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In Vitro Quality Evaluation of Fourteen 500 mg Paracetamol Tablets Brands in Ghana

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ABSTRACT

Paracetamol (acetaminophen) is an over-the-counter analgesic, antipyretic and anti-inflammatory drug. There are numerous generics of Paracetamol tablets, both locally produced and imported brands are available within the health care delivery system in Ghana. This study was undertaken to evaluate the quality of these brands. Pharmacopoeial and non-pharmacopoeial tests such as friability, thickness, hardness, uniformity of diameter, uniformity of weight, disintegration time, *in vitro* dissolution testing and assay tests were conducted on fourteen brands of 500 mg immediate release paracetamol tablets which were purchased from pharmacies within the Kumasi metropolis of Ghana.The brands were coded variously to prevent any biases. All brands complied with the official specifications for identification, diameter, thickness and hardness. Four out of the fourteen brands namely PLE, PMA, PPH, and POC passed the entire test conducted on it. Going by the British pharmacopoeia standard, eight brands (57%) recorded active pharmaceutical ingredients content less than the lower limit of 95% hence failing the assay test but the number reduced to four (33 %) when the United States pharmacopoeial lower limit of 90% standard was applied. The result of this study should be a source of worry for the drug regulatory body in Ghana and calls for an increased post market surveillance to ensure that persons who purchase 500 mg paracetamol tablets for the management of their pains receive the optimal benefit from the medication.

INTRODUCTION

Paracetamol (acetaminophen), N-(4-Hydroxyphenil)-acetamide is an over-the-counter analgesic, antipyretic and anti-inflammatory drug which has been in use for several years [1]. According to the WHO's definition, a generic product is "a pharmaceutical product, mostly intended to be interchangeable with an innovator product, manufactured without permission from the innovator company and mostly marketed after the expiry date of the patent or other exclusive rights [2]. The various sources of generic drugs which have been introduced into the health care delivery system are to help improve access and affordability of life-saving drugs in many developing countries [3]. However, the introduction and widespread distribution of counterfeit and substandard drugs have compromised the quality of medicinal drugs being used in many developing countries [4,5]. The World Health Organization (WHO) has estimated that medicinal products on sale in various countries in Africa, parts of Latin

America and Asia for consumption has about 30 % of it being substandard and counterfeit [6]. Counterfeiting or substandard production is not limited to only original branded products but generics as well [7]. A vast number of people have been affected by the negative effects of counterfeit pharmaceuticals worldwide, with persons in developing countries suffering the most [8]. Paracetamol is the most used analgesic or antipyretic agent in both developed and developing countries especially as an Over The Counter (OTC) medicine [9-11]. Considering the importance paracetamol plays even in the clinical setting worldwide, it is therefore very necessary to monitor and ascertain the quality attributes and the drug release proficiency of the various local brands of paracetamol available on the Ghanaian market for purpose of generic substitution and also for quality control assessment.

MATERIALS AND METHODS

Reagents and equipment

All the reagents used for the experiment were of analytical grade and obtained from the Quality Control Department of Pokupharma Limited, Kumasi-Ghana, a state accredited pharmaceutical manufacturing company in Kumasi, the second biggest city in Ghana. Equipment and apparatus used in carrying out the investigations included: DBK Friability test apparatus, Disintegration apparatus (DBK), Hardness tester (SR. No 123 -Eleclab India), FTIR spectrometer (PerkinElmer (UATR two), Analytical balance (SN: AE 436647 Adam Equipment, UK), pH meter (Eutech pH 510, pH/mV/°C meter, SN: 2025520, Singapore). Electronic Vernier callipers (Powerfix Milomex Ltd UK), Whatman filter paper, General-purpose glassware, UV spectrophotometer (2440 Double beam - Shimadzu Corporation Japan), Dissolution Apparatus (Shimadzu Corporation, Japan) Cuvettes (Shimadzu) and Thermometers.

METHODS

Sampling of paracetamol brands from the market: Fourteen brands of 500 mg paracetamol tablets in their original manufacturer's package were identified and purchased from different registered retail pharmacies in the Kumasi metropolis which is located in the middle belt of Ghana. All brands sampled had a remaining shelf life of at least one (1) year from the time they were purchased.

Subjective physical assessment of tablets: The external packages, labels, unique identification marks, foils, and leaflet inserts were carefully examined. The tablets to be analyzed were placed on a white sheet of paper and examined (both sides of each tablet) carefully for unique markings, colour, shape, and odour.

Weight uniformity: Digital analytical balance (Adam Equipment, SN: AE 436647, UK) was used for measuring the weight of the samples. Twenty (20) tablets of each brand of were picked at random and weighed together. This was followed by the weighing of the individual tablets. The average weight (measured in grammes) of the tablets that were weighed together was calculated and the weight of individual tablets was deducted from the mean weight to obtain the deviation which was then expressed as a percentage deviation of the individual tablet from the mean.

Uniformity of thickness of the paracetamol tablets: The thickness of twenty (20) tablets of each brand selected randomly from the brands was determined with Electronic Vernier calipers (Powerfix. Milomex Ltd UK). The mean and standard deviations of the readings were taken for all the brands.

Uniformity of diameter of the paracetamol tablets: The cross-sectional diameter of twenty (20) tablets of each brand selected randomly from the brands was determined with Electronic Vernier callipers (PowerfixMilomex Ltd UK). The mean and standard deviations of the readings were taken for all the brands.

Tablet hardness (Crushing strength): The hardness of 20 tablets (randomly selected) from each brand was determined individually at room temperature by diametrically compressing the tablets using a tablet hardness tester (SR. No 123 -Eleclab India). The hardness was read on the side scale of the tester. Results of tablets that split clearly into two halves without any sign of lamination were recorded. All measurements (kg/cm^2) were made in triplicate from which the mean crushing strength was calculated for each brand.

Tablet friability: The friability test was carried out using the DBK Friability test apparatus. A number of tablets having an estimated weight of 6.5 g was taken from each brand, weighed and placed in the Friabilator, which was then operated for four (4) minutes at 25 rpm (100 revolutions). The

friabilated tablets were de-dusted and reweighed. The percentage weight lost was subsequently calculated

Drug content: The British Pharmacopoeia [12] procedure for assaying Paracetamol was used in determining the active ingredient content of various brands. Twenty (20) Paracetamol tablets were weighed accurately and the average weight recorded. The tablets were crushed to a fine powder and a quantity of the powder equivalent to 0.15 g of Paracetamol was accurately weighed and dissolved in 50 ml of 0.1 M sodium hydroxide (NaOH) in a 200 ml volumetric flask. The solution was diluted with 100 ml of water, and shaken for 15 minutes. Adequate amount of water was added to the mixture to produce 200 ml. The resulting solution was filtered and 10 ml of the filtrate was diluted with water to 100ml. Absorbance of the resulting solution was measured at 257 nm on a UV spectrophotometer (2440 Double beam - Shimadzu Corporation Japan). The average content of Paracetamol was subsequently calculated using a calibration equation established with analytical grade paracetamol.

***In vitro* drug release (Dissolution Test):** The USP dissolution apparatus II (paddle apparatus) was used to conduct the dissolution test. The agitation intensity was 100 rpm. Ten (10) mililitres of samples dissolved in the dissolution medium was withdrawn from each vessel, at different time intervals of 5, 10, 15, 30, 45 and 60 minutes. Equal volume of fresh medium having same temperature was added to each vessel at each time to maintain a sink condition. Each sample withdrawn was filtered and 0.50 ml of each filtrate diluted to 50 ml with 0.1 M NaOH. The absorbance of the resulting solution was measured at 257 nm. The amount of drug (Paracetamol) released was then determined from the calibration curve

RESULTS AND DISCUSSIONS

Weight uniformity

Uniformity of weight is one of the tests which is conducted to ensure constant and uniform dosing among tablets within a batch and helps to prevent the incidence of underdosing or overdosing. The weight variation of the individual tablet is a valid indication of the variation corresponding to the drug content [11]. According to the British pharmacopeia 2018 specifications for uniformity of weight, eleven (11) brands passed the uniformity of weight test with brands PAR, PAE and PES failing the test (Table 1). The brands passing the test could be attributed to good flow properties of granules, regular movement of the lower punch resulting in uniform die volume and hence uniform distribution of weight of the tablets [11]. In several similar studies reported across Africa, Asia and Middle East regions, their paracetamol tablets passed the uniformity of weight test [1,13-17]. Manufacturers of the brands that failed in the current investigation need to investigate and correct potential errors in the production process which may have accounted for the failures. This is important because tablets having different weights potentially contain different quantities of active ingredients which ultimately could lead to different treatment outcomes.

Table 1: Uniformity of weight of the different brands of Paracetamol tablets (n=20).

Code	Total weight (g)	Mean weight (g)	No. of tablets deviating by ±5%	No. of tablets deviating by ±10%	Inference
PMA	11.4371	0.5719±0.005	Nil	Nil	Passed
PAR	12.9378	0.6469±0.035	Seven(7)	One(1)	**Failed**
PMG	11.5785	0.5789±0.008	Nil	Nil	Passed
PLE	12.0166	0.6008±0.006	Nil	Nil	Passed
PAE	11.3261	0.5665±0.022	One(1)	One(1)	Passed
PAS	10.0290	0.5015±0.005	Nil	Nil	Passed
POC	11.6928	0.5846±0.007	Nil	Nil	Passed
PDA	12.0949	0.6047±0.011	Nil	Nil	Passed
PES	11.5287g	0.5764±0.009	Eight(8)	Nil	**Failed**
PPH	10.9574	0.5479±0.006	Nil	Nil	Passed
PSA	10.8472	0.5424±0.009	Nil	Nil	Passed
PAN	10.9460	0.5473±0.018	Two(2)	Nil	Passed
PKI	11.1150	0.5580±0.006	Nil	Nil	Passed
PTA	12.1725	0.6086±0.015	One(1)	Nil	Passed

Uniformity of dimensions of the paracetamol tablets

Uniformity in the diameter and thickness of tablets are important parameters in assuring consistency in the weight of the formulated tablets. Uniformity of dimensions is an in-process quality control check which is routinely done to ascertain the possibility of the tablets failing or passing other quality control checks. The paracetamol tablets had an average thickness which was ranging from 3.52 ± 0.062 mm to 4.60 ± 0.067 mm with PAS having the least and PLE having the largest thickness as shown in Table 2. All the sampled brands passed this test, indicating consistency in force of compression and density of granulation. The paracetamol tablets had an average diameter which was ranging from 12.22 ± 0.040 mm

to 13.03 ± 0.033 mm with PLE having the least and PPH having the largest diameter. Brand PTA had the highest standard deviation value of ±0.48 while PSA had the least value of ± 0.027 indicating PMA was the most uniform brand in terms of thickness whereas PAR was the least. Dimensions of tablets plays an important role in determining their shapes, and size; characteristics that plays important role in patient's readiness to swallow dosage forms which can affect the therapeutic outcome of their treatment [18,19].

Table 2: Thickness and diameter of the various brands of Paracetamol tablets (n=20).

Code	Thickness(mm)	Number of tablets deviating by ±5 %	Diameter (mm)	Number of tablets deviating by ± 3 %	Inference
PMA	3.93±0.035	Nil	12.73±0.041	Nil	Passed
PMG	4.21±0.073	Nil	12.60±0.088	Nil	Passed
PDA	4.23±0.073	Nil	12.58±0.038	Nil	Passed
PAR	4.32±0.143	Nil	12.59±0.049	Nil	Passed
PAE	3.96±0.12	Nil	12.59±0.053	Nil	Passed
PSA	4.07±0.05	Nil	12.44±0.027	Nil	Passed
PLE	4.60±0.067	Nil	12.22±0.040	Nil	Passed
PPH	3.66±0.110	Nil	13.03±0.033	Nil	Passed
PES	4.41±0.093	Nil	12.54±0.037	Nil	Passed
PAN	3.92±0.085	Nil	12.65±0.031	Nil	Passed
PTA	4.28±0.078	Nil	12.67±0.48	Nil	Passed
POC	4.15±0.050	Nil	12.65±0.042	Nil	Passed
PAS	3.52±0.062	Nil	12.59±0.039	Nil	Passed
PKI	3.94±0.124	Nil	12.66±0.071	Nil	Passed

Disintegration time, hardness, friability and CSFR of the various brands

With regards to disintegration test, all the brands except PKI had their disintegration time within the specifications of the British Pharmacopoeia [12] as shown in Table 3. The disintegration time failure of PKI could be attributed to the use of high amount of binder, high compression force and inadequate amount of disintegrant. Similar studies in Saudi Arabia, Yemen, Gondar city in Ethiopia and Onitsha in Nigeria found the sampled paracetamol tablets passing the disintegration test [14,16,17,20]. In a study in Ethiopia by Teklu et al. [1], one out of the 16 (6.25%) sampled paracetamol tablets failed the disintegration test but as high as 25.0% and 33.3% failure were observed in studies in Abuja, Nigeria and Douala, Cameroun respectively [13,15]. The hardness of a tablet determines its resistance to capping and breakage under conditions of storage, handling and transportation. A diametrical crushing force of 4 kgf is considered the minimum force for satisfactory tablet hardness. All the brands of Paracetamol tablets had crushing force greater than 4 kgf and therefore had the optimal ability to withstand fracture. PAS had the least hardness of 6.10 ±1.00 kgf with PMA having the highest hardness of 12.89±1.17 kgf. These divergent values could be due to the incorporation of varied amounts of binder and compression force during the compression of the tablets. Just as in this study, paracetamol tablets tested in some other studies also passed [1,14,16,17,20] but Nga et al. [15] recorded an eighty percent non-conformance in 15 tablets brands sampled in a study in Douala, Cameroun. Friability test helps to assess the ability of a tablet to withstand abrasion that is usually associated with packaging, handling and transportation. This tablet property is influenced by the nature and amount of binder usually used and force of compression. All the brands passed the friability test with the exception of PAR which had a percentage weight loss of 1.22%. The failure of PAR could be due to the use of insufficient binder and inappropriate compaction force, making the tablets friable. The study in Onitsha, Nigeria by Iloamaeke, and Iwuozor, [20] found one of the eleven tablet brands tested to be friable. In several other studies, all their sampled paracetamol tablet brands passed the friability tests [1,14,16,17]. Crushing Strength-Friability Ratio (CSFR) is used to measure the strength of a tablet and generally higher CSFR indicates stronger tablets [21]. The top three strongest tablets were PLE (76.48), PMA (41.31) and PTA (28.26) but PAS recorded the lowest CSFR value of 6.98. The lowest value found in PAS is understandable as it had the lowest hardness and disintegration time values which could be due to high levels of disintegrants or comparatively lower compaction force applied during production.

Table 3

Dissolution rate test

Dissolution rate test is used to determine the dissolution profile in general and for profile comparison and establishing the similarity of pharmaceutical dosage forms [22]. The British Pharmacopoeia 2018 stipulates that, for conventional immediate-release tablets, each of the tablets tested for dissolution should release not be less than 70% of the stated or

prescribed amount within 45 minutes. In several previous studies [1,15-17] all the brands of the paracetamol tablets tested passed the dissolution test. In this study, four brands (PAS, PKI, PMG and PAN) of the paracetamol tablets failed this test (Figure 1). The failure of these four brands could plausibly be attributed to high amount of binder, high compression force and inadequate amount of disintegrants.

Table 3: Disintegration time, Hardness, Friability and CSFR of the various brands.

Brand	Disintegration time(minutes)	Hardness (Kg/f)	% Friability	Crushing strength to Friability ratio (CSFR)
PMA	2.34±0.01	12.89±1.17	0.3120	41.31
PMG	2.38±0.08	9.07±1.55	0.9239	9.82
PDA	3.35±0.25	9.91±1.29	0.8077	12.27
PAR	6.17±0.18	11.64±1.29	1.2219	9.53
PAE	3.17±0.06	10.58±1.06	0.3821	27.69
PSA	6.19±0.07	7.75±2.20	0.2978	26.02
PLE	4.17±0.04	7.12±1.55	0.0931	76.48
PPH	1.48±0.04	10.64±0.50	0.4675	22.76
PES	2.59±0.07	8.91±1.52	0.3359	26.53
PAN	4.18±0.03	10.77±1.41	0.4863	22.15
PTA	2.51±0.01	11.22±2.2	0.3970	28.26
POC	7.05±0.15	10.05±1.44	0.5108	19.68
PAS	1.27±0.05	6.10±1.00	0.8743	6.98
PKI	120.23±0.08	12.56±2.10	0.7413	16.94

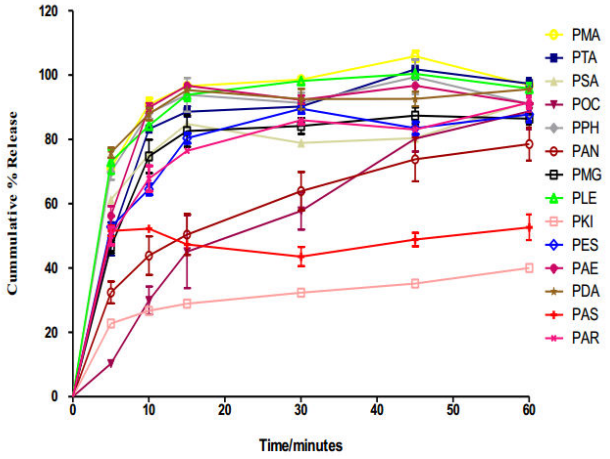

Figure 1: Dissolution profile of the various brands of paracetamol tablets investigated.

Assay of paracetamol tablets

According to the standards of the British pharmacopoeia [12], upon assay of Paracetamol tablets, between 95% and 105% of the label claim should contain the active ingredient. The results (Table 4) showed that six out of the fourteen (14) brands had values which fell within the monograph specifications, these six includes; PLE, PAE, POC, PPH, PMA and PKI. The other brands had percentage content of active ingredient below the lower limit of 95% and hence failed the assay assessment test. With reference to the USP standard, a reduced number of four (PAR, PAS, PES, and PSA) are considered to have failed the assay test. Using the USP standard, there were similar deviations in studies conducted in Ethiopia by Teklu, Adugna, and Ashenef, [1] where one brand out of sixteen failed the assay test while in a survey of brands of paracetamol tablets from pharmacies in Abuja, Nigeria, 50% of the eight samples failed [13]. The study by Iloamaeke, and Iwuozor, [20] in Onitsha, Nigeria found six out of eleven brands of paracetamol failing the assay test per the BP standard. All the samples from Riyadh in Saudi Arabia, a Yemeni market as well as Gondar city in Ethiopia however met the BP/USP pharmacopoeial standard [16].

Table 4: Assay of Paracetamol tablets (UV).

Code	Mean absorbance	% Assay	Inference (BP standard	Inference (USP standard
PAR	0.395	75.01	Failed	Failed
PMG	0.490	92.50	Failed	Passed
PLE	0.531	100.69	Passed	Passed
PAE	0.522	98.93	Passed	Passed
PAS	0.356	67.57	Failed	Failed
POC	0.522	98.99	Passed	Passed
PDA	0.490	92.93	Failed	Passed
PES	0.428	81.22	Failed	Failed
PPH	0.522	99.05	Passed	Passed
PSA	0.421	79.85	Failed	Failed
PMA	0.591	104.04	Passed	Passed
PAN	0.495	93.82	Failed	Passed
PTA	0.475	90.03	Failed	Passed
PKI	0.547	102.77	Passed	Passed

(BP Range = 95.0-105%; USP range = 90.0 – 110%)

CONCLUSION

Assessing quality of medications ensures that the users obtained the optimal therapeutic benefit of the formulation. Quality control parameters such as uniformity of weight and dimensions, friability, disintegration time, dissolution and assay test were conducted. It was found that all the sampled brands of 500 mg paracetamol tablets sampled from the pharmacies in Kumasi passed the uniformity of dimensions test but about a fifth had challenges with uniformity of weight. A brand each

failed the disintegration time and hardness tests with four out of fourteen brands failing the dissolution test. The active pharmaceutical ingredient content of at least four brands fell short of the international standards. The failure of quality control parameters of some brands of paracetamol which is a widely used analgesic in several parts of the world should be of concern to drug regulatory authorities. Effective post-market surveillance is required to ensure such substandard or counterfeits drugs are identified and taken out of the market.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interestregarding the publication of this article.

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