ORIGINAL ARTICLE

ISSN: 0331 - 670X

https://doi.org/10.51412/psnnjp.2024.27

The Nigerian Journal of PHARMACY
AS MEN OF HONOUR WE JOIN HANDS
THE OFFICIAL ORGAN OF THE PHARMACEUTICAL SOCIETY OF NIGERIA FOUNDED 1927

Quality Assessment of Fifteen Brands of Paracetamol Injections Marketed in Lagos, Nigeria

Oluwafunmilayo D. Akinnurun[1], Chinedu G. Ezeah[1,2], Moshood O. Akinleye[1,2]

[1]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Lagos, College of Medicine Campus, Idi-araba, Lagos, Nigeria.

[2]African Centre of Excellence for Drug Research, Herbal Medicine Development and Regulatory Science, University of Lagos, Lagos, Nigeria.

ARTICLE INFO

Article history:

Received 29th September 2024
Revised 11th October 2024
Accepted 12th October 2024
Online Published

Keywords:

Paracetamol injection,
sterility test,
quality,
assay of active ingredient,
Nigeria

*Corresponding Author:
Chinedu G. Ezeah
Email: ezeahchinedu@yahoo.com
Tel: +2348130545073

ABSTRACT

Background: Paracetamol injection is a widely used medication for the management of pain and fever in healthcare settings. Ensuring the quality and safety of pharmaceutical products is essential to protect public health, so there is need to investigate the quality of these Pharmaceutical preparations in Lagos, Nigerian drug market in compliance with international standards and guidelines.

Method: Fifteen brands of paracetamol injections were sourced from registered pharmacies in Lagos. The sampled products were subjected to a comprehensive quality assessment using standard protocols, including testing for the presence of specified indicator pathogens using compendial procedures like sterility testing and assessment of active pharmaceutical ingredient (API) content through high-performance liquid chromatography (HPLC).

Results: Results from the study indicated that 86.67 % of the paracetamol injection samples have the Active Pharmaceutical Ingredient (API) content within the acceptable limit of the United States Pharmacopoeia (USP) 2018, but 13.33 % of the paracetamol injection samples were found to be above the maximum acceptable limit. The sterility test results showed that none of the paracetamol injections samples recorded microbial load above the limit of USP.

Conclusion: The findings of this study highlight potential quality issues in the paracetamol injection products marketed in Lagos, Nigeria. Further investigations and continuous monitoring by regulatory authorities are recommended to ensure the consistent supply of safe and effective paracetamol injection formulations to healthcare providers and patients in Lagos and beyond.

Introduction

Paracetamol (acetaminophen) is a drug used to temporarily relieve mild to moderate pain associated with headaches, menstrual pains, toothaches, backaches, osteoarthritis, or cold/flu aches. It also has anti-pyretic activity and it is one of the most common over the counter (OTC) drugs and therefore can easily be counterfeited. Chemically, it is a 4-hydroxyacetanilide (acetaminophen). Prostaglandins involvement has been proposed in the analgesic mechanism of paracetamol, by inhibition of central cyclooxygenases (COX-1, COX-2, and COX-3)[1]. Paracetamol is the most frequently counterfeited medication; studies have been conducted on its quality assessment in different countries[2,3,4,5,6,7,8]. Usually, a single generic drug is manufactured by different companies under different brand names. In many countries, the drug is also manufactured by small scale manufacturers which may be widely distributed or locally consumed. It has been found in several studies that it is being consumed without proper prescription especially in rural areas[9, 10]. Even though a single generic

drug manufactured by different companies under different brand names should fulfill the pharmaceutical parameters, the variations in the pharmaceutical parameter have a definite impact on the therapeutic effect of the drug that may not provide the expected result[7]. The injection form of paracetamol just like the tablet is frequently prescribed in the hospitals to assuage pains and relief fever and for that reason; it is paramount that the qualities of paracetamol injections in circulation be monitored.

The World Health Organization (WHO) defines a counterfeit medicine as one which is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredient or with fake packaging[11]. The marketing of multisource drug products registered by national drug agencies in developing countries, with the view of improving health care delivery through competitive pricing, has its attendant problem of ascertaining their quality and interchangeability [12]. Variable clinical responses to drugs presented as generics and batch-to-batch inconsistencies have been reported [13].

The National Agency for Food and Drug Administration and Control in Nigeria (NAFDAC) works under the auspices of the Ministry of Health to regulate and control quality standards for drugs, chemicals and medical devices, detergents and bottled water. The Agency identified a number of different types of counterfeit drugs in Nigeria, including those with insufficient or an absence of active ingredients, counterfeits and copies, orthodox medicines mixed with herbal preparations, and expired drugs. Apart from the fact that counterfeiting medications are a waste of a patient's income[14], the use of them often provokes serious health complications and, in most cases, leads to premature deaths. Quality of the drug according to the modern definition requires that the product contain the quantity of each active ingredient claimed on its label within the applicable limits of its specifications, contain the same quantity of active ingredient from one dosage unit to the next, be free from extraneous substances, maintain its potency, therapeutic availability and appearance until used, and upon administration release active ingredient for full biological availability[15].

Preliminary physicochemical assessment of the products is very important and performing such evaluation in-vitro is gaining regulatory support and has the advantages of saving money and time and of not requiring involvement of human research subjects. Therefore, this in-vitro test can be used to determine batch consistency of drug formulations from the same manufacturer as well as in assessing the drug product quality from various manufacturers for comparing. Analytical methods such as High Performance Liquid Chromatography (HPLC) is employed in determining the quantity of the active ingredients in the formulation and comparing it with values which is already enclosed in all official publication.

Similarly, Sterility testing is another standard quality control tool to show not only the presence of microorganism in the formulation but also to check batch to batch consistency and quality. There is an increase of generic drug products from different multiple sources in Nigeria, and the physicians have noticed that some medicines which have the same active pharmaceutical ingredient from different companies differ in its effectiveness. So this study is covering the quality control tests of some brands of Paracetamol injections that are available in Lagos, Nigeria.

MATERIALS AND METHODS

Fifteen (15) different brands of Paracetamol injection were purchased from various Pharmacies across different areas in Lagos, Nigeria and were labelled as table 1. Sterility testing and assessment of active pharmaceutical ingredient (API) content through HPLC were carried out on them.

Table 1: Coded samples of paracetamol injections showing their drug information

Sample Code	Country of Manufacture	Batch No	Manufacture Date	Expiry Date	NAFDAC Reg No
001	China	211076	10/2021	09/2024	C4-0990
002	China	210149	01/2021	12/2023	A4-8944
003	China	210150	01/2021	12/2023	A4-7392
004	China	220138	01/2022	12/2024	B4-3487
005	China	167210301	03/2021	03/2024	B4-9693

006	China	220926	09/2022	09/2025	B4-8510
007	China	211138	11/2021	11/2024	B4-8504
008	China	210416	04/2021	04/2024	B4-6825
009	China	211078	10/2021	10/2024	B4-7936
010	China	167220105	01/2022	01/2025	B4-9693
011	China	167220801	08/2022	08/2025	B4-9098
012	China	201215	12/2020	11/2023	A4-8466
013	China	201227	12/2020	12/2023	B4-8504
014	China	167210601	06/2021	06/2024	B4-9693
015	China	210535	05/2021	05/2024	C4-1507

Preparation of Buffer for Mobile Phase

The salt Potassium Dihydrogen Phosphate 0.680 g was weighed using an analytical balance, it was then transferred into a 500 mL volumetric flask, and dissolved completely with addition of distilled water to the 500 mL mark to obtain 10mM KH_2PO_4.The pH was adjusted to 3.5 by adding phosphoric acid. This was then filtered and deaerated with a sonicator. The mobile phase used was Methanol: 10mM KH_2PO_4 (60:40).

Preparation of stock and gradient concentrations of paracetamol standard

A diluent of methanol: distilled water (50: 50) was prepared in a clean beaker and properly labelled. Then 10 mg of paracetamol standard was weighed using an analytical balance and then transferred into a 100 mL volumetric flask and made up to the 100 mL mark with the diluent. It was then sonicated for 5 minutes to obtain 100 µg/mL of the standard solution. The gradient concentrations were prepared by taking 50, 100, 150, 200, 250, 300 µL of the stock solution containing 100 µg/mL and made them to 1000 µL to achieve the gradient working concentration of 5, 10, 15, 20, 25, 30 µg/mL respectively.

Construction of Calibration Curve

The gradient concentration (10 µL) of the standard solution containing 5-30 µg/mL of paracetamol solution was injected into the HPLC in a duplicate and the chromatogram was recorded. Calibration graph was constructed by plotting the mean peak area versus concentration of paracetamol standard. The concentration of the unknown was calculated from the regression equation derived from the concentration and peak area data.

Preparation of Paracetamol Injection Samples

The paracetamol injection contains 300 mg in 2 mL in an ampoule. A quantity equivalent to 15 mg was measured and transferred into a 100 mL volumetric flask and the diluent (methanol: water, 50:50 %) HPLC grade was added up to the 100 mL mark and sonicated thoroughly to obtain the stock concentration of 150 µg/mL. To prepare the target concentration of 15 µg/mL using the formula 1 below, 100 µL of the stock concentration (150 µg/mL) was transferred into a 1000 mL volumetric flask and the diluent was added up to the 1000 mL mark. It was then filtered with a Millipore syringe filter (0.45 µm) and sonicated and it was then transferred into the HPLC vial and 10 µL was injected into the HPLC.

$C_1V_1=C_2V_2$ …….. Formula 1

Chromatographic Conditions

Chromatographic analysis was carried out at room temperature using the Agilent technologies® HPLC 1200 series. The column used was Agilent® Zorbax SB-C8, 4.6 × 150 mm, 5 µm diameter particle size. The utilized mobile phase consist of methanol: water (60: 40) % at pH 3.2 where the pH adjustment was achieved using phosphoric acid. Filtration of the mobile phase was carried out using 0.45 µm membrane filter, then deaerated ultrasonically prior to injection. The flow rate, injection volume, wavelength and retention time were 1.2 mL/minute, 10 µL, 243 nm and 1.351 minutes respectively.

Validation of HPLC analytical method

The HPLC analytical method used was validated for linearity, recovery and precision using ICH procedure [16].

Diluent Preparation for sterility test

A diluent of tween 80 solution was prepared by weighing 30 g of tween with an analytical balance and boiled water was slowly added to it to make up to the 1000 mL mark on the volumetric flask to give a concentration of 3 % tween 80 while mixing by shaking vigorously and bubbles were formed during mixing. The prepared tween 80 solution (80 mL) was then measured using a measuring cylinder into 100 mL amber coloured bottles and sterilized by autoclaving at 121 ^{0}C for 15 minutes.

Media Preparation for microbial test

The agar media were prepared according to the method of preparation stated by the manufacturer. The different agars used were Eosin Methylene Blue Agar (EMBA), Mannitol Salt Agar (MSA), Reinforced Clostridial Agar (RCA) (Sigma-Aldrich®), Salmonella Shigella Agar (SSA), Tryptone Soy Agar (TSA), Sabouraud Dextrose Agar (SDA), Thiosulfate Citrate Bile Sucrose (TCBS) Agar, MacConkey Agar (MAC) and Cetrimide Agar and are prepared as follows;

Eosin Methylene Blue Agar (EMBA)

Eosin Methylene Blue Agar (EMBA) was prepared by weighing 37.5 g of the powder, dispersed in 1 L of distilled water. After melting at 100 ^{0}C in a water bath, it was swirl to mix then sterilized by autoclaving at 121 ^{0}C for 15 minutes. Cool to 50 ^{0}C and agitated to ensure uniform distribution of the flocculant precipitate before pouring into the petri dishes. This was used to detect both gram-positive and gram-negative bacteria especially those from coliforms and fecal coliforms.

Mannitol Salt Agar (MSA)

Mannitol Salt Agar (MSA) was prepared by weighing 111.02 g of the powder, dispersed in 1 L of distilled water. It was heated in a water bath at 100 ^{0}C to dissolve completely and sterilized by autoclaving at 121 ^{0}C for 15 minutes. Cool to 50 ^{0}C before pouring into the petri dishes. This was used to detect the growth of pathogenic staphylococci.

Reinforced Clostridial Agar (RCA)

Reinforced Clostridial Agar (RCA) was prepared by weighing 51 g of the powder in 1 L of distilled water and boiled to dissolve completely, sterilized by autoclaving at 121 ^{0}C for 15 minutes and then allowed to cool at the laboratory ambient temperature before pouring into sterile petri dishes. This was used to detect clostridia and other anaerobic and facultative bacteria in sealed products.

Salmonella Shigella Agar (SSA)

Salmonella Shigella Agar (SSA) was prepared by weighing 60 g of powder into 1000 mL distilled water and boiled in a water bath with frequent agitation to completely dissolve them. It was then cooled to about 50 ^{0}C and poured into sterile petri dishes. This was used in the isolation of *Salmonella* and some *Shigella* species from pathological specimens, suspected foodstuffs.

Tryptone Soy Agar (TSA)

Tryptone Soy Agar (TSA) was prepared by weighing 40 g of powder into 1000 mL of distilled water. It was heated in a water bath at 100 ^{0}C to dissolve completely and sterilized by autoclaving at 121 ^{0}C for 15 minutes. Cooled to 50 ^{0}C before pouring into the petri dishes. This was used to detect the growth of most gram–negative bacteria and non-fastidious gram-positive as well as many yeasts and moulds.

Sabouraud Dextrose Agar (SDA)

Sabouraud Dextrose Agar (SDA) was prepared by weighing 65 g of powder into 1000 mL of distilled water. It was heated in a water bath at 100 ^{0}C to dissolve completely and sterilized by autoclaving at 121 ^{0}C for 15 minutes. Cool to 50 ^{0}C before pouring into the petri dishes. This was used to detect the growth of pathogenic and non-pathogenic fungi.

Thiosulfate Citrate Bile Sucrose (TCBS) Agar

Thiosulfate Citrate Bile Sucrose (TCBS) Agar was prepared by weighing 89.08 g of powder into 1000 mL distilled water and boiled in a water bath with frequent agitation to completely dissolve them. It was then cooled to about 50 ^{0}C and poured into sterile petri dishes. This was used in the isolation of *Vibrio cholerae* and *Vibrio parahaemolyticus* as well as other Vibrio species

MacConkey Agar (MAC)

MacConkey Agar (MAC) was prepared by weighing 55.07 g of powder into 1000 mL of distilled water. It was heated in a water bath at 100 ^{0}C to dissolve completely and sterilized by autoclaving at 121 ^{0}C for 15 minutes. Cool to 50 ^{0}C before pouring into the petri dishes. This was used for the isolation of gram-negative enteric bacteria.

Cetrimide Agar

Cetrimide Agar was prepared by weighing 46.7 g of powder into 1000 mL of distilled water containing glycerol. It was heated in a water bath at 100 ^{0}C to dissolve completely and sterilized by autoclaving at 121 ^{0}C for 15 minutes. Cool to 50 ^{0}C before pouring into the petri dishes. This was used to detect the growth of *Pseudomonas aeruginosa*.

Sample Preparation for Sterility testing

The two working dilutions were one-in-ten (1 in 10) and one-in-hundred (1 in 100) dilutions of the sample. This procedure was carried out in the Biosafety cabinet to prevent microorganism contamination from the atmosphere. 10 mL of the paracetamol injection sample was added to 90 mL of the diluents (tween 80) in a 100 mL amber coloured bottle to make 1 in 10 dilution. With the aid of a measuring cylinder, 10 mL of the 1 in 10 dilution was added to another 90 mL of the diluents (tween 80) in a 100 mL amber coloured bottle to make 1 in 100 dilution and labelled appropriately. It was shaken for uniform mixing and 1 mL of each dilution was aseptically transferred to appropriately labeled petri dishes and they were overlayed with 19 mL of the already prepared sterile agars type and allowed to set. The petri dishes for bacterial load were incubated at 37 ^{0}C and observed daily for 72 hours. The petri dishes for fungal load were incubated at 25 ^{0}C and observed daily for 7 days. The petri dishes were observed for the presence or absence of microbial growth.

Statistical Analysis

Descriptive statistics was employed to determine the mean value of the peak area calculated using Microsoft excel 2013 software and the graphical representation was generated using Microsoft excel sheets.

RESULTS

Of the 15 brands of paracetamol injection assayed for active ingredient, two (2) did not comply with USP pharmacopoeia assay requirements. The calibration plot equation (Figure 2) used for estimation of assay of the paracetamol injection is y = 22.913x with coefficient of determination (R^2 = 0.99), where y is peak area and x is the concentration. The linearity of the assay was determined by assessing the coefficient of determination showed a perfect correlation between the concentration measured and the response which is the peak area. The recovery rate was 98 % while intra-day and inter-day precision were 5 and 10 %. The retention time of paracetamol standard preparations gave 1.353 minutes while paracetamol injection samples eluted at retention time of 1.365 minutes as shown in figure 1a and 1b. These chromatogram authenticated the presence of paracetamol in the injection of the examined brands as found in the paracetamol injection standard. After the fifth day for bacteria and the seventh day for fungi sterility testing, no turbidity was noticed in the culture medium, indicating the absence of growth of microorganisms. Both the assay of active ingredient and sterility testing of paracetamol injection samples are summarized in table 2.

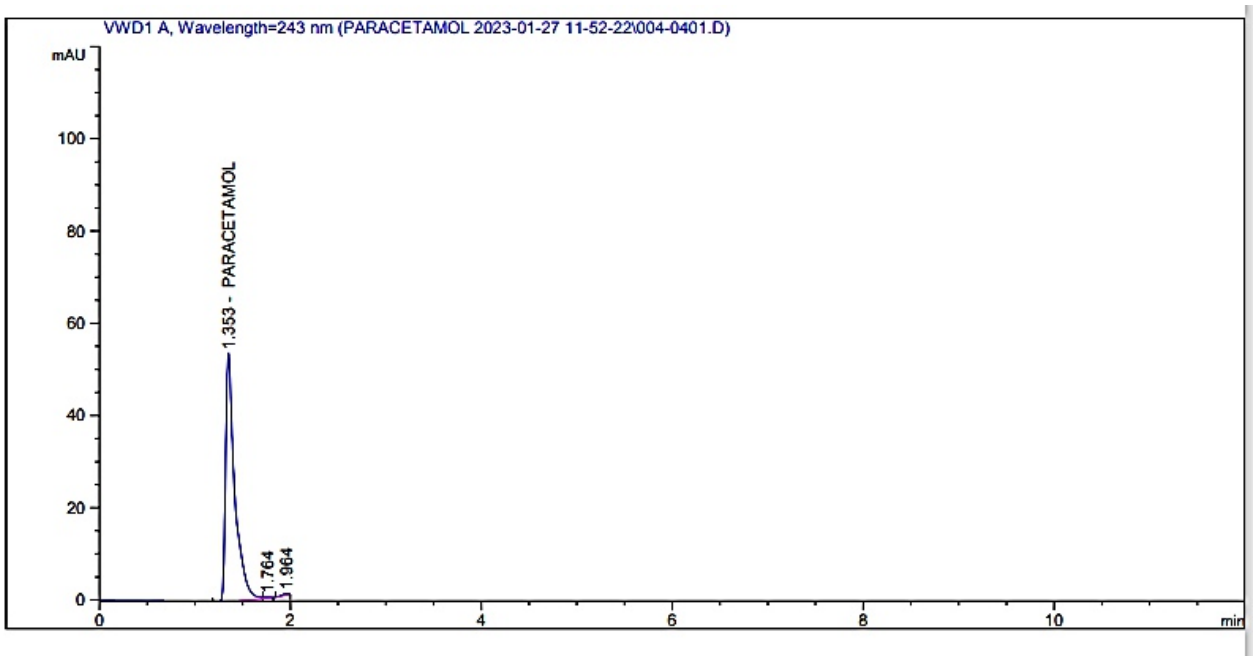

Figure 1a:Chromatographic peak for paracetamol standard solution (15 µg/mL) at a retention time of 1.353 minutes

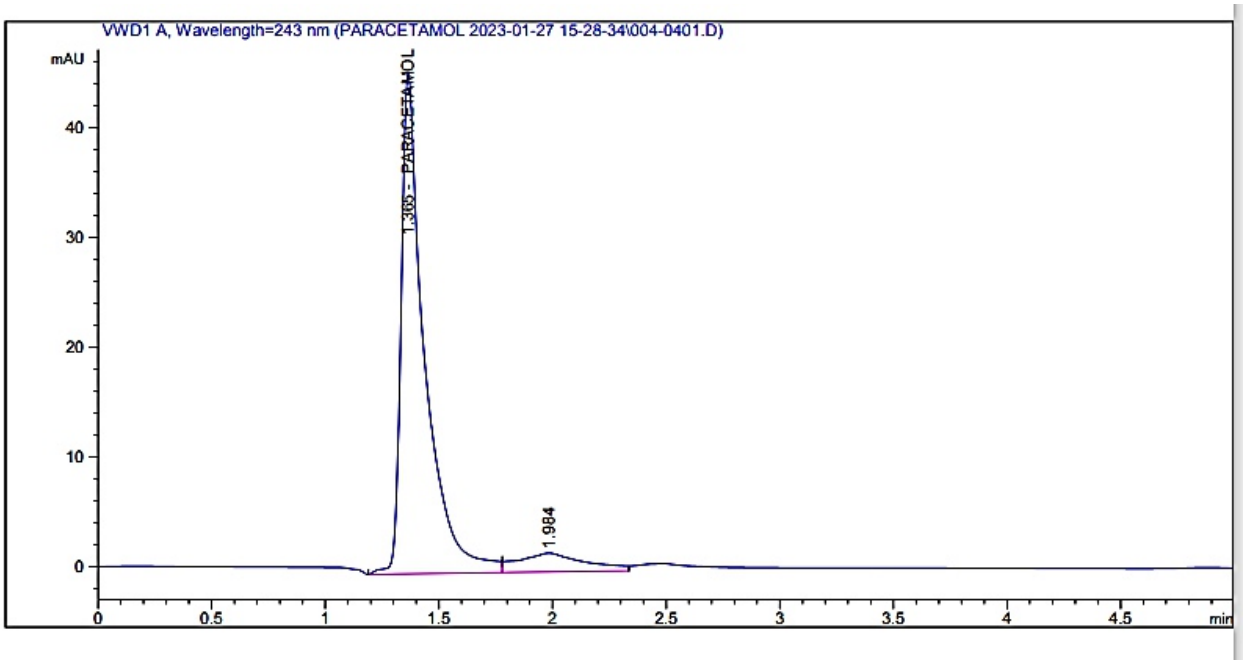

Figure 1b:Chromatographic peak for paracetamol injection sample (Vinco®) (15 µg/mL) at a retention time of 1.365 minute

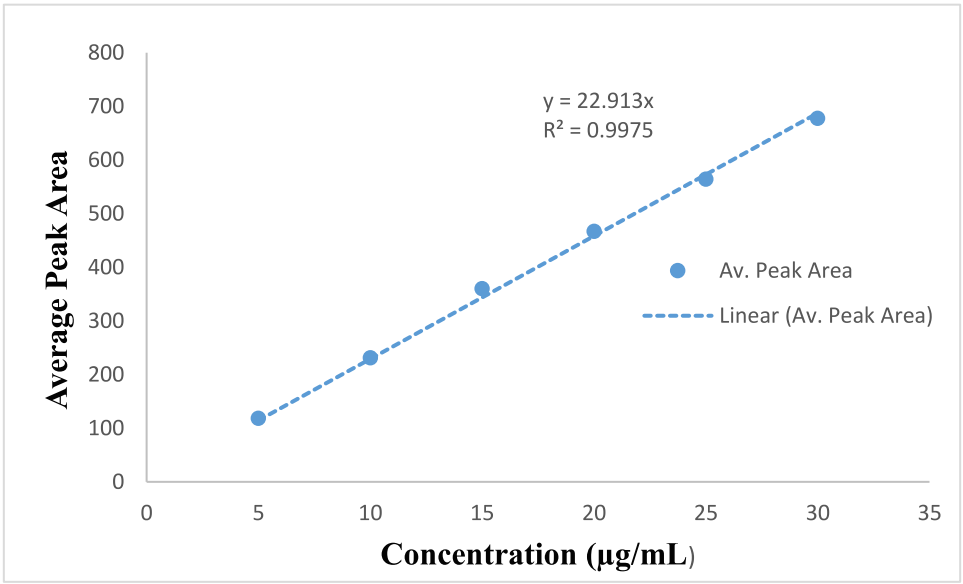

Figure 2: Calibration plot of paracetamol reference standard

Table 2:Percentage purity of 15 brands of paracetamol injection sample (USP: 90-110 %) and Plate Count Results for the paracetamol injection samples for sterility testing

Sample code	% purity	Sterility Test Medium									Inference
		EMBA	MSA	RCA	SSA	TSA	SDA	TCBS	MAC	CET	
001	98.94	NG	NG	NG	NG	NG	NG	NG	NG	NG	Passed
002	105.00	NG	NG	NG	NG	NG	NG	NG	NG	NG	Passed
003	98.59	NG	NG	NG	NG	NG	NG	NG	NG	NG	Passed
004	101.67	NG	NG	NG	NG	NG	NG	NG	NG	NG	Passed
005	120.49	NG	NG	NG	NG	NG	NG	NG	NG	NG	Failed
006	104.94	NG	NG	NG	NG	NG	NG	NG	NG	NG	Passed
007	95.38	NG	NG	NG	NG	NG	NG	NG	NG	NG	Passed
008	96.25	NG	NG	NG	NG	NG	NG	NG	NG	NG	Passed
009	103.45	NG	NG	NG	NG	NG	NG	NG	NG	NG	Passed
010	104.15	NG	NG	NG	NG	NG	NG	NG	NG	NG	Passed
011	95.52	NG	NG	NG	NG	NG	NG	NG	NG	NG	Passed
012	110.57	NG	NG	NG	NG	NG	NG	NG	NG	NG	Passed
013	98.77	NG	NG	NG	NG	NG	NG	NG	NG	NG	Passed
014	111.55	NG	NG	NG	NG	NG	NG	NG	NG	NG	Failed
015	101.88	NG	NG	NG	NG	NG	NG	NG	NG	NG	Passed

NG represents: NO GROWTH DETECTED

DISCUSSION

The rise in counterfeit drugs in Nigeria has highlighted the importance of ensuring the quality of injections for public health and safety. Substandard or counterfeit paracetamol injections can seriously endanger patients, leading to treatment failures and potential harm. The study evaluated the quality parameters of various brands of paracetamol injection, using USP pharmacopeia procedures[17] to conduct tests from percentage purity to sterility. Results of the assay showed that Sample 005 had the highest content (120.49%) and Sample 007 had the lowest (95.38%). 86.67% of the brands contained paracetamol within 100% ±10% of the label claim. However, 13.33% did not comply with USP pharmacopeia requirements. The non-compliance of sample 005 and sample 014 with the official compendium may stem from substandard manufacturing practices employed during the production process and this emphasizes the necessity for the relevant regulatory agency to diligently monitor the influx of pharmaceuticals into the market.

Sterility testing was performed to ensure no viable contaminating microorganisms were present in the sterile final product. Different agars were used to detect and isolate various microorganisms, and after the designated culture periods, no growth of microorganisms was observed in any of the samples.

The agars used and the microorganism in which they can detect and isolate are Eosin Methylene Blue Agar (EMBA) which is used to detect both gram-positive and gram-negative bacteria, particularly coliforms and fecal coliforms that may be introduced by production workers during the manufacturing of sterile products. This agar can detect organisms such as Escherichia coli, Klebsiella spp, Salmonella spp, Staphylococcus aureus, and Enterococcus faecalis. Mannitol Salt Agar (MSA) is employed to identify the growth of pathogenic staphylococci, while Reinforced Clostridial Agar (RCA) is used to detect clostridia and other anaerobic and facultative bacteria in sealed products. Salmonella Shigella Agar (SSA) is utilized to isolate Salmonella and some Shigella species from pathological specimens, and Trypticase Soy Agar (TSA) is used to detect the growth of most gram-negative bacteria, non-fastidious gram-positive bacteria, as well as many yeasts and molds. Sabouraud Dextrose Agar (SDA) is employed to detect the growth of pathogenic and non-pathogenic fungi, while Thiosulfate Citrate Bile Sucrose (TCBS) Agar is highly selective for the isolation of Vibrio cholerae, Vibrio parahaemolyticus, and other Vibrio species. MacConkey Agar (MAC) is used for the isolation of gram-negative enteric bacteria, and Cetrimide Agar is used to detect the growth of Pseudomonas aeruginosa.

The study's credibility was enhanced by the anonymous and in situ samplings, which were collected from different areas in Lagos, Nigeria. Common brands from various manufacturers were included in the sample, and the analysis was conducted using validated methods, with consideration for routine testing in developing countries like Nigeria.

CONCLUSION

The findings of this study indicate that 86.67% of the sampled paracetamol injections conformed to the USP specification, while 13.33% did not comply with the USP specification for API content. Notably, all paracetamol injection samples demonstrated zero microbial load within the acceptable limits of the USP. Post-market evaluation plays a crucial role in assessing the quality, therapeutic effectiveness, and safety of approved medicines for end-users. It is imperative for regulatory bodies to enhance monitoring programs and post-marketing surveillance, as well as enforce Good Manufacturing Practices and storage facilities to uphold and enhance the quality of pharmaceutical products in the Lagos market. The relevant authority must take necessary steps to ensure ongoing product quality, including addressing the non-compliance of the two brands of paracetamol injection with the required specification standard.

The authors declare no conflicts of interest.

ACKNOWLEDGEMENT

I wish to extend my sincere appreciation to my supervisor, Professor M.O Akinleye, whose invaluable guidance and counsel were instrumental in the successful completion of this work. His unwavering support steered us through the various phases of conducting and documenting this research. Additionally, I am grateful to God for granting us the strength to surmount all challenges. It is through His benevolence and protection that we were able to bring this research to fruition.

REFERENCES

1. Teklu L, Adugna E, Ashenef A (2014) Quality Evaluation of Paracetamol Tablets Obtained From the Common Shops (Kiosks) In Addis Ababa, Ethiopia. *International Journal of Pharmaceutical Sciences* and *Research* 5(8): 3502-10. doi: 10.13040/IJPSR.0975-8232.5

(8).3502-10.
2. *Mosharraf, Z (2012) Determination of the Quality Control Parameters of Paracetamol Tablets in Bangladesh Pharma Market.[*Google Scholar]
3. Kar A, Amin MN, Hossain MS, Mukul MEH, Rashed MSU, Ibrahim M (2015) Quality analysis of different marketed brands of paracetamol available in Bangladesh. *International Current Pharmaceutical Journal* 4(9): 432 – 435. Doi: 10.3329/icpj.v4i9.24473
4. Salisu I, Muazu S, Sabi'u J, Bello S (2017) Assessment of the quality of paracetamol tablet brands sold in Katsina Metropolis Nigeria. *MAYFEB Journal of Chemistry and Chemical Engineering* - ISSN 2560-693X Vol 2 - Pages 1-10
5. Attaran A, Barry D, Basheer S, Bate R, Benton D, Chauvin J, Garrett L, Kickbusch I, Kohler JC, Midha K, Newton PN, Nishtar S, Orhii P, McKee M (2012) How to achieve international action on falsified and substandard medicines. *BMJ*. 345:e7381. doi: 10.1136/bmj.e7381
6. Eraj A, Ayub M (2015) Quality analysis of different brands of Acetaminophen available in the market. *International Journal of Innovative Pharmaceutical Sciences and Research* 3 (10):1457–1462. [Google Scholar]
7. Sahle, SB, Ayane, AT, Wabe, NT (2012). Comparative quality evaluation of paracetamol tablet marketed in Somali region of Ethiopia. *International Journal of Pharmaceutical Sciences and Research*, *3*(2), 545. http://dx.doi.org/10.13040/IJPSR.0975-8232.3(2).545-50
8. Kibwage IO (2008) Counterfeiting of Drugs and the Necessity of Quality Control Systems in Developing Countries. An invited lecture Delivered at the Interdisciplinary Courses on Development and Cultures at the Invitation of CADES, Katholieke Universiteit Leuven February 26. http://hdl.handle.net/11295/52064
9. Shankar P, Partha P, Shenoy N (2002) Self-medication and non-doctor prescription practices in Pokhara valley, Western Nepal: a questionnaire-based study. *BMC Family Practice* 3(1):1–7. doi: 10.1186/1471-2296-3-17 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
10. Okumura J, Wakai S, Umenai T (2002) Drug utilisation and self-medication in rural communities in Vietnam. *Social Science & Medicine* 54(12):1875–1886. doi: 10.1016/S0277-9536(01)00155-1 [PubMed] [CrossRef] [Google Scholar]
11. World Health Organization. (2010). Counterfeit medical products. Sixty-Third world assembly. 22nd April. A63/23.
12. Olaniyi AA, Babalola CP, Oladehinde FO, Adegoke AO (2001) Towards Better Quality Assurance of Drugs. Proceedings of 4th National Workshop, Department of Pharmaceutical Chemistry, University of Ibadan. pp 59-60.
13. Remington (2001) the Science and Practice of Pharmacy, 20th ed.; Troy, D.B., Ed.; Lippincott Williams & Wilkins: Philadelphia, pp 473-474.
14. Blackstone EA, Fuhr JP Jr, Pociask S (2014) The health and economic effects of counterfeit drugs. *American Health & Drug Benefits* 7 (4):216-24.
15. Banker GS (2002) Drug Products: Their role in the treatment of disease, their quality and their status and future as drug-delivery systems In GS Banker, CT Rhodes (Eds) Modern pharmaceutics. New York: Marcel Dekker, Inc; 1-21. PMID: 24389146
16. International Conference on Harmonisation ICH (1997). Guideline on the Validation of Analytical Procedure: Methodology; Availbility. The food and drug administration published this guideline on May 19; (62) 27464 - 27467 (62 FR 27463).
17. United States Pharmacopeia (USP) (2018). US Pharmacopeia National Formulary, USP 41 NF 36. US Pharmacopeia Convention, United Book Press Inc. Rockville, Baltimore, MD.