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# UV-Spectroscopic Analysis and *In vitro* Equivalence Study of Generic Paracetamol Tablets under Biowaiver Conditions

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**Abstract**
The current study aimed to determine the in vitro equivalence of generic paracetamol tablets applying UV-spectroscopic analysis and biowaiver settings. In-vitro equivalency investigations, including weight uniformity, disintegration, dissolution, hardness, and friability assays, and UV-spectroscopic analysis, were utilized to determine the compliance of various paracetamol brands to the innovator standard. The tablets' hardness ranged from 6.7 ± 0.42 to 9.5 ± 0.33, with P1 and P5 having the highest and lowest values, respectively. The percentage friability ranged from 0.0294 ± 0.003 to 0.1696 ± 0.01, with P3 ranking higher than P2, P4, P5, and P1. The brands fell well below the USP-specified limit of < 1.0%. The disintegration time ranged between 6.4 and 9.1 minutes. Within 30 minutes, the dissolution profile showed percentage releases ranging from 79.89 to 87.88%. Except for P2, all brands met the BP criterion for paracetamol, with quantities ranging from 87.17 ± 0.32 to 100.44 ± 0.17%. The innovator brand P5 contained 96.94 ± 0.33% of the label claim of 500 mg/tablet, while generics ranged from 87.17 ± 0.32 to 100.44 ± 0.17%. There was no significant difference between label claims on brands of paracetamol and computed assay values between the P5 (innovator) and P1, P2, P3, and P4 (generics) in the recovery assay. The RSD and SEM values ranged from 0.17 to 0.37, and 0.49 to 0.96. All of the paracetamol brands examined in this study passed the disintegration test requirements established by the USP and BP, and the procedure can be utilized for routine quality control of solid dose medications.

**Keywords:** Paracetamol, Fever, Analgesic, Anti-inflammatory, Biowaiver, Equivalence

## 1. Introduction

Paracetamol is a non-opioid analgesic and antipyretic used to treat fever, mild to moderate pain, and post-surgical discomfort [1-3, 4]. Combining paracetamol with other opioids or non-opioid analgesic medications can augment its pharmacological effects [5]. Paracetamol provides only modest and clinically inconsequential pain relief in osteoarthritis, and there is insufficient evidence to support its use in cancer, low back pain, or neuropathic pain [6-10]. Paracetamol is a safe alternative for patients who cannot tolerate the stomach-irritating side effects of nonsteroidal anti-inflammatory drugs (NSAIDs) [11-13]. Chronic paracetamol use can lead to low hemoglobin levels, indicating inaccurate liver function tests and gastrointestinal hemorrhage [14]. Excessive doses can cause toxicity, including liver failure and paracetamol poisoning. Paracetamol poisoning is a leading cause of acute liver failure in several Western nations [15–17]. It can also result in deadly skin allergies such as toxic epidermal necrolysis and Stevens-Johnson syndrome [18].

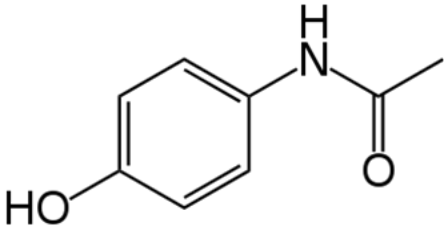


*Figure 1: Structure of Paracetamol (para-acetaminophen).*

Paracetamol appears to exert therapeutic effects by suppressing COX (cyclooxygenase) enzymes and the activity of its metabolite, N-arachidonoylphenolamine (AM404) [19]. When arachidonic acid and peroxide concentrations are low, paracetamol works on cyclooxygenase enzymes in the same way that selective inhibitors of COX-2 do. It is mostly metabolized by the liver by glucuronidation and sulfation, with the resulting metabolites eliminated in the urine. Approximately 2-5% of the medication is eliminated unaltered in urine [22]. UGT1A1 and UGT1A6 glucuronidate paracetamol, account for 50-70% of its metabolism. The SULT1A1, SULT1A3, and SULT1E1 enzymes convert around 25-35% to sulfate [23]. N-acetyl-p-benzoquinone imine (NAPQI) is a hazardous metabolite that results from the cytochrome P450 (CYP2E1) enzymes pathway (5-15%). At average quantities, glutathione can easily metabolize NAPQI, which causes paracetamol-induced liver injury. The non-toxic conjugate APAP-GSH gets absorbed in the bile and transformed into mercapturic and cysteine conjugates, which are eliminated in the urine [23]. The last process makes use of AM404, which is abundant in animal brains and cerebrospinal fluids of paracetamol users. Fatty acid amide hydrolase in the brain transforms 4-aminophenol, another paracetamol metabolite, into AM404 [19, 24]. The cannabinoid system and TRPV1 are critical to paracetamol's analgesic actions, because AM404 stimulates CB1 and CB2 (cannabinoid) receptors, inhibits the endocannabinoid transporter, and activates TRPV1 [19, 25].

When given orally, it is rapidly absorbed in the small intestinal tract but poorly in the stomach. The rate of absorption is controlled by stomach emptying time, which is typically slowed after eating. The highest plasma levels of paracetamol occurred 20 minutes after fasting and 90 minutes after eating. The bioavailability of paracetamol rises with dosage, from 63% at 500 mg to 89% at 1000 mg [22]. The elimination half-life from plasma is between 1.9 and 2.5 hours, with a distribution volume of about 50 L [20]. Protein binding is low, except in cases of overdose, where it might range from 15% to 21%. Following a normal dose, serum concentrations decrease below 200 μmol/L (30 μg/mL). After 4 hours, the drug level often declines to 66 μmol/L (10 μg/mL) [22, 26]. Paracetamol is harmful to a variety of species [27–29]. Paracetamol is sold as a generic medication under several brand names, including Tylenol and Panadol [30]. In 2021, it was one of the most commonly prescribed medications in the United States, with over 5 million prescriptions [31]. The growing quantity of generic pharmaceuticals in the local pharmaceutical market makes it increasingly difficult for patients and physicians to choose the optimal drug [32]. As a result, there is a need to create simple, brief, and low-cost procedures for routinely assessing the in-vitro bioequivalence of medications generally available on the drug market [33-38]. The current study intends to examine the in vitro equivalency of generic paracetamol tablets using UV-spectroscopy and under biowaiver conditions.

## 2. Materials and Methods

### Materials

### Reagents and Equipment

All the chemicals used were of analytical grade. Pure paracetamol powder (99.88%, secondary standard (donated by Primex Nigeria Ltd., Ikeja, Lagos), Sodium hydroxide pellet manufactured by Lobal Chemie Lab reagents Mumbai 400005 India. Hydrochloric acid (37%) manufactured by Riedel-DeHaan Sigma-Aldris chemical Germany, potassium dihydrogen orthophosphate anhydrous 98% manufactured by Loba Chemie PVT LMT, Disodium hydrogen orthophosphate manufactured by J.T Baker USA. All reagents were prepared using distilled water. Spectrumlab 752pro UV-VIS spectrophotometer, analytical weighing balance, spatula, refrigerator, mortar and pestle, test tube, Monsanto hardness tester, friabilator (Erweka friabilator), separating funnel, dissolution tester. Five

brands of Paracetamol coded - P1, P2, P3, P4, and P5 (innovator) were purchased from KETO DEVINE Pharmacy, Amassoma, Bayelsa state. Their brand names, manufacturing dates, expiry dates, batch numbers, NAFDAC numbers, and strength were documented.

**Methods**

**Table 1:** *In vitro* Equivalence Study

| Test | Methodology |
|---|---|
| **Weight Uniformity Test** | Twenty (20) tablets of various brands of paracetamol were weighed separately using an analytical balance (Ohaus Adventure, USA), and the weights were recorded. The average weight and variation were also calculated [39]. |
| **Hardness Test** | Ten (10) tablets were taken from each batch. The tablet was held within a fixed and movable jaw, and the indicator's reading was adjusted to 0. The force exerted on the tablet's edge was steadily increased by turning the screw knob forward until the tablet broke. The reading was taken from the scale and represents the pressure required in kg/m2 to shatter the tablet [39]. |
| **Friability test** | Ten tablets of each brand were weighed and abraded individually with a friabilator (ERWEKA, Germany). Following 100 spins, the tablets were weighed. The weight loss showed friability, which was expressed in percentage. The percentage friability should not exceed 1% (w/w) [40]. The friability was estimated by measuring the weight difference using the equation below. |
| **Disintegration test** | The disintegration study is critical for evaluating medication release. A disintegration test is used to determine how long it takes for tablets or capsules to disintegrate entirely. Previously, a disintegration test was used to determine the homogeneity of compression characteristics. We now favor this test for optimizing compression qualities. If disintegration time is not uniform, there will be a lack of batch homogeneity and consistency [41]. |

**Determination of maximum wavelength and calibration curve in 0.1M NaOH**

To dissolve the powder, 10 mL of 0.1 M NaOH solution was poured into a 100 mL volumetric flask containing 100 mg of paracetamol standard. The 0.1M NaOH solution was then marked. To obtain a concentration of 10 $\mu gmL^{-1}$, an aliquot of 0.1mL of the solution was transferred to a 10 $mL^{-1}$ volumetric flask and filled to the mark with 0.1M NaOH. This was subsequently scanned in the UV range (200-380 nm). The wavelength with the highest absorption was designated as the $\lambda_{max}$. Concentrations of 2, 4, 6, 8, and 10 ug $mL^{-1}$ were obtained from a stock solution of 1000 µg/mL. The absorbance associated with these amounts was determined at the peak wavelength of the resulting spectrum. Absorbance results were utilized to create a calibration curve for calculating the amount of medication in the formulations.

**Determination of maximum wavelength and calibration curve in 0.1M HCl**

To dissolve the powder, 10 mL of 0.1 M HCl solution was poured into a 100 mL volumetric flask containing 100 mg paracetamol standard. The 0.1M HCl solution was then marked. To obtain a concentration of 10 $\mu gmL^{-1}$, an aliquot of 0.1mL of the solution was transferred to a 10 $mL^{-1}$ volumetric flask and filled to the mark with 0.1M HCl. This was then scanned in the UV range (200-380 nm). The wavelength with the highest absorption was designated as the $\lambda_{max}$. Concentrations of 2, 4, 6, 8, and 10 ug/mL were generated using a stock solution of 1000 µg/mL. The absorbance of these concentrations was measured at the peak wavelength of the produced spectrum. Absorbance results were utilized to create a calibration curve for measuring the medication released during the dissolving test

**Dissolution test and drug release**

Dilute HCl (0.1M HCl): To make 0.1M HCl, transfer 8.5 ml concentrated HCl to a 1000 ml volumetric flask holding a tiny amount of water, then add more distilled water to fill the flask to 1000 ml. The dissolution test was performed using the USP Basket method in six replicates for each brand [39]. The dissolution medium was 900 ml of 0.1M HCl maintained at 37 ± 0.5 ℃. In all tests, 5 mL of dissolving sample was taken at intervals of 0, 5, 10, 15, 30, 45, and 60 minutes and replaced with an equal volume to keep the sink condition. UV spectrophotometry was used to analyze samples after they had been filtered and diluted with the dissolving liquid. The analyte concentration in each aliquot was calculated from a calibration curve [39].

**Application of the method to formulated drugs**

Paracetamol (10 tablets) was crushed into powder, and an equivalent of 500 mg was weighed into a 100 mL volumetric flask, gently agitated with 30 mL of 0.1M NaOH for 3-5 minutes, and filled to the mark with 0.1M NaOH. After filtering, discard the first 5 mL of the filtrate and transfer aliquots of 100, 200, and 300 µL to a 100 mL volumetric flask. Dilute to mark with 0.1M NaOH (representing 5, 10, and 15 µg mL-1). The absorbance of the final solution was measured at 257 nm. The method was repeated for each brand (Innovator and generics), and the percentage content was determined.

**Dissolution profile comparison and bioequivalence of generics to innovator brand**

The US FDA performance validation test requirements [41] were used to compare the dissolving profiles of innovator and generic pharmaceuticals, together with the USP and BP specified limit of at least 80% of the medication discharged within 30 minutes. Furthermore, the independent model technique of difference factor ($f_1$) and similarity factor ($f_2$) was used to examine the dissolution profiles of the generics in comparison to the innovator brand using all-time amplitudes. The FDA and the European Agency for the Evaluation of Medicinal Products (EMEA), through the Committee for Proprietary Medicinal Products (CPMP), have accepted the similarity factor $f_2$ as a criterion for comparing the similarity of two or more dissolution profiles [42]. The use of kinetics - a comparative-dependent model for bioequivalent studies, assuming a first-order kinetic release of active was also adopted.

$$f_1 = \{[\sum_{t=1}^{n} |R_t - T_t|]/[\sum_{t=1}^{n} R_t]\} x100 \quad (1)$$

$$f_2 = 50\, x \log\left\{\left[1 + (\tfrac{1}{n}) \sum_{t=1}^{n} (R_t - T_t)^2\right]^{-0.5} x\ 100\right\} \quad (2)$$

$$\log C = \log C_0 - {}^{kt}/_{2.303} \quad (3)$$

**Data analysis**

The weight uniformity was analyzed using simple statistics, while dissolution profiles of the generics and innovator were done graphically and by calculation using the independent and dependent models. The difference factor ($f_1$), similarity factor ($f_2$), and kinetic drug release variables – release rate constant k, half-life ($t_{1/2}$), correlation coefficient ($R^2$), etc., were determined using Microsoft Excel, 2016.

**Results and Discussion**

Weight variations give some indication of both good manufacturing procedures (GMP) and the amount of the API (active pharmaceutical ingredient) in the formulation [43]. The hardness test is known to influence disintegration time since it indicates how quickly a tablet disintegrates and the active component is released into a medium, followed by absorption in pharmacokinetics. As a result, proper tablet hardness and ability to resist powdering are necessary for drug quality [44]. The hardness of tablets ranged from 6.7 ± 0.42 to 9.5 ± 0.33, with P1 and P5

showing the highest and least values respectively (Figure 2). All brands of paracetamol were found satisfactory. The BP requirement for hardness of uncoated tablets ranges from 4 to 10 kg/m$^2$.

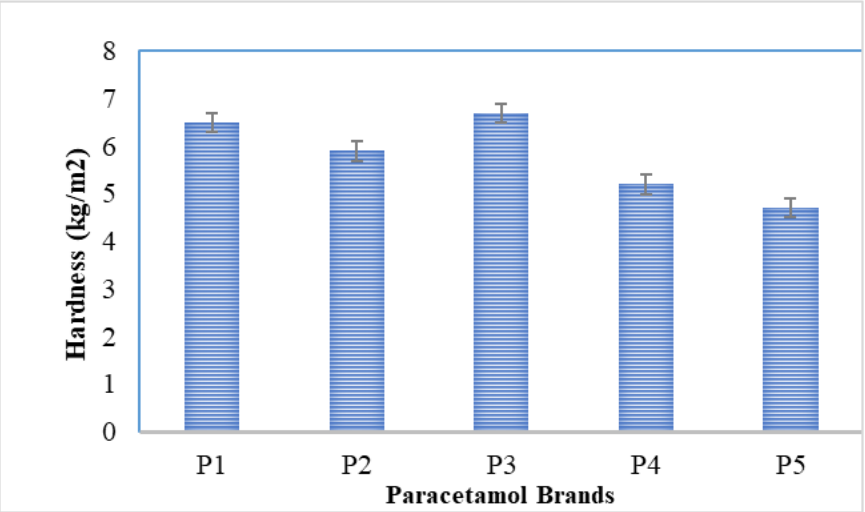


*Figure 2: Hardness of paracetamol tablets*

The percentage of friability for Innovator and generic brands is shown in Figure 3. The friability test is used in conjunction with the hardness test to measure the ability of finished drug products to withstand the pressure that emanates from handling, packaging, transportation, and storage [40]. This is largely dependent on the type and quantity of binders and other excipients used in the tablet formulation. Percentage friability ranged from 0.0294 ± 0.003 to 0.1696 ± 0.01, in the order P3 > P2 > P4>P5 >P1. All brands of paracetamol were significantly below the USP specified limit of ≤ 1.0 % friability.

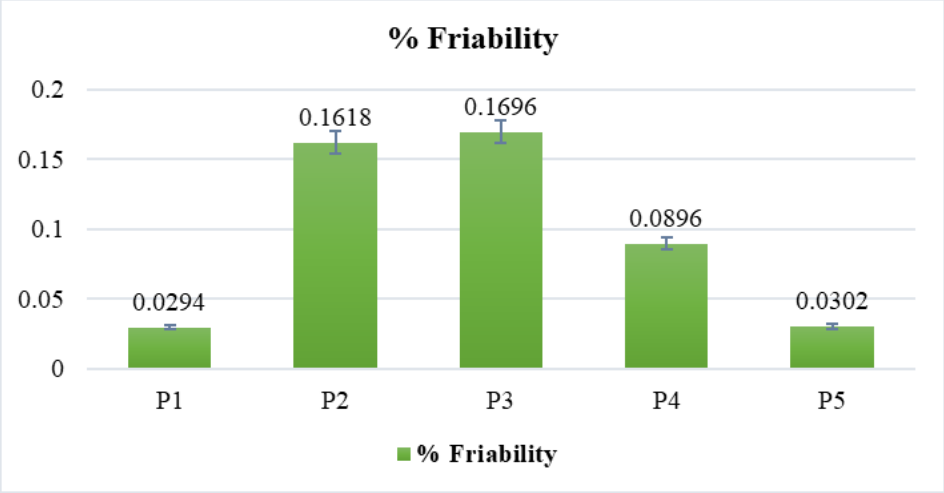


*Figure 3: Friability of paracetamol tablets.*

All brands of paracetamol tablets had disintegration time ranging from 6.4 to 9.1 minutes, this implies that all brands of drug complied with USP/BP specifications for the disintegration test [39, 45].

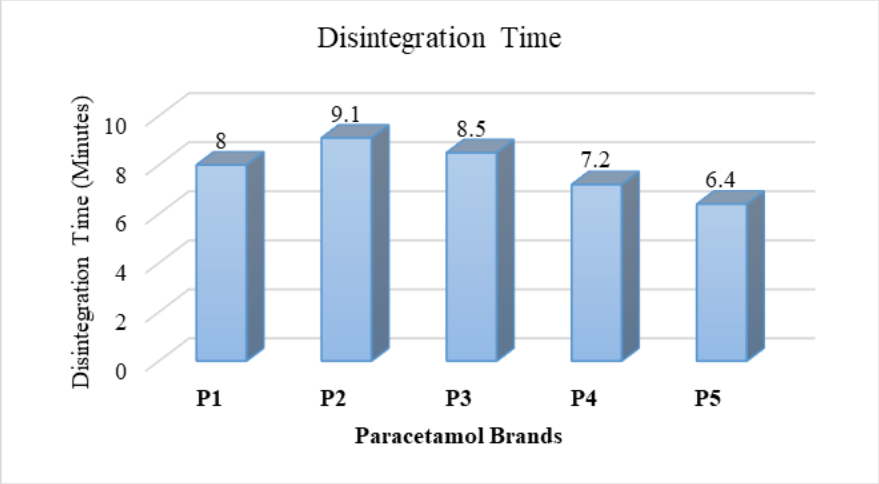


*Figure 4: Disintegration time for innovator and brand paracetamol.*

Figure 5 shows the UV absorption spectra for paracetamol in 0.1 M NaOH and 0.1 M HCl solution, with maxima at 257 and 245 nm respectively. The observed maximum for paracetamol in 0.1 M NaOH medium agrees with the maximum stipulated by the BP (2009). Also, the calibration curves were straight-line graphs, with the equation as Y=0.0724x + 0.0353, with the correlation coefficient ($R^2$) being 0.9983 in 0.1 M NaOH, and Y=0.0816x + 0.1688, $R^2$ = 0.9959 in 0.1M HCl. These $R^2$ values depicted good linearity between absorbance and concentration, with Beer's Law obeyed in the concentration range of 2 – 10 µg $mL^{-1}$. In addition, the slope and intercepts were 0.0724 and 0.0353 respectively in 0.1 M NaOH, with corresponding values in 0.1 M HCl being 0.0816 and 0.1688.

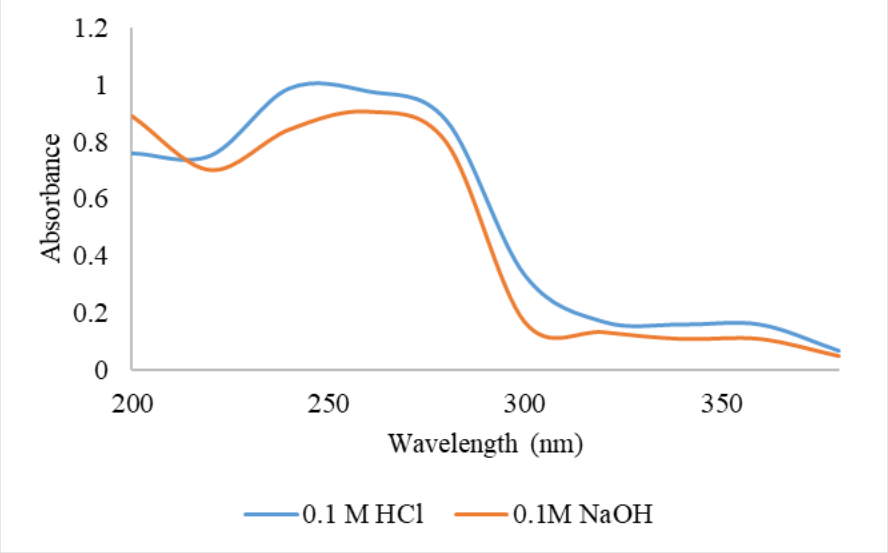


*Figure 5: UV Spectrum of Paracetamol in 0.1 M NaOH and 0.1M HCl*

The therapeutic effectiveness of a dosage form is a function of the amount of drug released into the body fluids, followed by its absorption into the circulatory system [46], thus making the *in-vitro* dissolution (bioequivalence) studies of solid dosage form imperative and by extension determination of the dissolution rate of a dosage form in mimicking the physical action of ingested drugs. Figure 6, shows the dissolution profile of the innovator and the generic brands, with the percentage release of paracetamol ranging from 79.89 – 87.88% within 30 minutes. All brands except P2 (with a percentage release of 79.89% - slightly below the stipulated acceptable minimum of 80%) were considered satisfactory concerning the USP/BP requirements for the dissolution rate of tablet formulation at

$t_{30}$. This implies that all generic brands except P2 could be considered bioequivalent to Innovator brand P5 [34, 47 - 49].

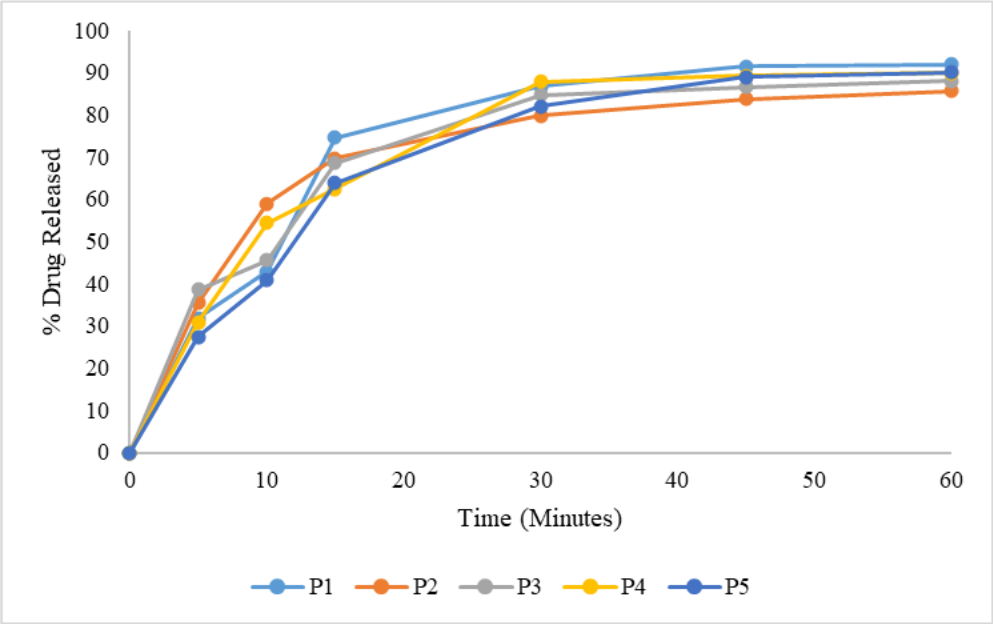


*Figure 6: Dissolution profile of paracetamol brands (Innovator - P5, and generics - P1. P2, P3, and P4*

All brands except P2 complied with the BP specification for solid dosage form paracetamol – as quantities in brands ranged from 87.17 ± 0.32 – 100.44 ± 0.17%. The BP specification for paracetamol tablets ranges from 95 to 105%. [39]. The innovator brand A5 was found to contain 96.94 ± 0.33 % of the label claim per tablet, while the content of paracetamol in the P2 brand was found to be 87.17 ± 0.32%. This corroborates the recent report on substandard paracetamol in the Nigerian market [50, 51]. The paired t-tests for accuracy and precision between the label claim and amount found in brands ranged from 1.399 – 1.496 (Table 2), while values between P5 (innovator) and generics – P1, P2, P3, and P4 were 1.499, 1.500, 1.441 and 1.489 respectively – all test values were < 3.18 (tabulated) at 95% confidence level for 3 replicates. This suggested that no significant difference between label claims on brands of paracetamol and calculated assay values, in addition, there is a difference between the P5 (innovator) and P1, P2, P3, and P4 (generics) respectively in the recovery assay. Furthermore, the relative standard deviation (%RSD, n = 3) and standard error of the mean (SEM) ranged from 0.17 to 0.37 and 0.49 to 0.96 respectively, with the least values recorded by the innovator brand for both properties. These values indicated high reproducibility and reliability, with satisfactory precision and accuracy of method.

**Table 1:** Assay of different brands of Paracetamol

| Sample ID | Label claim (mg/tablet) | Amt found ± Sd(mg/tablet) | %RSD | SEM | Drug Content (%) |
|---|---|---|---|---|---|
| P1 | 500 | 482.84 ± 1.63 | 0.34 | 0.94 | 96.57 ± 0.33 |
| P2 | 500 | 435.84 ± 1.60 | 0.37 | 0.92 | 87.17 ± 0.32 |
| P3 | 500 | 502.18 ± 0.87 | 0.17 | 0.50 | 100.44 ± 0.17 |
| P4 | 500 | 484.72 ± 1.66 | 0.34 | 0.96 | 96.94 ± 0.33 |
| P5 | 500 | 499.42 ± 0.85 | 0.17 | 0.49 | 99.78 ± 0.17 |

**Table 2:** Paired t-test of label claim/Brands and Innovator/Generic Brands

| | BRANDS OF PARACETAMOL | | | | |
|---|---|---|---|---|---|
| | **P1** | **P2** | **P3** | **P4** | **P5** |
| Label Claim(500 mg/tablet) | t = 1.496 | t = 1.460 | t = 1.408 | t = 1.490 | t = 1.399 |
| Innovator (**P5**) | t = 1.499 | t = 1.500 | t = 1.441 | t = 1.498 | Nil |
| Sample size (n) | 3 | 3 | 3 | 3 | 3 |
| Tabulated t-value | 3.18 | 3.18 | 3.18 | 3.18 | 3.18 |

Calculated $f_1$ and $f_2$ values for the *in vitro* dissolution profile (Table 3) ranged from 6.35 - 11.24 and 99.14 - 110.16 respectively. In applying this independent model, two dissolution profiles are considered similar and bioequivalent, only if the $f_1$ value lies between 0 and 15, while $f_2$ must be between 50 and 100 [41]. This implies that all generic brands were comparable to the innovator brand, concerning the difference factor $f_1$, while for similarity factor $f_2$, three of the profiles (P1, P3, and P4) were considered comparable to the innovator brand P5. The $f_2$ values for P2 were> 100. However, some researchers/scientists think that the similarity factor $f_2$ is a biased and conservative estimate, which does not consider the dissolution differences between innovator and generic brands and the unequal time amplitudes during sampling [52, 53].

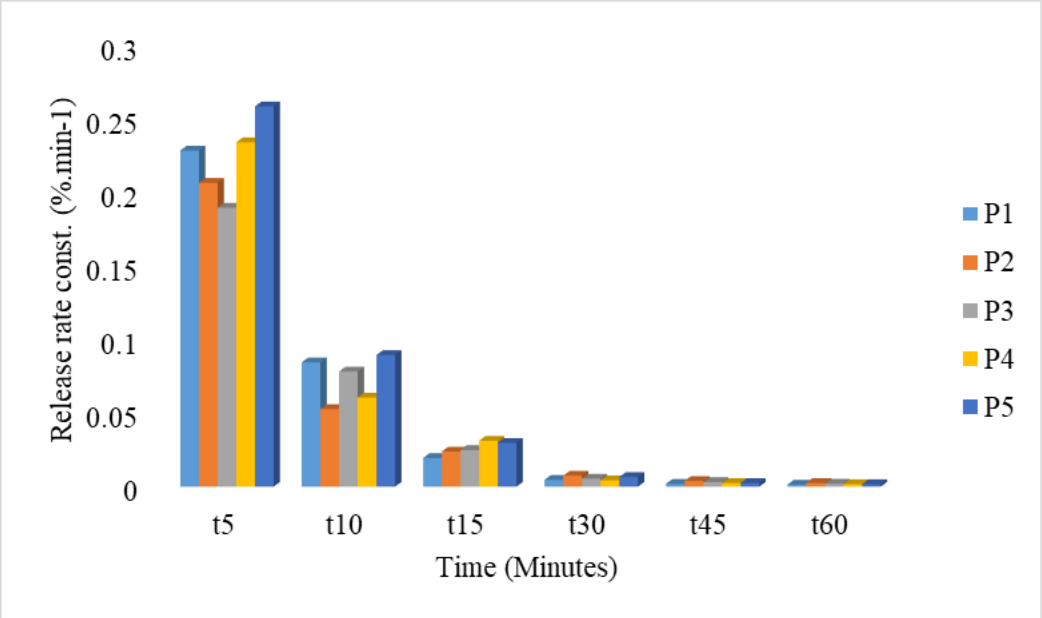


*Figure 7: Drug release rate constant per time amplitude ($t_5$, $t_{10}$, $t_{15}$, $t_{30}$, $t_{45}$, $t_{60}$) ($1^{st}$ order kinetics)*

**Table 3:** *In vitro* kinetic variables for innovator and generic brands

| Sample code | Dependent model | | | Independent model | |
|---|---|---|---|---|---|
| | Release rate const. (*k*) (%.min$^{-1}$) | Half-life ($t_{1/2}$)(min) | Correlation coefficient ($R^2$) | $f_1$ | $f_2$ |
| P1 | 5.69 x $10^{-2}$ | 12.18 | 0.7215 | 6.70 | 99.4 |
| P2 | 4.96 x $10^{-2}$ | 13.97 | 0.7100 | 11.24 | 110.16 |
| P3 | 5.07 x$10^{-2}$ | 13.67 | 0.7612 | 7.17 | 100.32 |
| P4 | 5.59 x$10^{-2}$ | 12.40 | 0.7617 | 6.35 | 102.49 |
| P5 | 6.49 x $10^{-2}$ | 10.68 | 0.8037 | - | - |

Also, a comparative dependent model for bioequivalent studies was applied by assuming first-order kinetics [54], with the drug release rate constant *k* calculated iteratively. The *in vitro* drug release constant *k* for paracetamol over a six-time amplitude ($t_5$ – $t_{60}$) ranges from (4.96 - 6.49) x$10^{-1}$ (%.min$^{-1}$) (Table 3), while half-life ($t_{1/2}$) – time taken for 50% of the drug's label claim to be released, was from 10.68 – 13.97 minutes. The correlation coefficients $R^2$ were all ≥ 0.7100 and implied a strong correlation between the amount of drug released and time. The order of the drug release was P5>P1> P4>P3> P1, respectively.

## Conclusion

The weight uniformity, hardness, friability, and disintegration time of all paracetamol brands examined in this study met the USP/BP standards. The dissolution profiles of the innovator and generic brands were found satisfactory, except for brand P2, which had a percentage release slightly less than the permitted requirement of 80% at $t_{30}$. Based on the in-vitro drug release profile, all generic brands except P2 may be regarded as bioequivalent to Innovator brand P5. There was no significant difference between label claims for paracetamol brands and estimated assay values, nor was there a significant difference between P5 and P1, P2, P3, and P4 (generics) in the recovery assay. The RSD and SEM results indicated strong reproducibility and dependability, as well as satisfactory procedure precision and accuracy. All generic products were comparable to the innovator brand in terms of difference factor $f_1$, whereas two of the profiles (P1 and P3) were regarded as comparable to the innovator brand P5. Thus, this method can serve as a routine check for solid-dose pharmaceutical quality control.

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