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COMPARATIVE BIOAVAILABILITY AND PHYSICOCHEMICAL QUALITY  
ASSESSMENT OF INNOVATOR AND GENERIC BRANDS OF DICLOFENAC AND  
PARACETAMOL IN NIGERIA

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### Abstract

**Background:** Substandard and falsified analgesics remain a major public health threat in low- and middle-income countries. This study evaluated the physicochemical quality and relative bioavailability of widely used innovator and generic brands of diclofenac (50 mg) and paracetamol (500 mg) marketed in Nigeria. **Methods:** Six brands (three diclofenac, three paracetamol) were subjected to pharmacopoeial tests (weight uniformity, hardness, friability, disintegration, dissolution, and assay). A randomized, open-label, single-dose, three-period crossover bioavailability study was conducted in 33 healthy volunteers with a 7-day washout. Plasma concentrations were quantified by validated UV-spectrophotometry. Bioequivalence was concluded if the 90% confidence interval (CI) for  $C_{max}$  and  $AUC_{0-1}$  fell within 80.00–125.00%. **Results:** Two generic paracetamol brands (Brand P and Brand E) failed assay (<70% labelled content). One generic diclofenac (Brand G) showed markedly reduced exposure ( $C_{max}$  ratio 76%, AUC ratio 67%). Brand C (diclofenac) and all paracetamol brands that passed quality control were bioequivalent to their respective innovators. **Conclusion:** While some generics are bioequivalent and interchangeable, others are substandard and pose clinical risks. Strengthened post-market surveillance and routine bioavailability testing are urgently needed in Nigeria.

**Keywords:** bioavailability, bioequivalence, generic medicines, diclofenac, paracetamol, substandard drugs, Nigeria

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### Introduction

Bioavailability is defined as the rate and extent to which the active pharmaceutical ingredient (API) is absorbed and becomes available at the site of action (FDA, 2014;EMA, 2010). It is most commonly assessed from plasma concentration–time profiles after a single dose using key pharmacokinetic parameters: maximum

concentration ( $C_{max}$ ), time to reach  $C_{max}$  ( $T_{max}$ ), and area under the curve (AUC). Intravenous administration yields 100% bioavailability; all other routes are compared against this reference or, more commonly in generic studies, against an innovator product.

Generic medicines can dramatically reduce treatment costs and improve access, especially in resource-limited settings (Dunne et al., 2013). Regulatory authorities worldwide accept generic approval based on demonstration of bioequivalence—typically 90% CI of geometric mean ratios for C<sub>max</sub> and AUC within 80.00–125.00% of the reference product in healthy volunteers (FDA, 2014; EMA, 2010; FDA 2014). However, in many African countries, including Nigeria, weak regulatory oversight and porous supply chains allow substandard and falsified products to proliferate (WHO, 2017; Ozawa et al., 2018).

Substandard analgesics are particularly concerning because pain is a leading reason for healthcare visits, and therapeutic failure prolongs suffering, increases healthcare costs, and may drive irrational use of stronger analgesics or antibiotics. Previous surveys in Nigeria and neighbouring countries have reported assay failures in up to 40% of paracetamol and diclofenac samples (Fadeyi et al., 2015, Khuluza & Haefele-Abah, 2019).

**Project summary:** The present study therefore aimed to (1) evaluate the physicochemical quality of three widely sold brands each of diclofenac (50 mg enteric-coated) and paracetamol (500 mg immediate-release) tablets available in Rivers State, Nigeria, and (2) determine their relative bioavailability and bioequivalence in healthy volunteers using validated UV-spectrophotometric methods. By combining *in vitro* quality testing with *in vivo* performance data, the study provides evidence to guide rational generic substitution and inform regulatory policy.

## Materials and Methods

### Ethical approval and volunteers

The study was approved by the Research Ethics Committees of Rivers State University Teaching Hospital and University of Port Harcourt Teaching Hospital (approval numbers RSUTH/REC/2021/087 and UPH/REC/2021/112). All procedures followed the Declaration of Helsinki (WMA, 2013). Written informed consent was obtained from 33 healthy adult volunteers (18–25 years, BMI 18.5–24.9 kg/m<sup>2</sup>, 13 males/20 females) after medical examination and laboratory screening.

### Test products and coding

To avoid commercial bias and because no formal permission was obtained from manufacturers, brands are coded as follows:

- Diclofenac (50 mg enteric-coated): Brand O (innovator), Brand C, Brand G
- Paracetamol (500 mg immediate-release): Brand N (innovator), Brand P, Brand E

All batches were purchased from registered community pharmacies in Port Harcourt in 2022 and were within expiry.

### Physicochemical evaluation

Tests were performed according to USP 43/NF 38 and BP 2020 monographs:

- Weight variation (n=20)
- Hardness (Monsanto hardness tester, n=10)
- Friability (Erweka TAR 220, n=20)

- Disintegration (Erweka ZT 122, n=6)
- Dissolution (Erweka DT 600, USP Apparatus II, 900 mL medium, 50 rpm for diclofenac (pH 6.8 buffer), 75 rpm for paracetamol (pH 5.8 buffer), n=6)
- Assay and content uniformity (UV spectrophotometry after extraction,  $\lambda=276$  nm diclofenac sodium in methanol,  $\lambda=243$  nm paracetamol in 0.1 M NaOH, validated per ICH Q2(R1))

### Pharmacokinetic study design

Randomized, open-label, single-dose, three-period, three-sequence crossover with  $\geq 7$ -day washout. Volunteers fasted overnight, received 50 mg diclofenac or 500 mg paracetamol with 240 mL water, and remained fasted for 4 h post-dose. Venous blood (5 mL) was collected at 0, 1, 2, 3, 4, 6, 8, 12, and 24 h (diclofenac) or 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 h (paracetamol). Plasma was separated and stored at  $-80$  °C until analysis.

### UV-spectrophotometric method and validation

Diclofenac: protein precipitation with acetonitrile, supernatant read at 276 nm. Paracetamol: direct dilution in 0.1 M NaOH, read at 243 nm. Validation parameters (linearity 0.5–50  $\mu\text{g/mL}$ , accuracy 98–102%, precision <4% CV,

specificity, stability) met ICH Q2(R1) criteria. Calibration curves are presented in Supplementary Figures S1–S2.

### Pharmacokinetic and statistical analysis

Non-compartmental analysis (Kinetica 5.0/Thermo Fisher). Primary parameters:  $C_{\text{max}}$ ,  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ .  $T_{\text{max}}$  reported as median (range). Bioequivalence assessed on ln-transformed data using ANOVA with 90% CI (Phoenix WinNonlin 8.3). Sample size provided >80% power to detect 20% difference in AUC ( $CV \approx 30\%$ ,  $\alpha=0.05$ ).

### Results

#### Physicochemical quality

All brands met weight variation, hardness, friability, and disintegration requirements (Supplementary Table S1, Table S2 and Table S3). However, assay results varied widely (Table 1). Brands P and E (paracetamol) contained only  $68.0 \pm 5.6\%$  and  $47.8 \pm 6.3\%$  of labelled paracetamol, respectively. "Dissolution testing confirmed the expected profiles: the innovator diclofenac brand (Brand O) exhibited typical enteric-coated behaviour with minimal release (80% in 45 min) after buffer change to pH 6.8, whereas the innovator paracetamol brand (Brand N) showed immediate-release characteristics with >85% dissolved within 30 min in pH 5.8 acetate buffer

**Table 1.** Assay and content uniformity results

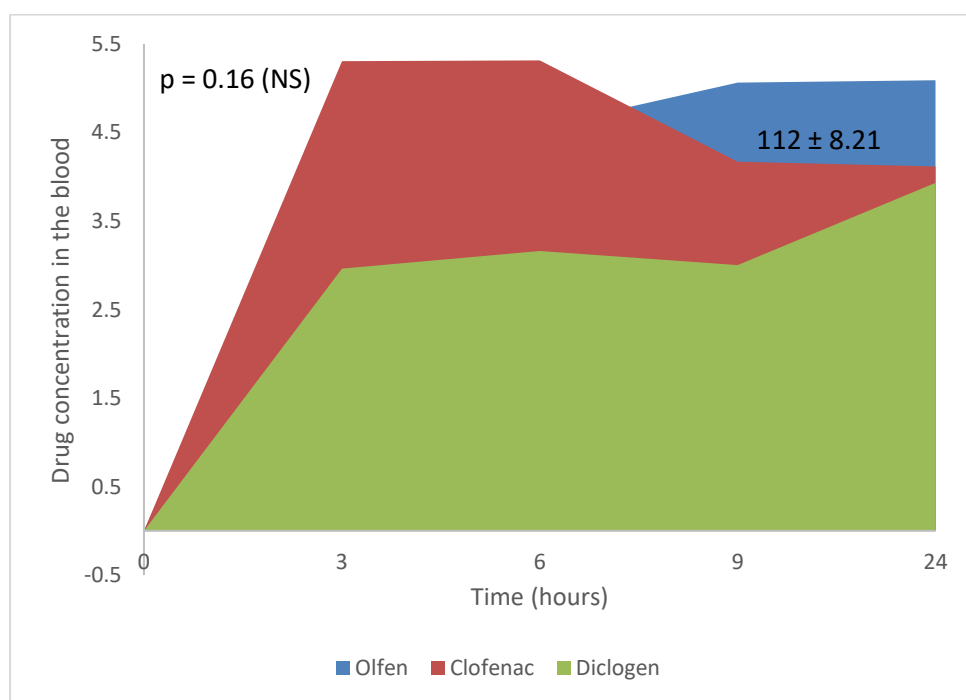
Drug	Brand	Labelled content (%) ± SD	Pass/Fail (85–115%)
Diclofenac	O	95.2 ± 2.1	Pass
	C	92.4 ± 3.5	Pass
	G	88.7 ± 4.2	Pass
Paracetamol	N	99.8 ± 1.8	Pass
	P	68.0 ± 5.6	Fail
	E	47.8 ± 6.3	Fail

### Pharmacokinetic parameters and bioequivalence

**Diclofenac** (Table 2, Figure 1): Brand C was bioequivalent to Brand O (90% CI within 80–125%). Brand G exhibited significantly lower exposure (C<sub>max</sub> ratio 76.4%, AUC<sub>0-t</sub> ratio 66.8%) and failed bioequivalence.

**Table 2.** Pharmacokinetic parameters of diclofenac brands (mean ± SD, n=33)

Parameter	Brand O (Reference)	Brand C	Brand G	90% CI (C/O)	90% CI (G/O)
C <sub>max</sub> (µg/L)	5.09 ± 0.19	5.31 ± 0.35	3.89 ± 0.42	98.2–112.4%	72.1–80.9%
AUC <sub>0-t</sub> (µg·h/L)	112.0 ± 8.2	108.3 ± 12.4	74.9 ± 10.1	93.1–104.8%	63.9–69.8%
T <sub>max</sub> (h), median	4.0	4.0	6.0	—	—



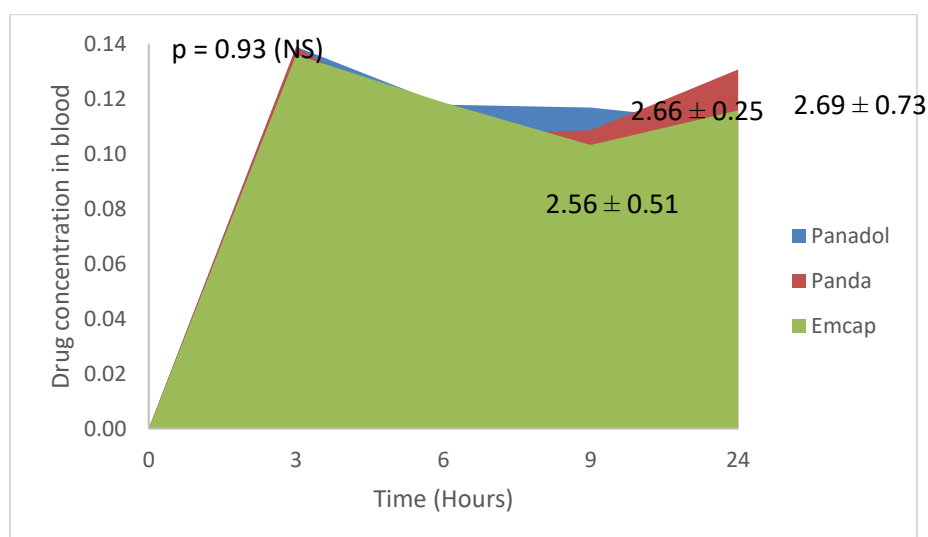
**Figure 1: The area under curve (AUC) of innovator (O) and generic (C and G) brands of Diclofenac**

**Paracetamol** (Table 3, Figure 2): Brands N and P were bioequivalent. Brand E, despite extremely low content, paradoxically showed comparable early exposure due to

rapid dissolution of the small amount of API present, but total AUC was only ~50% of reference (failed bioequivalence).

**Table 3.** Pharmacokinetic parameters of paracetamol brands (mean ± SD, n=33)

Parameter	Brand N (Reference)	Brand P	Brand E
C <sub>max</sub> (mg/L)	18.4 ± 3.1	18.1 ± 3.4	10.2 ± 2.8
AUC <sub>0-t</sub> (mg·h/L)	92.5 ± 14.2	90.8 ± 15.1	46.3 ± 11.4
T <sub>max</sub> (h), median	1.0	1.0	0.75
Bioequivalence	—	Pass	Fail



**Figure 2: Area under the curve (AUC) for the innovator (N) and generic (E and P) brands of Paracetamol**

### Discussion

The study confirms the coexistence of high-quality and grossly substandard analgesic products in the Nigerian market. Two of five generic brands failed basic content requirements, consistent with earlier reports from Nigeria and other African countries (Fadeti et al., 2015; WHO, 2017). The extremely low paracetamol content in Brands P and E (<70%) almost certainly reflects falsification or severe

manufacturing defects rather than simple degradation.

Brand G (diclofenac) passed in vitro assay but failed in vivo bioequivalence, possibly due to differences in enteric coating or excipient effects on absorption in the alkaline intestine (Aulton & Taylor, 2017). Such “bio-inequivalent despite passing dissolution” cases have been documented elsewhere (Gajendragadkar et al., 2021).

From a mechanistic viewpoint, substandard analgesics deliver lower systemic exposure, reducing efficacy and potentially selecting for resistance when used in infectious diseases (e.g., malaria with fever). Public-health implications are profound: treatment failure prolongs morbidity, increases healthcare utilisation, and erodes confidence in generic medicines overall. Regulatory gaps in Nigeria include limited post-market surveillance and absence of mandatory bioavailability studies for locally manufactured generics (NAFDAC, 2019). The findings support calls for routine bioequivalence testing, adoption of WHO prequalification for essential medicines, and stronger supply-chain controls (WHO, 2021).

**Limitations:** Single-dose design, healthy young volunteers, and moderate sample size. Multi-dose studies in patients would further strengthen conclusions.

### Conclusion

While some generic analgesics marketed in Nigeria are bioequivalent and interchangeable with innovators, others are substandard or falsified and pose serious risks to patients. Routine post-marketing bioavailability surveillance and stricter enforcement are essential to protect public health.

### Acknowledgements

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## Supplementary Material

Figures S1–S2: Calibration curves

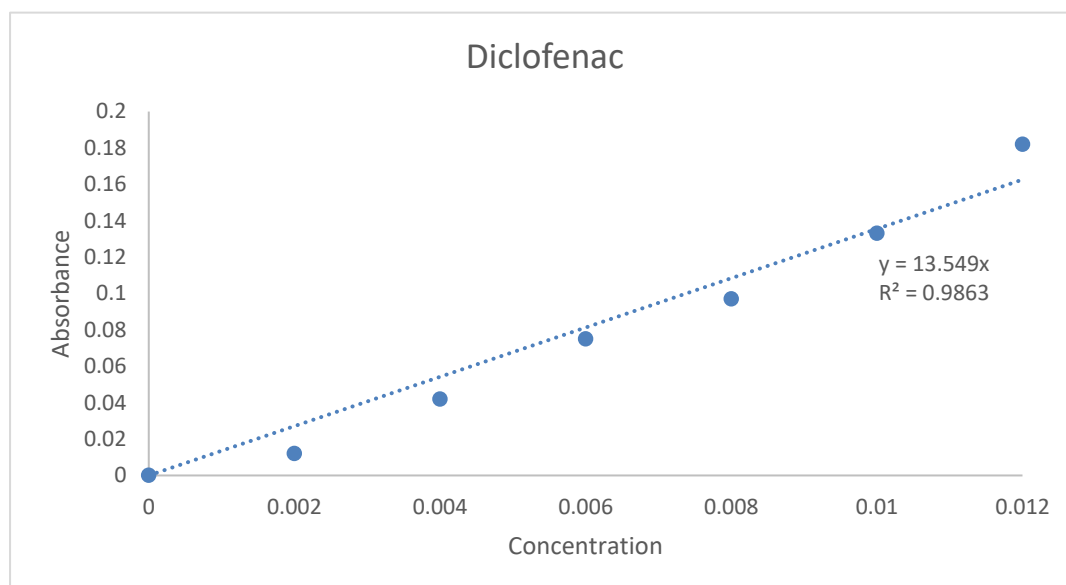


Figure S1 Calibration Curve of Diclofenac at the wavelength of 243nm

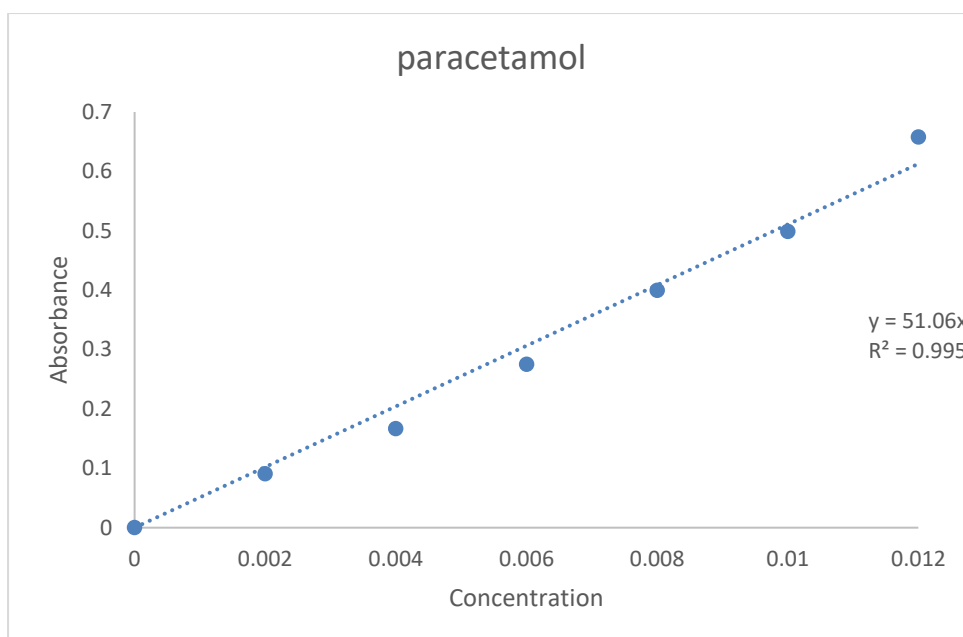


Figure S2 Calibration curve for paracetamol at absorbance of 240nm

Table S1: Full physicochemical results

**Table S1 Hardness, Friability. Disintegration and Assay of the three Paracetamol brands**

Brands	N	E	P	p-value
<b>Weight uniformity (mg)</b>				
Mean ± CV	670 ± 1.11 <sup>a</sup>	560 ± 2.53 <sup>b</sup>	580 ± 1.62 <sup>c</sup>	p < 0.0001
<b>Hardness (KgF)</b>				
Mean ± Sd	10.73 ± 1.87 <sup>a</sup>	3.90 ± 0.32 <sup>b</sup>	8.55 ± 1.36 <sup>c</sup>	p < 0.0001
<b>Disintegration time (mins)</b>				
Mean ± Sd	1.53 ± 0.29 <sup>a</sup>	1.98 ± 0.01 <sup>b</sup>	0.84 ± 0.19 <sup>c</sup>	p < 0.0001
<b>Friability (%)</b>	0.10	0.18	0.09	
<b>Assay (%)</b>	83.24	47.79	68.94	

Key: SD = standard deviation, CV = coefficient of variation, DT = Disintegration time

<sup>a,b,c</sup> = shows the brands with significant differences across the different variables

p ≤ 0.05 is considered significant.

*The N had the highest weight uniformity in addition to highest assay in percent, followed by P having the 2<sup>nd</sup> highest weight uniformity and 2<sup>nd</sup> highest assay (content of active ingredient). All the brands passed the friability test, disintegration test, etc.*

**Table S2 Hardness, Friability. Disintegration and Assay of the three diclofenac brands**

Brands	O	G	C	p-value
<b>Weight uniformity (mg)</b>				
Mean ± CV	260 ± 1.12 <sup>a</sup>	230 ± 1.45 <sup>b</sup>	220 ± 1.71 <sup>c</sup>	p < 0.0001
<b>Hardness (Kg)</b>				
Mean ± SD	11.10 ± 1.88 <sup>a</sup>	2.98 ± 0.32 <sup>b</sup>	4.80 ± 0.31 <sup>c</sup>	P < 0.0001
<b>Disintegration (mins)</b>				
Mean ± SD	10.28 ± 1.70 <sup>a</sup>	5.30 ± 2.67 <sup>b</sup>	13.44 ± 2.79 <sup>c</sup>	p < 0.0001
<b>Friability (%)</b>	0.08	0.21	0.09	
<b>Assay (%)</b>	147.61	112.92	117.35	

Key: SD = standard deviation, CV = coefficient of variation, DT = Disintegration time

<sup>a,b,c</sup> = shows the brands with significant differences across the different variables

p ≤ 0.05 is considered significant.

One can see that there is only a 23.1% influence of hardness on the disintegration of the tablet. (Table S3) This signifies that other factors could affect the disintegration of a tablet. There is a positive correlation between hardness and disintegration meaning that with increasing hardness comes longer disintegrating time.

**Table S3 Pearson correlation and linear regression between Hardness test and disintegration test**

Pearson R	R <sup>2</sup>	Significant
0.481	0.231	0.003

Figures S3–S4: Individual dissolution profiles

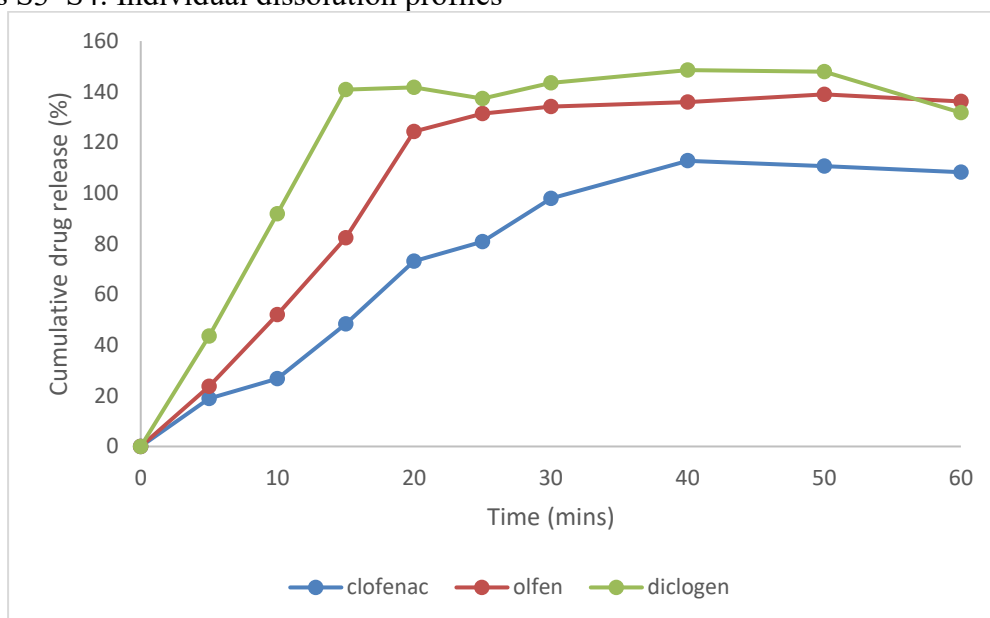


Figure S3: Drug release curve for the 3 brands of diclofenac

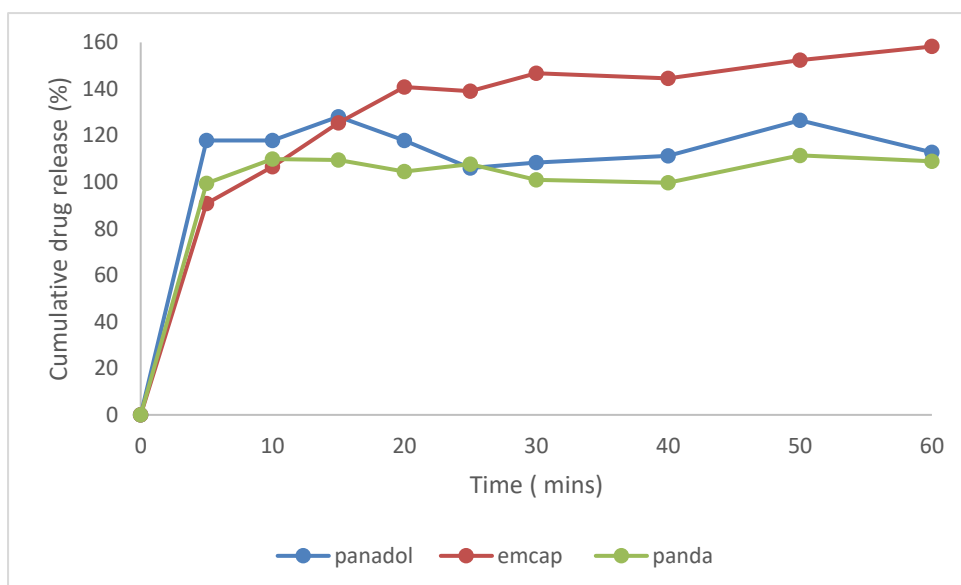


Figure S4 : Drug release curve for the 3 brands of paracetamol

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