$ with correlation coefficient 0.998 (**Figure 2**) which approved with another study was conducted as method development and validation of assay of Paracetamol tablet formulation^[28].

Hardness Test

Sufficient tablet hardness is an essential and conducted to assess ability of tablets to withstand mechanical^[12]. In this study, has been found that B3 and B4 had acceptable crushing strength less than 10 Kg as shown in **Table 6**. Meanwhile, the rest brands showed crushing strength higher than 10 Kg, where B2 represented the highest value (12.46 Kg, **Table 6**). The variation in results could be related to formulation or manufacturing process parameters such as; compression force, amount of binder (more binder a more hardness) and method granulation in preparing the tablet (wet method gives more hardness than direct method, slugging method gives the best hardness)^[29]. British Pharmacopeia did not mention specific limit of hardness but another studies mentioned that crushing strength of between 4 Kg to 10 Kg is considered minimum requirement for a satisfactory tablets. If the tablet hardness is too high, disintegration time should be tested firstly before rejecting the batch. If it was within the limit, then accept the batch^[29]. The obtained results in this study almost close compare to results in another study achieved on Paracetamol tablets and their results were range between of 4.31 Kg to 11.55 Kg which emphasis acceptability of obtained results in this study^[30]. However, the statistical comparative analysis illustrated that there was a significant difference between the brands as shown in appendix.

Friability Test

The ability of the tablets to withstand abrasion in packing, handling and transporting can be investigated by attaining friability test^[31]. The current study demonstrating that most of brands had a suitable friability values with range of 0.137% to 0.368% as displayed in **Table 6**. The gained results conformed to BP standards ($\leq 1\%$) and approximately similar to other study conducted on three brands of Paracetamol tablets and their values were ranged from 0.1% to 0.3%^[32]. However, only B3 exhibited extremely high value of friability. It was found 20.23% as presented in **Table 6**, which means around twenty times more than BP limit. The reason behind this high value could be increasing of tablet crumbling which depends on many factors such as compression force, binders and additives that used in the manufacturing procedures. Compression force and concentration of binder should be adjusted to avoid high and low values of tablet strength^[12,33]. The statistical comparative analysis represented that there is no any significant difference between the brands when compared to each other's, except when they compared with brand 3 as shown in appendix.

Weight Variation

The purpose of this test is to verify the uniformity of each brand which ultimately reflect the drug content uniformity in all the brands^[34]. According to B.P. specification all the paracetamol tablets of five brands were predictable not to deviate by $\pm 5\%$ of the average tablet weight. Auspiciously, there were no tablet of each five brands deviate from the specified limit and all tablets passed the Weight variation test as shown in **Table 5**. The weight variation between the tablets in each brand could be related to many factors such as; percentage of fines within the formulation, particle size of granules, flowability of granules, diameter of punch, depth of die cavity, speed of compression and friability of tablets^[35].

Uniformity Content Test

This test was performed to ensure the proper mixing of the tablet contents and if verifying with stated dose (500 mg)^[36]. In this study, most of the results of drug assay of five different brands of Paracetamol tablets shows that average amount of Paracetamol drug available in all these brands is very close to 100%, means drug are available as per their stated value and the dosage form is in stable form. Out of all these brands the B5 is having the highest average amount of 100.35% (**Table 4**) as compare to others but it is still in therapeutic window so no chance of under and over pharmacological action. These results were found accomplished with BP standard specification (85-115%)^[18]. Additionally, the data relatively similar to results obtained in another study which was achieved on four different brands^[31]. Nevertheless, the variation in percentage of drug content could be related to mixing time where a short mixing time would not be enough and long mixing time may result in demixing. Additionally, the particle size distribution of the filler may has an important impactation. In this case, using ingredients with small particle size will enhance and facilitate mixing process but also could have opposite effect on powder flow. Therefore, optimizing the particle size distribution will produce good mixing and powder flow; thereby enhance uniformity of content^[37]. The statistical comparative analysis indicated that there is no any significant difference between all the brands ($P>0.05$) as shown in the appendix.

Disintegration Test

Disintegration time is the period of time required to disintegrate the tablet to small particles, then discharge the drug to become fully available for dissolving in body fluid^[23,38]. This test clarified that all brands displayed satisfied disintegration time with average ranged from 1.51 to 6.79 min as represented in **Table 6**. Brand 4 showed the shortest time with average of 1.51 min, while the longest time achieved by B5 with average time of 6.79 min as shown in **Table 6**. The obtained results were found met with BP limit (should disintegrate within 15 minutes)^[18]. Furthermore, they were established with another study was applied on five brands and their disintegration time was ranged from 1 to 10 minutes^[39]. The variation in disintegration time could be related to several factors such as; binder, lubricant, surfactant disintegrating agent and hardness.³⁵ According to statistical comparative analysis, there was a significant difference between all the brands ($P<0.05$), except comparing brand 3 with brand 4 ($P=0.6578$) as presented in appendix.

Dissolution Test

It is an important quality control parameter. It is directly related to the absorption and bioavailability of a drug^[40]. The present study was found that after 45 minutes, the release rate of different brands of Paracetamol was satisfactory and ranged from 71.15% to 100.84% as displayed in **Table 6**. The B5 showed the highest percentage of drug release and value was 100.84%, while the lowest value was gained by B2 and value was 71.15% as shown in **Table 6**. All obtained percentage of drug release of brands verified with BP standards which stated as no tablet should has % drug release less than 70% after 45 minutes dissolution time^[18]. In addition, the gained results in this study were approximately identical with results reached by two studies were achieved on compressed tablets of Paracetamol and the values were found as range of 80% to 100%^[34]. 79.82% to 103.53%^[23]. The difference of drug release rate between the brands may be due to some factor such as drug product formulation and processing factors. Dissolution rate of pure drug can be altered significantly when mixed with various assistants during manufacturing process such as diluents, dyes, binders, granulating agents, disintegrants and lubricants. Furthermore, method of granulation and compression force may influence the dissolution rate^[33]. According to statistical comparative analysis, there is significant difference between all the brands ($P<0.05$), except comparing brand 2 with brand 3 there was no significant difference ($P<0.9366$) as shown in appendix.

CONCLUSION

The quality of medicines must be reevaluated by responsible committees during their shelf life in order to ensure safety and effectiveness of consumed drugs by populations. Paracetamol is a widely used and well established antipyretic and analgesic drug^[41]. This study was conducted to evaluate five different brands of Paracetamol tablet available in Misurata market. However, the quality of five different brands of the paracetamol assessed and was found most of the obtained results verifying with British Pharmacopeia quality requirements. Brand 3 was failed the friability test and was found deviated twenty times more than the desired limit (20.23%). Overall the quality evaluation results found in this research are similar to the results observed from the previous studies on quality evaluation studies of paracetamol tablets. Therefore, it is evident from the study that most of the brands tested showed reliable results.

RECOMMENDATIONS

Bioavailability studies should be conducted to find out any physiological effects on absorption and efficacy of selected brands.

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