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In Vitro–In Vivo Correlation-Based Evaluation of Bioequivalence in Commercial Paracetamol Brands in Nigeria

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ABSTRACT

Background: Paracetamol is a widely used over-the-counter analgesic and antipyretic in Nigeria. Ensuring the quality and therapeutic consistency of oral paracetamol products is a critical public health concern. Bioequivalence assessment is essential to confirm that generic drugs match the reference product in terms of rate and extent of systemic drug exposure.

Methodology: This study employed a convolution-based *in vitro-in vivo* correlation (IVIVC) model to evaluate the bioequivalence of 18 commercial paracetamol tablet brands marketed in Nigeria. The physicochemical properties of the tablets were evaluated, and *in vitro* dissolution tests were conducted. The IVIVC model was used to predict the pharmacokinetic parameters of the tablets.

Results: While most products met basic pharmacopeia standards for assay, disintegration and dissolution, none reached full bioequivalence when compared to worldwide regulatory benchmarks for systemic exposure. Although C_{max} estimates were acceptable for the majority, all generics had high AUC prediction errors, ranging up to 51.8 % indicating potential underexposure and treatment variability.

Conclusions: The findings emphasize the limits of using only in vitro testing to determine therapeutic equivalency, particularly for medicines with fast absorption and broad use, such as paracetamol. Regulatory authorities should consider incorporating IVIVC-based assessments and dissolution similarity indicators into routine post-market surveillance to ensure the quality and efficacy of paracetamol products.

1. Introduction

Paracetamol (acetaminophen) is a widely used first-line analgesic and antipyretic, available over-the-counter (OTC) in various oral formulations including tablets, capsules, and syrups[1]. It is on the borderline between Biopharmaceutics Classification System (BCS) I and III. In Nigeria, it holds a particularly prominent place in pain management. Community surveys report that over 67% of adults use paracetamol, and nearly 70% of students report taking it for headaches or other types of pain[2,3]. This widespread use reflects both its OTC availability and the high burden of self-managed pain and fever in the country. Given its ubiquity, ensuring the quality and therapeutic consistency of oral paracetamol products is a critical public

health concern.

Bioequivalence (BE) assessment ensures that a generic drug matches a reference (innovator) product in both the rate and extent of systemic drug exposure[4]. In practical terms, two products are considered bioequivalent when pharmacokinetic parameters, primarily the area under the concentration-time curve (AUC) and maximum plasma concentration (C_{max}), fall within an accepted range, typically 80–125% for the 90% confidence intervals of their geometric mean ratios[5]. Establishing BE confirms that the generic and innovator products are pharmaceutically equivalent, thereby supporting their interchangeability in clinical practice. Consequently, regulatory agencies require well-controlled crossover trials in healthy volunteers to assess BE under fasting conditions.

In contrast, *in vitro* dissolution tests serve as quality control tools and initial screening methods[6]. Dissolution testing can occasionally anticipate BE outcomes, but it does not guarantee *in vivo* performance[7]. For many oral solid dosage forms, particularly those with rapid dissolution and absorption characteristics, good in vitro dissolution behavior in simulated gastric or intestinal fluid is often correlated with acceptable bioavailability[8]. This is especially relevant for oral paracetamol, where variability in gastrointestinal pH, gastric emptying, and first-pass metabolism can influence drug absorption and systemic exposure[9].

An *in vitro–in vivo* correlation (IVIVC) is a mathematical model that links a drug's in vitro dissolution profile to its in vivo absorption or plasma concentration profile[10]. When validated, an IVIVC can allow dissolution testing to serve as a surrogate for human BE studies, thereby reducing the need for repeated clinical trials[11]. IVIVC models are typically developed using either deconvolution (extracting absorption profiles from observed plasma data) or convolution methods[12]. In the convolution approach, the predicted fraction of drug absorbed, derived from in vitro dissolution, is input into a pharmacokinetic model to simulate the plasma concentration-time profile[13]. This is done using known pharmacokinetic parameters such as clearance and volume of distribution. The convolution method is often simpler and more robust than classical deconvolution and has been successfully applied to both extended- and immediate-release formulations.

For immediate-release drugs such as paracetamol, where absorption is rapid and pharmacokinetic parameters are well established, convolution-based IVIVC offers an efficient and reliable means of predicting systemic exposure. A validated IVIVC model demonstrates low prediction error, less than 15 % for AUC and C_{max}, when compared with observed clinical data[14]. When two products exhibit similar dissolution profiles and their convolution-predicted plasma profiles align closely, it provides strong evidence of bioequivalence. Subsequently, this supports the regulatory approval, market authorisation, and rational drug substitution of generic formulations[15].

However, despite the widespread use of generic paracetamol in Nigeria, existing studies have largely concentrated on routine in vitro quality assessments, including content uniformity, tablet hardness, and dissolution, without establishing direct correlations with in vivo pharmacokinetics or therapeutic outcomes. A notable gap persists in the literature concerning the development and application of *in vitro–in vivo* correlation (IVIVC) models, particularly those utilizing the convolution method, to evaluate the bioequivalence of paracetamol products available in the Nigerian market. This study seeks to address that gap by implementing a convolution-based IVIVC framework to assess the bioequivalence of orally administered paracetamol tablets. The objective is to determine whether *in vitro* dissolution data alone can serve as a reliable predictor of therapeutic equivalence or if comprehensive in vivo bioequivalence studies are still warranted for these generic formulations.

2. Materials and Methods

Eighteen brands of paracetamol immediate release tablets (500 mg) were sourced from a retail pharmacy outlet in Abuja metropolis of Nigeria. All brands (A-Q) were compared to an Innovative Brand ®.

All other chemicals and solvents employed in this study were of analytical grade.

Physicochemical evaluations of various batches

Identification test

After 3 minutes of boiling 0.10 g of powdered paracetamol in 10 mL of concentrated hydrochloric acid TS, 10 mL of water was added and allowed to cool; no precipitate developed. When one drop of potassium dichromate TS was applied, a gradually developing violet colour that does not turn red was generated[16].

Weight Variation Test

The uniformity of tablet weight was evaluated using a digital analytical balance (Mettler Toledo, USA). Twenty (20) tablets were individually weighed, and the average weight was calculated. Each tablet's deviation from the average was expressed as a percentage. For tablets with a mean weight of 324 mg or more, not more than two tablets should deviate by more than ±5%, and none by more than ±10%, following the British Pharmacopoeia specifications[17].

Crushing Strength Test

The mechanical resistance of the tablets was determined using a hardness tester (Monsanto Type, India). Ten (10) randomly selected tablets were placed individually between the platens, and the force required to break each tablet diametrically was recorded in kilogram-force (kgF). The average crushing strength and standard deviation were calculated. Although the British Pharmacopoeia does not specify a limit, an acceptable range of 4–10 kgF is generally recommended for uncoated tablets to ensure appropriate handling and disintegration properties[17,18].

Friability Test

Tablet friability was determined using a friabilator (Roche Type, Erweka, Germany). A sample of ten (10) tablets was weighed (initial weight, W_1) and placed in the drum of the friabilator, which was rotated at 25 rpm for 4 minutes (100 revolutions). The tablets were then removed, de-dusted, and reweighed (final weight, W_2). The percentage weight loss was calculated using the formula:

$$\% f = \frac{W1 - W2}{W1} X100$$

A friability value not exceeding 1.0% was considered acceptable per BP guidelines[17].

Disintegration Test

The disintegration time was determined using a USP-compliant disintegration tester (Electrolab ED-2L, India). One tablet was placed in each of the six tubes of the apparatus, which were immersed in distilled water maintained at 37 ± 0.5 °C. No disc was used for uncoated tablets. The basket assembly moved up and down at a fixed rate, and the time taken for each tablet to disintegrate completely, leaving no residue except fragments of insoluble coating, was recorded. According to the British Pharmacopoeia, uncoated tablets should disintegrate within 15 minutes[17].

Assay of Paracetamol Content

Twenty (20) paracetamol tablets were weighed and finely powdered. A portion of the powder equivalent to 0.15 g of paracetamol was transferred into a volumetric flask containing 50 mL of 0.1 M sodium hydroxide. The mixture was diluted with 100 mL of distilled water, shaken vigorously for 15 minutes, and then further diluted to 200 mL with water. The resulting solution was mixed thoroughly and filtered through Whatman No. 1 filter paper. An aliquot of 10 mL of the clear filtrate was diluted to 100 mL with distilled water. From this, 10 mL was further mixed with 10 mL of 0.1 M sodium hydroxide and diluted to 100 mL with water. The absorbance of the final solution was measured at the maximum wavelength of 257 nm using a UV-Visible spectrophotometer (Cary 60, Agilent Technologies), in accordance with Appendix II B of the British Pharmacopoeia. The paracetamol content was calculated using a specific absorbance A (1%, 1 cm) value of 715. The result was expressed as the percentage of the labelled amount of paracetamol in the tablet formulation

In vitro dissolution test

The USP apparatus II at 50 rpm was used to generate the in vitro dissolution profiles. The dissolution tester (RC-6, China) was first subjected to a performance verification test using a prednisone reference tablet to ensure it conforms to USP requirements. The equipment was maintained at 37±0.5°C, and the dissolution medium was 900 mL of phosphate buffer with pH 5.8. Aliquot of 10 mL were withdrawn and replaced at 0.08, 0.17, 0.33, and 0.5 h. The withdrawn portion were filtered with the aid of a 0.45 µm filter paper, and the filtrate analyzed using UV/VIS spectrophotometer (Cary 60, Agilent Technologies) at 257 nm to reflect the extent of drug release. This information was used to extrapolate the discrete amount of drug release, and eventually the expected blood level profile[12].

Pharmacokinetic parameters.

Pharmacokinetic parameters for paracetamol tablets obtained from authentic literature were as follows:

Bioavailability (F) = 0.76; Volume of distribution (Vd)=0.85L/Kg; Half-life ($T_{1/2}$) = 1.5h; Elimination rate

constant (Ke) = 0.11h-¹; Peak plasma concentration (C_{max}) = 6.17 µg/mL; (T_{max}) = 1.06 h; Area Under Curve (AUC) =31.2 µgh/mL; Adult human body weight = 62 kg[12].

Mathematical expression.

Similarity factor (f2) and dissimilarity factor (f1) were calculated as follows:

$$f1 = \left\{ \sum_{t=1}^{n} \frac{[\![Rt - Tt\}}{\{\sum_{t=1}^{n} [\![Rt\}]\!]} \right] x100$$

$$f2 = 50xlog \left\{ 1 + \frac{1}{\left(n \sum_{t-1}^{n} [\![(Rt - Tt)2\}^{\overline{\ }} \, ½]\!] \right)} \right\} x100$$

Where Rt is the percentage of dissolved reference or innovative brand at a given time t, T_t is the percentage of dissolved generic product, while n is the number of time points. Discrete amounts in (mg) were calculated from the percentage of drug release obtained from the dissolution test. The elimination rate was computed using:

$$te = \left(\ln C1 - \frac{\ln[\![C2)}{t2 - t1}]\!] \right.$$

Where the predicted drug amount in blood at times t1 and t2 are C1 and C2, and Ke represents the first-order elimination rate constant. The expected profile in blood level was extrapolated using:

predicted conc. at times = predicted total blood amount ×F/Vd×body wt

F and Vd represent bioavailability and volume of distribution, respectively[12]

$$\%PE = Observed\ parameter - Predictedparameter\ x\ 100/Observed\ parameter$$

And PE depicts predicted error[12].

3. Results

Physicochemical Properties of Paracetamol Tablets

The quality assessment of various paracetamol tablet brands revealed some interesting findings. Upon performing the standard qualitative test, a violet coloration was observed for all batches, confirming the presence of paracetamol. The weight variation across the brands was within the pharmacopeial specifications for tablets weighing 250 mg or more, with percentage relative standard deviations (RSD) ranging from 2.99 % to 9.88 %. While most brands had assay values within the acceptable range of 100 ± 5%, two brands, G and O, failed to meet this requirement, with assay values of 38.3 % and 64.2 % respectively. The hardness test results showed varying level of compliance. The innovator brand R and some other brands had hardness values within or near the acceptable range of 4-10 KgF for conventional tablets. However, brands L and F exceeded the upper limit significantly, with hardness values of 18.36 KgF and 15.15 KgF, respectively. The friability test also revealed some issues. Not all brands complied with the ≤1% limit, with brands I, J, L, M and N exceeding the threshold. Finally, the disintegration test showed a wide range of results, with disintegration times varying from 0.41 minutes to over 15 minutes (Table 1).

Table 1. Physicochemical properties of the different paracetamol tablet brands.

BRANDS	WV (RSD)	A	T (RSD)	D (RSD)	H (SD)	F	Dt (SD)
A	0.547 (4.50)	99.3	5.68 (1.84)	7.20 (0.92)	8.30 (1.96)	0.42	2.19 (0.15)
B	0.572 (3.88)	100.9	3.92 (1.01)	12.93 (0.03)	8.42 (0.94)	0.57	0.41 (0.00)
C	0.557 (5.22)	100.9	4.06 (2.35)	12.60 (0.26)	9.78 (3.62)	0.55	1.35 (0.88)
D	0.565 (5.01)	99.8	4.09 (0.70)	12.76 (0.19)	10.77 (1.76)	0.25	0.98 (0.36)
E	0.558 (5.88)	98.9	4.06 (2.08)	12.52 (0.24)	11.30 (1.77)	0.78	1.84 (0.64)
F	1.135 (2.99)	97.7	7.60 (0.23)	10.23 (2.33)	15.15 (1.47)	0.27	1.03 (0.00)
G	0.486 (9.88)	38.3	8.41 (2.18)	17.92 (0.26)	8.17 (1.57)	0.15	3.14 (0.98)

H	0.574 (4.38)	99.0	9.06 (0.99)	17.88 (0.44)	13.23 (2.44)	0.33	1.31 (0.95)
I	0.609 (4.71)	98.1	4.11 (1.40)	12.09 (0.08)	5.16 (1.04)	2.42	5.89 (2.27)
J	0.536 (3.66)	97.5	4.06 (1.72)	12.66 (0.64)	10.98 (2.68)	1.14	4.61 (0.57)
K	0.576 (3.55)	97.0	4.10 (0.68)	12.54 (0.23)	9.38 (2.21)	0.40	3.77 (1.85)
L	0.560 (4.50)	98.3	4.04 (1.20)	12.39 (0.55)	18.36 (1.96)	1.45	3.45 (0.50)
M	0.538 (4.99)	100.4	4.00 (0.61)	12.60 (1.22)	10.25 (0.91)	1.36	7.60 (4.06)
N	0.546 (8.22)	99.5	4.06 (1.45)	12.57 (0.66)	11.35 (2.13)	2.24	>15
O	0.551 (4.81)	64.2	3.89 (0.88)	12.52 (3.65)	6.63 (2.90)	0.35	1.76 (0.49)
P	0.553 (5.00)	104.3	4.07 (1.37)	12.59 (2.04)	10.83 (1.23)	0.46	2.00 (0.73)
Q	0.551 (4.91)	104.8	4.67 (3.33)	12.77 (2.01)	13.90 (2.86)	0.33	2.26 (0.34)
R	0.664 (4.88)	101.7	2.93 (1.28)	7.86 (0.24)	6.93 (1.01)	0.29	1.32 (0.00)

WV = weight variation (g), A = assay (%) test, T = thickness (mm), D = diameter (mm), H = hardness (KgF), F = friability (%), Dt = disintegration time (min), SD = standard deviation, RSD = relative standard deviation (%)

For dissolution testing, results are presented as cumulative drug release over time. Figure 1a shows brands A–I, while Figure 1b displays brands J–R. While some brands demonstrated rapid and complete dissolution consistent with pharmacopeial standards, others exhibited slower or incomplete release, which could potentially affect bioavailability.

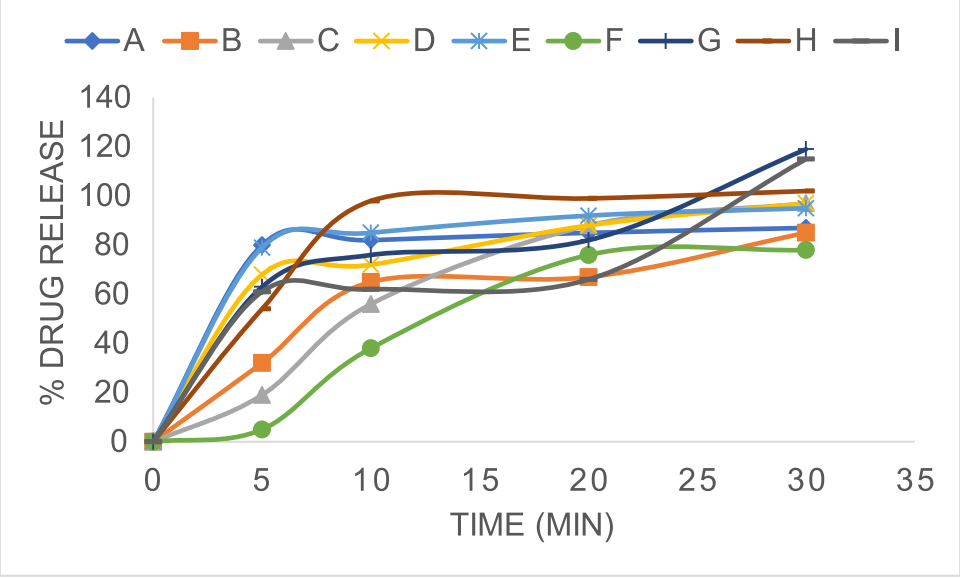

Figure 1a: Dissolution profile of the different brands of paracetamol tablets: A to I;

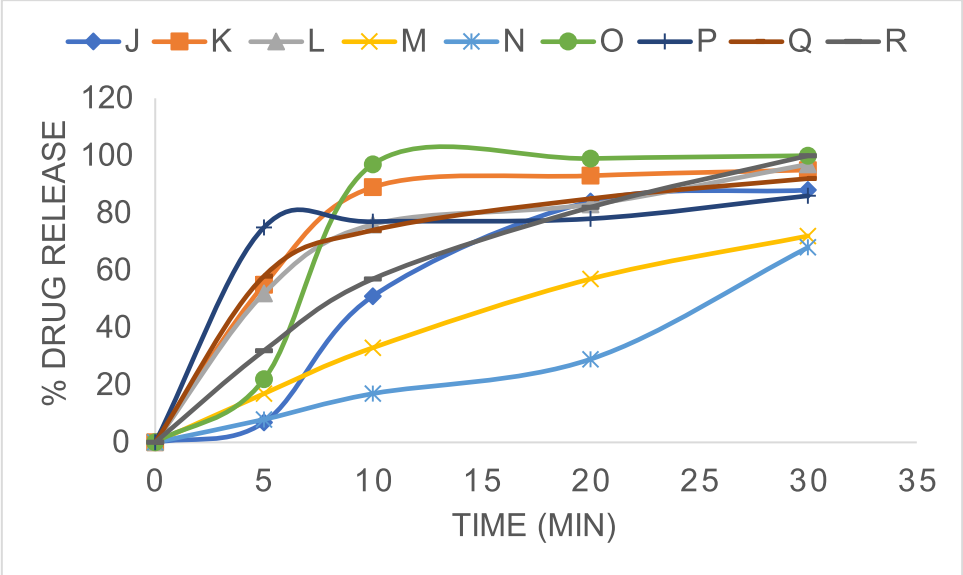

Figure 1b: Dissolution profile of the different brands of paracetamol tablets: J to R

Dissolution Efficiency and Similarity Evaluation

To quantify the differences in dissolution profiles, the model-independent fit factors, f_1 (difference factor) and f_2 (similarity factor), were calculated alongside mean dissolution time (MDT) and dissolution efficiency (DE). Several brands fell below the accepted f_2 threshold of 50, indicating dissimilar release patterns compared to the reference. This highlights possible clinical implications for interchangeability.

Table 2. Dissimilarity factor (f_1), Similarity factor (f_2), mean dissolution time (MDT), and dissolution efficiency (DE) values for the paracetamol tablet brands.

BRANDS	f2	f1	MDT	DE
A	54.5	16.4	0.13	0.18
B	57.0	14.3	0.15	0.14
C	56.0	14.9	0.16	0.13
D	45.8	22.9	0.11	0.19
E	37.1	36.1	0.06	0.27
F	43.8	29.4	0.20	0.07
G	43.1	29.1	0.18	0.09
H	38.6	34.8	0.10	0.23
I	48.4	21.1	0.20	0.05
J	51.6	19.6	0.17	0.12
K	42.5	30.1	0.08	0.26
L	52.7	18.1	0.13	0.33
M	41.6	34.2	0.22	-0.12
N	31.1	54.6	0.31	0.22
O	41.5	26.6	0.11	0.20
P	41.9	27.5	0.10	0.20
Q	49.9	20.6	0.12	0.19
R	-	-	0.19	0.08

In Vitro-In Vivo Correlation (IVIVC) and Pharmacokinetic Predictions

To establish an *in vitro–in vivo* correlation (IVIVC), the percent drug dissolved at various time points for the reference brand (R) was first determined and used to derive the corresponding *in vivo* pharmacokinetic parameters. This correlation formed the basis for estimating drug plasma levels from dissolution data. Table 3 presents the percentage dissolution at specific time points alongside the correlated values within the sampling interval for brand R. These data were then used to calculate drug concentrations over time, as shown in Table 4. The same IVIVC procedure was subsequently applied to brands A to Q to predict their respective pharmacokinetic profiles.

Table 3. Percent dissolution at different times with correlated quantities obtained within the sampling interval for the reference brand (R) .

T	CPR	AR	DAR
0.08	32	160	160
0.17	57	285	125
0.33	82	410	125
0.5	100	500	90

AR = Amount of drug release (mg), CPR = cumulative percent drug release (%), DAR = discrete quantity of drug release within sampling interval (mg), T = time (hours)

Table 4: Calculated drug level at different times from the reference brand ®

T	PBA				PTA	PC
0.08	160				160	2.3072
0.17	158.4238	125			283.4238	4.086971
0.33	155.6599	122.8192	125		403.4792	5.81817
0.5	152.7762	120.5439	122.6842	90	486.0042	7.008181
1	144.6004	114.093	116.1188	85.18366	459.9958	6.633139
2	129.5379	102.2084	104.0232	76.31043	412.0799	5.942193
3	116.0445	91.56176	93.18751	68.36149	369.1553	5.323219
4	103.9566	82.02415	83.48056	61.24056	330.7019	4.768721
5	93.1279	73.48004	74.78473	54.86138	296.254	4.271983
6	83.42715	65.82592	66.99472	49.1467	265.3945	3.826989
7	74.73689	58.96911	60.01615	44.02729	237.7494	3.428347
8	66.95186	52.82654	53.76452	39.44115	212.9841	3.07123
9	59.97776	47.32382	48.16409	35.33273	190.7984	2.751313
10	53.73012	42.39429	43.14704	31.65226	170.9237	2.46472
11	48.13328	37.97825	38.65259	28.35518	153.1193	2.20798
12	43.11943	34.02222	34.62631	25.40154	137.1695	1.977984
13	38.62786	30.47826	31.01943	22.75556	122.8811	1.771946
14	34.60416	27.30347	27.78826	20.38521	110.0811	1.587369

15	30.99958	24.45938	24.89367	18.26177	98.61441	1.42202
16	27.77049	21.91155	22.3006	16.35951	88.34215	1.273894
16	27.77049	21.91155	22.3006	16.35951	88.34215	1.273894
17	24.87775	19.62911	19.97764	14.65541	79.13991	1.141198
18	22.28634	17.58443	17.89665	13.12882	70.89624	1.022324
19	19.96486	15.75273	16.03243	11.76124	63.51127	0.915330
20	17.88520	14.11183	14.36240	10.53612	56.89556	0.820434
21	16.02218	12.64186	12.86633	9.438619	50.96899	0.734973
22	14.35321	11.32501	11.52610	8.455437	45.65976	0.658414
23	12.85810	10.14533	10.32547	7.574669	40.90357	0.589829
24	11.51872	9.088535	9.249909	6.785647	36.64281	0.528389

PBA = predicted blood quantity after oral absorption (mg), PC = predicted concentration at times (µg/ml), PTA = predicted total blood amount following oral absorption (mg), T = time following absorption (hours).

Furthermore, the pharmacokinetic parameters C_{max} and AUC were predicted from the computed *in vivo* pharmacokinetic profile of each brand. The observed values showed considerable inter-brand variation. Based on the percentage prediction errors (% PE) for C_{max} and AUC relative to the innovator (R) (Table 5), none of the generics met the ±15 % threshold for both parameters. While brands A, B, C, D, E, H, J, K, L, O, P, and Q each fell within ±15 % for C_{max}, all exceeded ±15 % for AUC (ranging from 20.4 % to 51.8 %). Conversely, brands F, G, I, M and N also breached the C_{max} limit (Table 5).

Table 5. Observed pharmacokinetic parameters (C_{max} andAUC) for each paracetamol brand based on IVIVC along with their percentage predicted errors (% PE).

BRANDS	C_{max} (% PE)	AUC (% PE)
A	6.00 (-2.83)	47.41 (34.19)
B	5.94 (-3.87)	46.26 (32.56)
C	6.01 (-2.66)	46.83 (33.38)
D	6.74 (8.46)	52.84 (40.95)
E	6.57 (5.95)	51.77 (39.73)
F	5.47 (-12.79)	42.48 (26.55)
G	8.33 (25.93)	64.77 (51.83)
H	7.06 (12.61)	55.56 (43.84)
I	8.09 (23.73)	62.58 (50.14)
J	6.16 (-0.16)	47.19 (34.88)
K	6.58 (6.23)	51.75 (39.71)
L	6.75 (8.59)	52.82 (40.83)
M	5.06 (-21.94)	39.19 (20.39)
N	4.84 (-27.48)	36.97 (15.61)
O	7.00 (11.86)	54.45 (42.70)
P	5.95 (-3.70)	46.86 (33.42)
Q	6.39 (3.44)	50.12 (37.75)
R	7.01 (11.98)	54.44 (42.69)

*C_{max} = peak plasma concentration (µg/ml), AUC = area under the curve, % PE = percentage predicted error

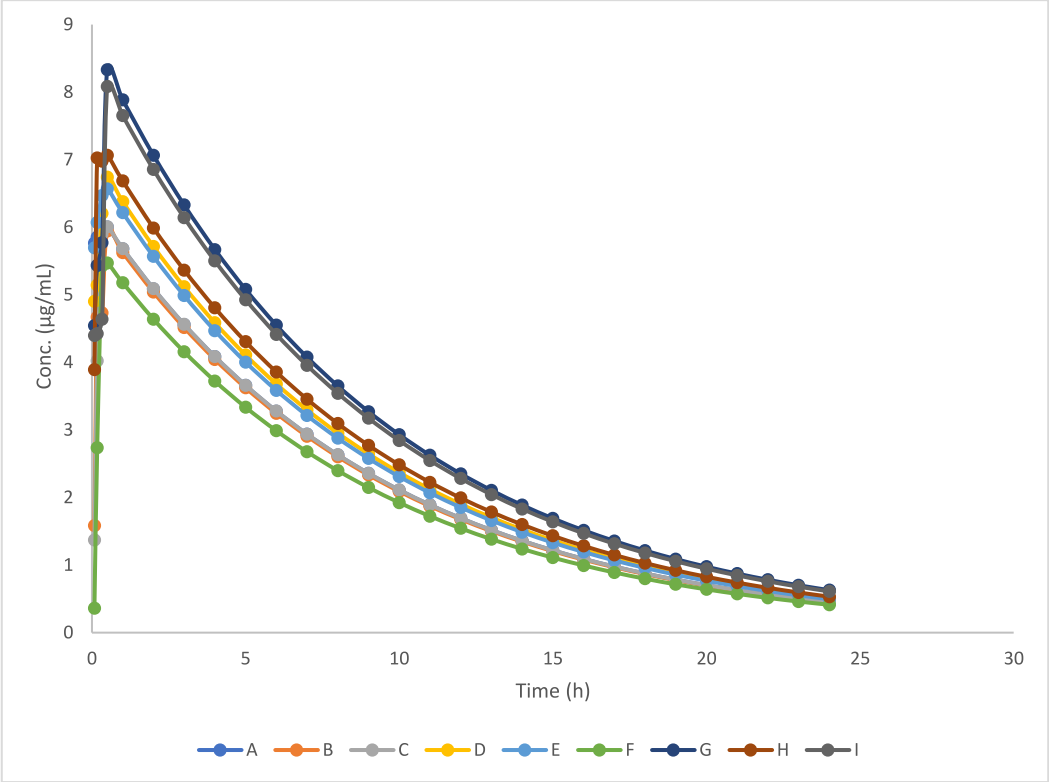

Figure 2a: Plasma drug concentration time profiles derived from *in-vivo* dissolution profiles for different brands of paracetamol tablets: A to I;

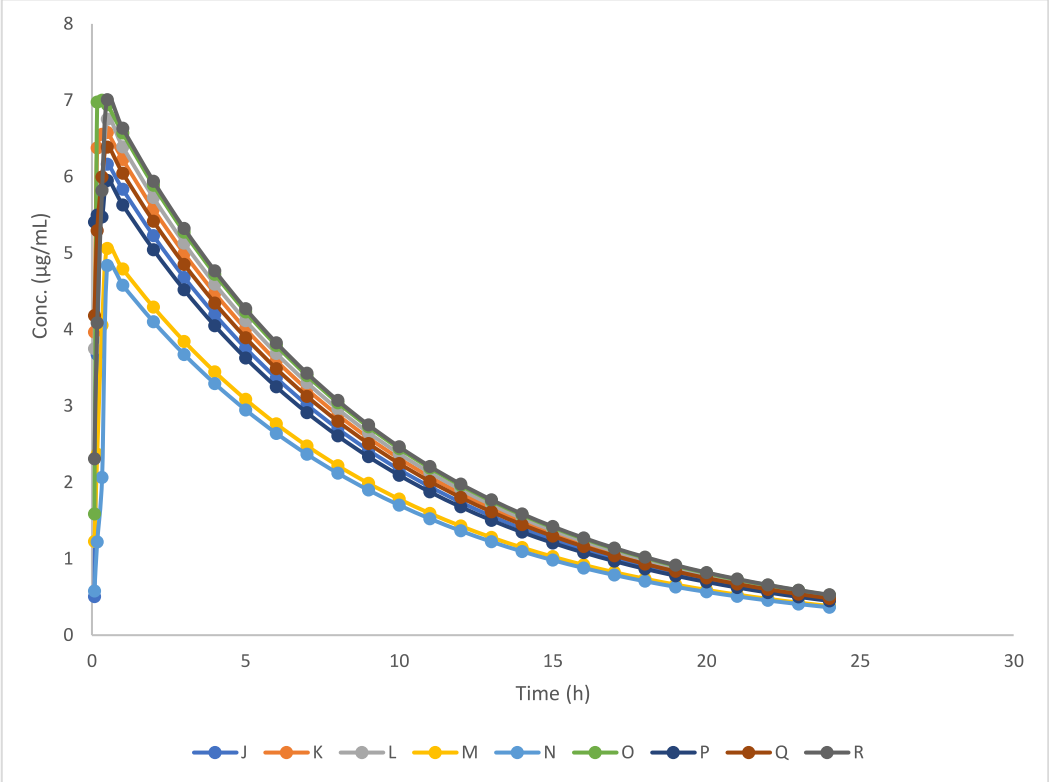

Figure 2b: Plasma drug concentration time profiles derived from *in-vivo* dissolution profiles for different brands of paracetamol tablets: J to R

4. Discussion

This study applied a convolution-based *in vitro-in vivo* correlation (IVIVC) model to assess the bioequivalence of 18 commercial paracetamol tablet brands marketed in Nigeria. The predictive accuracy of pharmacokinetic parameters, specifically the peak plasma concentration (C_{max}) and area under the curve (AUC), was used to infer systemic drug exposure. While most generics showed acceptable C_{max} predictions within the United States Food and Drug Administration (FDA)'s ±15% threshold[19], none met this criterion for AUC. This disparity suggests that although the IVIVC model reliably captured the rate of absorption, it consistently underpredicted the extent of drug absorption across formulations.

The IVIVC model's shortcomings in AUC prediction likely stem from fixed assumptions in the bioavailability parameter and the model's limited ability to account for formulation-specific variability. For immediate-release (IR) drugs like paracetamol, classified as Biopharmaceutics Classification System (BCS) Class I, absorption is rapid, making it difficult to establish a Level A IVIVC[20,21]. This is consistent with prior studies indicating that convolution models for IR drugs often yield only Level C correlations, capturing Cmax but not full systemic exposure. Other studies have noted similar challenges in achieving robust AUC predictions, emphasizing the influence of excipients, gastric emptying, and dissolution kinetics on absorption outcomes[22,23].

Furthermore, content assay results also revealed concerning quality disparities. Brands G and O contained only 38.3% and 64.2% of labelled drug content, respectively (suggesting a lapse in good manufacturing practices (GMP) by the manufacturers), and both exhibited high AUC prediction errors. These substandard products failed both chemical and biopharmaceutical evaluations, posing a clear risk to therapeutic efficacy. Although other brands passed content and dissolution criteria, they still showed underperformance in predicted systemic exposure, reflecting either subtle formulation differences or systemic underestimation by the model.

Dissolution profile comparison for each of the brands with the innovator brand using the similarity factor f_2 provided additional insights. Regulatory agencies such as the FDA and European Medicines Agency (EMA) regard an f_2 value of ≥ 50 as evidence of comparable dissolution behaviour[24]. In this study, only five generics met this threshold, despite all brands releasing at least 80% of the drug within 30 minutes. This suggests that while the quantity of drug released was acceptable, the release kinetics deviated significantly from the reference product in most cases. Notably, the brands with $f_2 \geq 50$ also demonstrated the lowest C_{max} prediction errors but still failed the AUC equivalence test. This finding highlights a critical limitation where the similarity in dissolution profiles does not necessarily translate to equivalence in systemic exposure.

The mismatch between dissolution similarity and predicted AUC raises questions about the sufficiency of dissolution testing as a surrogate for bioequivalence investigations in paracetamol formulations. Although two products may exhibit similarity in vitro release profiles, this does not guarantee comparable systemic exposure[7]. Studies have shown that even minor variations in excipients or tablet hardness can significantly influence drug dissolution and absorption, particularly in immediate-release formulations where rapid disintegration is critical[25]. Standard dissolution conditions, such as those specified in the USP, may therefore fail to replicate key physiological variables that affect in vivo drug behaviour[26]. To address this, several researchers have advocated for the use of biorelevant dissolution media, which more closely simulate gastrointestinal conditions and can enhance the predictive power of IVIVC models[23,27].

Despite concerns about the method's validity, our results align with other studies from Nigeria and West Africa, which have documented inconsistent quality among paracetamol generics[28]. While most brands passed identification and content uniformity tests, 30% of sampled paracetamol brands failed disintegration, friability, or active ingredient assays, issues similar to those observed in our Brands G and O. Though most products in both studies met BP dissolution standards, this did not ensure equivalence in drug release profiles, as shown by our f_2 and IVIVC analyses. In Sierra Leone, it has been reported even more concerning results, with two of the brands releasing only approximately 21% of the drug in 45 minutes, underscoring the presence of substandard formulations in the region[26]. In contrast, paracetamol brands in Saudi Arabia, under strict regulatory control, consistently met assay, dissolution, and other quality benchmarks with minimal variability[18]. This comparison emphasis the critical role of regulatory oversight in ensuring therapeutic equivalence and product reliability.

The broader implication of this study is that meeting dissolution and assay specifications alone may not guarantee therapeutic equivalence. Given the widespread use of paracetamol as an over-the-counter analgesic, establishing reliable methods to confirm bioequivalence is essential. Although the drug's wide therapeutic window

may mask minor inconsistencies in clinical response, persistent underexposure, such as that predicted for several generics, can result in inadequate pain relief or suboptimal treatment outcomes. In response, patients may unknowingly increase their dosage or combine multiple products, increasing the risk of hepatotoxicity. Moreover, the circulation of substandard or therapeutically inequivalent formulations undermines public confidence in generic medicines and weakens efforts to promote safe, self-directed medication practices[29].

From a regulatory standpoint, these findings call for enhanced post-marketing surveillance and stricter enforcement of bioequivalence requirements. The National Agency for Food and Drug Administration and Control (NAFDAC) could adopt tiered evaluation strategies, using dissolution similarity and IVIVC prediction as screening tools to identify potentially substandard products for confirmatory *in vivo* testing[30]. Products that fail both tests, particularly those with low assay content, should be prioritized for regulatory action, including recalls or suspension of registration. In this regard, the WHO guidelines advocating for routine assessment of multisource medicines using both dissolution and pharmacokinetic metrics would be followed[31]. Additionally, it supports the FDA's vision of BCS-based biowaivers, where highly soluble and permeable drugs can be exempted from in vivo studies if dissolution similarity is demonstrated under strict conditions[24]. However, as this study shows, these surrogates must be validated carefully to avoid approving therapeutically inequivalent products under simplified protocols.

This work has a few limitations. First, it was based on previously established pharmacokinetic parameters and in vitro dissolution under a laboratory setting; no clinical BE study was carried out. As a result, unmodeled aspects like inter-patient variability, dietary effects, and gastrointestinal dynamics were not represented. Second, the convolution method assumes linear pharmacokinetics with fast absorption. Subsequently, saturation and metabolic effects were not explicitly modelled, limiting the method's generalizability. Finally, we restricted our brand sampling to the most prevalent tablet formulations; other products, such as effervescent or pediatric modifications, may react differently. Consequently, while the IVIVC predictions appear promising, they should be regarded with caution due to these limitations and would benefit from validation using *in vivo* data.

5. Conclusion

This study employed a convolution-based *in vitro-in vivo* correlation (IVIVC) model to evaluate the bioequivalence of 18 immediate-release paracetamol tablet brands that are widely accessible in Nigeria. While most products met basic pharmacopeial standards for assay, solubility, and disintegration, none reached full bioequivalence when compared to worldwide regulatory benchmarks for systemic exposure. Although C_{max} estimates were acceptable for the majority, all generics had high AUC prediction errors, indicating potential underexposure and treatment variability. The high AUC prediction errors (%PE values exceeding the ±15% regulatory benchmark) for all generic brands confirm that dissolution profiles are not reliable surrogates for the extent of absorption. This outcome confirms that reliance on basic *in vitro* dissolution and physicochemical tests alone is insufficient for assessing BE for this BCS Class I drug and poses a risk of variable therapeutic outcomes for the Nigerian populace.

Regulatory bodies must mandate confirmatory *in vivo* BE studies for the most concerning brands and revise quality control standards to require more rigorous, formulation-specific predictive testing for all widely used analgesics to guarantee patient safety and confidence in generic drugs.

Finally, establishing quality control for commonly used analgesics is vital for guaranteeing therapeutic consistency, protecting public trust, and supporting the sensible use of generic pharmaceuticals in Nigeria.

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