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Oral Biopharmaceutics and *In vitro* Pharmacokinetics of Commercially Available Pharmaceutical Formulations of Paracetamol: Implications in Paediatric Medicine

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Authors' contributions

This work was carried out in collaboration among all authors. Author NMN managed the literature searches, and co—performed the bench work. Author NMN curated the methodology, & project administration and Supervision. Author OKO conceptualized the work, reviewed & edited writing. Author IGO designed the study, performed the bench work, curated the data and performed the statistical analysis, wrote the protocol and the first draft. All authors read and approved the final manuscript.

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ABSTRACT

Aim: This study aimed to compare the oral pharmacokinetics of different paediatric paracetamol dosage forms that are commercially available in Nigeria.
Study Design: Experimental.
Place and Duration of Study: Faculty of Pharmaceutical Sciences, Enugu State University of Science and Technology, between March and December 2023
Methodology: The study used the regular *in vitro* dialysis membrane method to predict the *in vivo* drug release of commercially available paracetamol syrups (n=5) and dispersible tablets (n=5) in the Nigerian market. The sink condition followed the Conventional USP dissolution method, using a dialysis membrane sac. The drug samples were studied in simulated salivary fluid of pH 7.4, simulated gastric fluid of pH 1.2, and simulated intestinal fluid of pH 6.5 over 8 hours to simulate their passage in the gastrointestinal tract. At predetermined time intervals, 5 ml of the dissolution medium was drawn out from the system, diluted appropriately and its absorbance measured against a suitable blank at λ = 250 nm using a UV/Vis Spectrophotometer, while a fresh volume of 5 ml of dissolution medium was introduced into the dissolution vessel after each withdrawal.
Results: Syrup dosage forms showed a faster drug release kinetics, based on their K_0 values. Kinetic parameters obtained from the linear regression analysis of the *in vitro* release resulted in a zero-order release kinetics, with $1.610 \geq \mathrm{K}_0 \geq 11.06$ for paracetamol paediatric syrups, and $1.612 \geq \mathrm{K}_0 \geq 7.663$ for tablets. Two-way ANOVA test of the AUC of dosage forms showed that the time required to elicit therapeutic response was extremely significant (F=44.37, DFn=3, DFd= 32 and P-value < 0.0001).
Conclusion: The comparative *in vitro* pharmacokinetic study of paracetamol dosage forms revealed that the paediatric syrup formula has a better release kinetics than the scaled down adult formula.

Keywords: Paracetamol; dosage forms; paediatric medicine; biopharmaceutics; in vitro pharmacokinetics.

1. INTRODUCTION

"Irrespective of modern technological applications towards improving outcomes in healthcare delivery around the world, childhood illness continues to be a cause of substantial distress and burden" (Kean and Adeleke, 2023). "About one out of every four children are thought to be affected by a chronic medical condition while up to 80% of deaths under the age of five are due to infectious disease and neonatal conditions" (Compas *et al.,* 2011; World Health Organization, 2022). "Examples of illnesses resulting in death in paediatrics include pneumonia, diarrhoea, malaria, and meningitiss" (World Health Organization, 2022). "It is believed that many of these deaths could be prevented with proper medical treatment and care" (World Health Organization, 2022). "In addition to their physical symptoms, both acute and chronic health conditions in paediatrics can have other negative consequences. The cost of medicating childhood illnesses is relatively high-end for both the families and the healthcare system. What's more, consequences comprise limited access to education, social isolation, and increased levels of stress" (Kean and Adeleke, 2023). Therefore, it is crucial that adequate steps, such as medication and medical procedures, are globally taken to minimize the effects of childhood ailments.

"Biopharmaceutical science is infamous within drug development for predicting the *in vivo* performance of a medicine. However, its use within paediatric formulation development is limited and has previously remained highlighted as an area in which further study is necessary" (Abdel-Rahman *et al.,* 2012). Certain practical and ethical issues limit the conducting of clinical trials that involve paediatric subjects. Which is why studies are usually performed after examining the pharmacokinetics and efficacy/safety of the drugs in adults, taking into consideration the physiological characteristics of a specific age group. Since the main challenge in paediatric pharmacotherapy is the optimization of the dosing regimen to achieve effective and safe treatment (Jovanović, and Vučićević, 2022), prediction of *in vivo* performance of medicines requires knowledge about the physiology and anatomy of the site of drug absorption (Batchelor *et al.,* 2013), as differences among the paediatric and adult population are not just in size, but also

due to physiological and biochemical processes. Pharmacokinetic studies measure the concentration of drugs found within body fluids, usually blood or plasma, over time. Such studies are particularly useful where there is a clear link between the pharmacokinetic profile and the pharmacodynamics of a drug. The aim of a pharmacokinetic study is typically to match the exposure in paediatric patients to that found in adults.

"In traditional medicine, children were historically regarded as miniature adults, leading to the practice of simply scaling down the dosage based on linear weight" (Anderson and Holford, 2013). This approach posed the risk of potential overdosing in very young children, particularly neonates, whose kidneys and liver are not yet fully developed, leading to slower drug elimination. Hence, all through the evolution of modern drug development, paediatrics and neonatology were largely neglected, rendering children and infants 'therapeutic orphans' (Germovsek *et al.,* 2019). Pharmacokinetic/ pharmacodynamics (PKPD) modelling and simulation (M&S) play a pivotal role in paediatric drug development by supporting rational trial design and increasingly replacing traditional trials through extrapolation of efficacy and safety information (Kimko, and Pinheiro, 2015). Thus, the application of PKPD modelling to enhance dosing recommendations and therapeutic drug monitoring (TDM) strategies is also increasingly recognized. However, as awareness of developmental pharmacology subsequently expanded, the physiological differences in drug handling between children and adults were emphasized, leading to the notion that 'children are not small adults' (Germovsek *et al.,* 2019).

Accordingly, childhood can be divided into various classes of age where each group should be considered as a special population. Any classification of the paediatric population into age categories is to some extent arbitrary. For this study, International Conference on Harmonization (ICH) E11 classifications are used (Batchelor and Marriott, 2013) where the paediatric population is divided into Preterm new-born, New-born (0–28 days), Infant (>28 days–12 months), Toddler (>12 months–23 months), Preschool child (2–5 years), School-age child (6–11 years), Adolescents (12–18 years). When selecting medicines for children, it is important to consider the child's age (Smith *et al.,* 2022), so that the drugs administered in paediatric patients are compliant to dosing accuracy, as they are more vulnerable to harm resulting from medication errors than adult patients (de Dios *et al.,* 2023). At home, parents and/or caregivers may make medication errors related to dose. In 2019, Glick and his colleagues found that 38% of parents or legal guardians committed some type of error when administering medication to their children (Glick *et al.,* 2019).

Paracetamol, otherwise known as acetaminophen or acetyl-para-aminophenol (APAP), is an analgesic and antipyretic drug that is extensively used in Nigeria. It is indicated for treatment of headaches, stomach ache, earache and cold symptoms. It can also be used to bring down a high temperature and/or treat post-vaccination fever in infants. When administered in the right dosage it is not associated with many side effects; however prolonged use may produce renal injury and massive overdose may produce hepatic injury (Barry, 2010). It is the most common pharmaceutical agent involved in overdose particularly below the age of 6 years (Utpal, 2004; Suzan, 2005; Obu, 2012). There is a particularly significant risk of paracetamol overdose in infants and children because of the varying dosing schedules and the variety of formulations with different strengths (Utpal, 2004; Obu, 2012).

For infants and young children in Nigeria, paracetamol is generally available as a liquid formulation (syrup) in 120mg/5 mL strength. Several nursing parents in Nigeria, and indeed, paediatricians trust the administration of paracetamol in infants and children as safe, consequently leading to a prevalence in the routine usage of the drug within the population. Alemany *et al.* (2021) reports that the use of paracetamol in the paediatric populations is above 90%. This use persists even under situations in which the drug may have no benefits, such as prophylaxis preceding some vaccinations and medication of mild fevers (Lawton *et al.,* 2022).

A cross-sectional study was conducted to assess the pattern and predictors of medication use among adults in south-western Nigeria (Adedeji *et al.,* 2023). The study revealed that 81% of the respondents had used analgesics in their lifetime and 65.9% were current users. The most commonly consumed analgesics among the respondents was paracetamol. In another survey to measure the risk perception of paracetamol use among undergraduate students, Ejeikwu (2019) reported that 93.1% of the participants had taken paracetamol in their lifetime.

In an observational prospective study to determine the dosage, formulation, and frequency of paracetamol administration to children by caregivers and factors associated with its use and/or misuse conducted at the paediatric outpatient clinic of the University of Nigeria Teaching Hospital, Enugu, Obu *et al*. (2012) reported that Paracetamol was commonly given to children on "self-prescription" basis and that the tablet formulation was most frequently used, with the possibility of misuse and overdose. According to Obu and co-workers, 75.6% of the children who participated in the study (n=231) received paracetamol from caregivers at home before presenting. Conversely, 71.2% of caregivers relied on past experience rather than on enclosed information leaflet to decide the appropriate dosage.

Also, in a matched case–control study of suspected paracetamol overdose in children, Haidar *et al.* (2020), using an in-hospital syndromic surveillance tool, studied a cluster of cases of unexplained multi-organ failure reported in children at Bardnesville Junction Hospital (BJH), Monrovia, Liberia. Seventy-seven case-patients were captured by syndromic surveillance; 68 (88%) were under three years old and 35 (46%) died during hospitalisation. Of these 77, 30 children met the case definition and were matched with 53 hospital and 48 community controls. Haidar and co-workers reported that Paracetamol was the most frequently implicated medication in both groups (the case and control groups). Also, the chances of caregivers reporting supra-therapeutic paracetamol consumption preceding admission was higher in cases compared to controls (OR 6.6, 95% CI 2.1–21.3).

Nwaiwu *et al.* (2023) opines that the knowledge regarding toxicity of paracetamol was poor. The therapeutic dose of APAP is well-defined on the basis of mg paracetamol per kg bodyweight. It is the common convention that the therapeutic range for both analgesic and antipyretic activity is a plasma paracetamol level of 10–15 mg/L[2] which equates to a dose of 10-15 mg/kg (Nahata *et al.,* 1984). In line with this, a range of studies have demonstrated that paracetamol is effective at doses between 10-20 mg/kg administered every 4–6 hours (Autret *et al.,* 1994; O'Donnell *et al.,* 2007).

Although a number of anatomical and physiological differences are highlighted between paediatric and adult populations, this topic has been the subject of some excellent reviews and the reader is directed to these papers for a full discussion (Bowles *et al.,* 2010; Kaye, 2011; Mooij *et al.,* 2012). It is noteworthy that such remarkable differences exist in several aspects of pharmacotherapy between adults and infants, including the abilities for drug administration, medicine-related toxicity, and taste preferences. Several factors are taken into consideration in producing paediatric formulations, such as paracetamol syrup, to best suit the child's age, size, physiologic condition and treatment requirements.

Safe and effective paediatric pharmacotherapy requires careful evaluation of the type of drug substance, the necessary dose and the age-appropriateness of the formulation (van Riet-Nales *et al.,* 2016; Thabet *et al.,* 2018). Generally, the younger the child, the more the attention that is required. For decades, there has been a general lack of (authorised) formulations that children are able to take (van Riet-Nales *et al.,* 2016). Moreover, little was known on the impact of pharmaceutical aspects on the age-appropriateness of a paediatric medicine. According to Ranmal *et al*. (2016), a lack of evidence to guide the design of age-appropriate and acceptable dosage forms has been a longstanding knowledge gap in paediatric formulation development.

Hence, the paediatric population has always suffered from a lack of medicines tailored to their needs, especially in terms of accurate dosage, stability and acceptability (Cornilă *et al.,* 2022). According to the Australian National Prescribing Service (NPS), medicines given incorrectly by parents and child caregivers is one of the most common reasons for accidental poisoning in children (Vilaça *et al.,* 2019). Small mistakes or an inaccurate knowledge, attitude or practice in paediatric drug administration can cause big problems in little bodies, hence, parents and child caregivers need to be educated on how to give medicine to children safely (Nwaiwu *et al.,* 2023). Accurately measuring and administering medicine to children helps avoid accidental overdosing or under-dosing.

Accordingly, a survey recently conducted by the authors, and preceding the present study revealed that many nursing mothers and childcare givers prefer to administer infants with the 'adult' formulation of dispersible tablets of

paracetamol in water, with the claim that it elicits a relatively faster therapeutic response in children than the syrup formulations would (Nwafor et al., 2024). This may give credence to the findings of Obu et al. (2012), where 75.6% of children studied were regularly and ordinarily administered Paracetamol tablet formulation without professional advice in order to treat a real or imagined condition. However, in a randomized comparative trial of the efficacy of paracetamol syrup and dispersible tablets for the treatment of fever in children, Okereke *et al.* (2021) analysing data from paediatric clinics reported that there was statistically no difference in the antipyretic effects of syrup and dispersible tablets administered in populations exclusively treated with them respectively.

To quell or affirm either position, there is the need to directly apply knowledge regarding the pharmacokinetics of paracetamol formulations to a therapeutic situation in a population. Hence, a systematic comparative *in vitro* pharmacokinetic study of commercially available brands of paracetamol syrups and dispersible tablets within the Nigerian market was conducted, vis-a-vis paediatric population.

2. METHODOLOGY

2.1 Materials

Pharmaceutical-grade paracetamol powder manufactured by Granules India Limited was received as a gift from Cobbler and Farmer Ltd, Nigeria. HPLC-grade methanol was purchased from CDH Chemicals, India. All chemicals used in this study were all of analytical grade. Spectrophotometric measurements were carried out using a 752W UV–Vis Spectrophotometer with a 1 cm quartz cuvette. All other reagents used in this study were as received. Dialysis tubing cellulose membrane (molecular weight cut-off 10 kDa, avg. flat width 10 mm) were purchased from Sigma-Aldrich (São Paulo, Brazil). Commercial brands of paracetamol syrups and dispersible tablets produced by FIDSON, EMZOR, RICO, LOTEMP and MAY&BAKER were purchased from community Pharmacies across the country. They were all registered products in Nigeria by NAFDAC as required by local laws. For the purposes of the present study, the various brands were coded as EZ, LT, BM, CR, and FD.

2.1.1 Product information

A total of five (5) commercial brands of paracetamol syrups and dispersible tablets were purchased from Enugu State, Abuja and Kano State. The product information distribution is shown in Table 1.

2.2 Methods

2.2.1 Preparation of standard stock and calibration curve

The standard stock solution was prepared by dissolving 50 mg of pharmaceutical grade Paracetamol in 50 mL of Methanol. From this stock solution, 5 mL was diluted to 50 mL with base solvent to get a concentration of 100 μg/mL and scanned in the entire UV range of 200–400nm to determine the wavelength of maximum absorption (λ max) of the drug as seen in the absorption spectrum in Fig. 1a.

Six working standard solutions for the drug having concentrations 4, 8, 12, 16, 20, and 24 μg/mL were prepared with distilled water from the stock solution. The absorbance of the resulting drug solutions were measured at the λ max = 250 nm, and a calibration curve (Fig. 1b) plotted to get the linearity and regression equation.

Table 1. Distribution of sample sites and samples collected

Product	Formulation information	Production date	Expiry date
EMZOR SYRUP	EMZOR (125 MG / 5 ML)	January 2021	January 2024
EMZOR TABLET	EMZOR (500 MG)	March 2023	March 2028
M&B SYRUP	M&B (120 MG / 5 ML)	December 2022	November 2025
M&B TABLET	M&B (500 MG)	February 2023	January 2028
RICO SYRUP	RICO (125 MG / 5 ML)	April 2021	April 2024
RICO TABLET	RICO (500 MG)	May 2023	May 2026
LOTEMP SYRUP	LOTEMP (125 MG / 5 ML)	February 2023	January 2026
LOTEMP TABLET	LOTEMP (500 MG)	January 2023	December 2025
FIDSON SYRUP	FIDSON (125 MG / 5 ML)	September 2022	August 2025
FIDSON TABLET	FIDSON (500 MG)	February 2023	January 2026

Table 2. Composition of Simulated Salivary Fluid, SSF (Guhmann *et al.,* 2012)

S/No.	Component	Amount
1	Potassium dihydrogen phosphate	12 mM
2	Sodium chloride	40 mM
3	Calcium chloride	1.5 mM
4	Sodium hydroxide	To pH 7.4
5	Demineralized water	To 1 L

Table 3. Composition of Simulated gastric fluid, pH 1.2; USP 26

S/No.	Component	Amount
1	NaCl	3 g
2	Deionized water	1.45 L
3	HCl	To pH 1.2

Table 4. Composition of Simulated intestinal fluid, pH 6.8; USP 26

S/No.	Component	Amount
1	KH_2PO_4	34.0 g
2	Na_2HPO_4	35.3 g
3	Deionized water	10.0 L

2.2.2 Preparation of simulated GIT fluids

Simulated gastric intestinal fluids used to study the *in vitro* pharmacokinetic study of the drug products were simulated salivary fluid (SSF), simulated gastric fluid (SGF) and simulated intestinal fluid (SIF). The composition of each medium is described in Tables 2—4.

2.2.3 Sample preparation

For paracetamol syrup sample, preparation involved measuring 5 mL of the dosage form accurately and carefully introducing it into a dialysis membrane sac with one end tied, after the drug was loaded in, the other end was tied up. Tablet dosage form were prepared according to the following procedure: initially, the tablets were triturated into a powder using a pestle and mortar. Subsequently, 125 mg of the triturated drug powder was meticulously weighed using an analytical weight balance. The weighed sample was reconstituted in 5 mL of deionized water and transferred into a dialysis membrane bag. The dialysis membrane sac was properly tied after loading drug sample into it.

2.2.4 *In vitro* drug release studies

Conventional dialysis sac method (de Andrade et al., 2015) was used to evaluate the *in vitro* drug diffusion profiles of orally-administered drug release kinetics for both oral formulations. The dissolution vessel consisted of a ten 500 mL-beaker containing 400 mL of simulated gastric fluid (SGF) each. The respective dialysis sac loaded with 5 mL of the various prepared samples were submerged into the dissolution vessels. Throughout the entire duration of the study, the SGF system was maintained at a temperature of 37 ^{o}C, a volume of 400 mL, and a constant magnetic stirring (speed = 50 rpm). At predetermined time intervals, 5 mL of the dissolution medium was drawn out from each system, while a fresh volume of 5 mL of SGF was introduced into the dissolution vessel to ensure the sink condition. The study was conducted for 8 hours. The same protocol was followed with Simulated Saliva (SSF), and Simulated intestinal fluid (SIF) as dissolution media. All dialyzing membranes were soaked in phosphate buffers pH 8.0 overnight before use.

2.2.5 UV/Visible spectrophotometry

Five millilitres sample of withdrawn media-drug complexes were diluted appropriately and analysed spectrophotometrically (752W UV–Vis Spectrophotometer) at an analytical wavelength of λ = 250 nm using a 1 cm quartz cuvette. The respective absorbance was recorded.

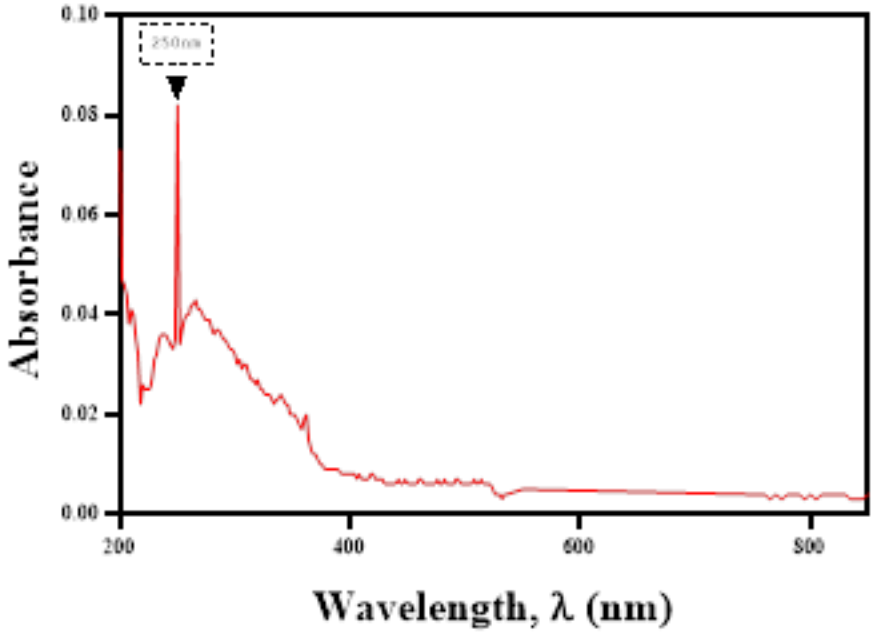
2.2.6 Statistical analysis

The *in vitro* study was analysed using Microsoft Excel version 2013 developed by Microsoft® and GraphPad Prism 5 developed by Dotmatics Limited.

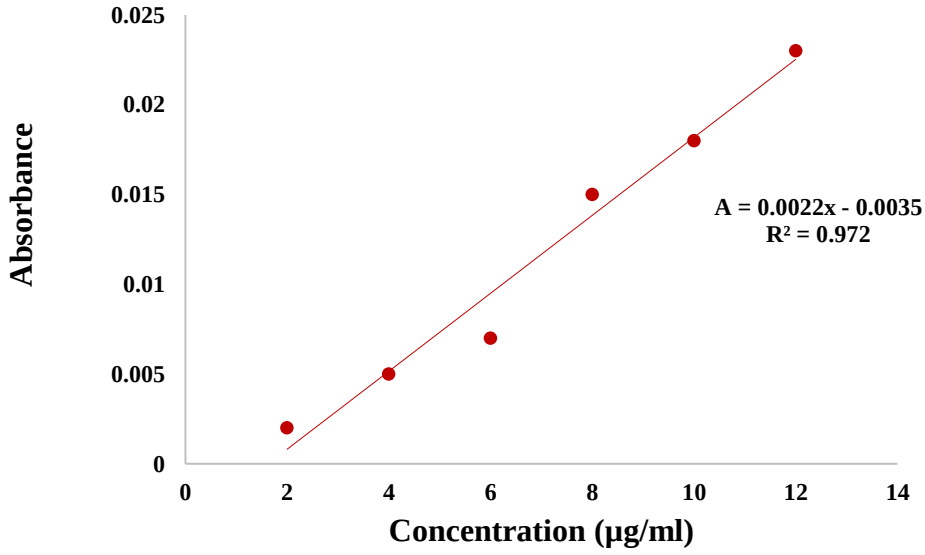
3. RESULTS

3.1 Linearity Curve and Absorption Spectrum of Paracetamol

The absorption spectrum of paracetamol in methanol gave its maximum molar absorptivity at λ=250 nm.



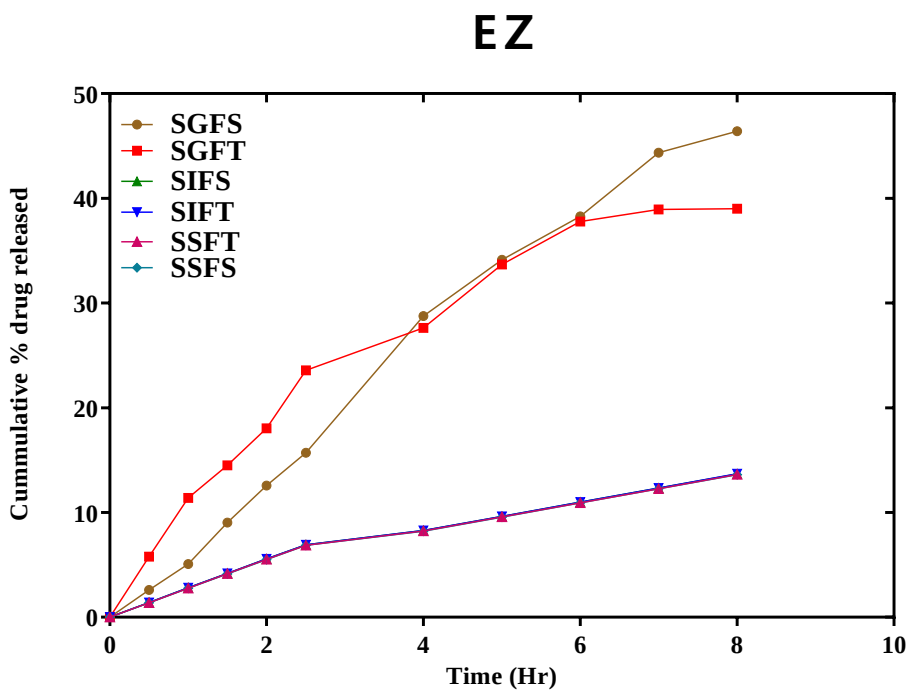
a



b

Fig. 1. (a) Absorption spectra (b) Calibration curve for paracetamol–methanol complex

3.2 *In vitro* Release Profile of Paracetamol Formulations from Different Commercial Brands

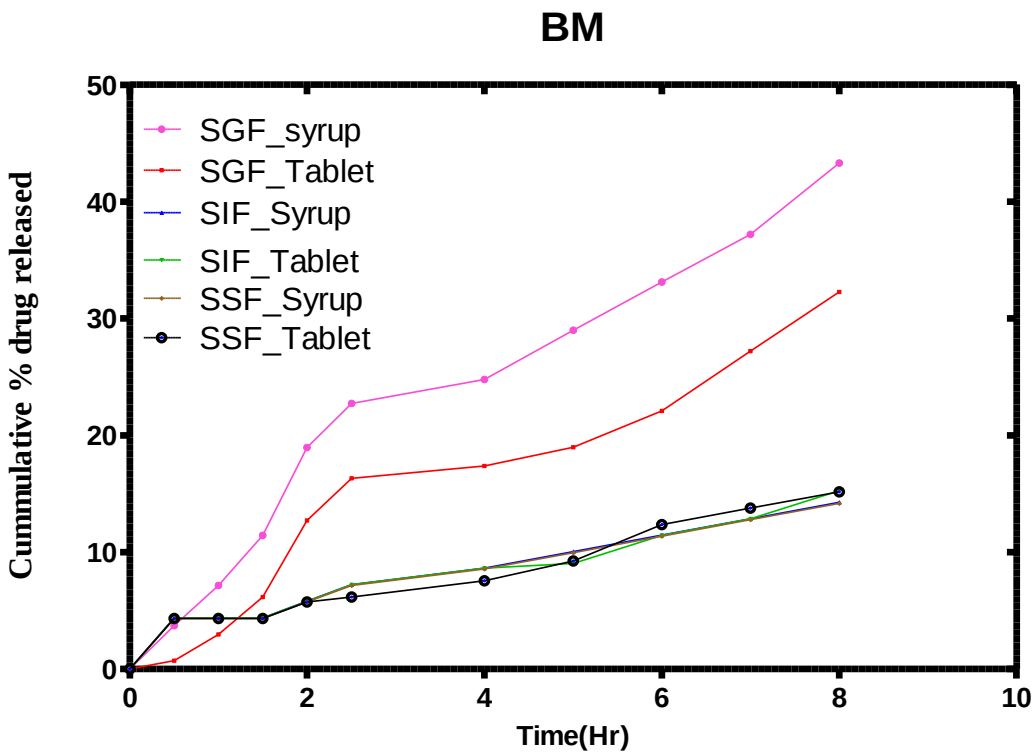


a

	Area under curve (AUC)					
	SGFS	**SGFT**	**SIFS**	**SIFT**	**SSFS**	**SSFT**
Baseline	0.0	0.0	0.0	0.0	0.0	0.0
Total Area	206.2	212.9	64.04	64.06	63.57	63.66
Number of Peaks	1.000	1.000	1.000	1.000	1.000	1.000

b

Fig. 2. (a) *In vitro* release profile (b) AUC of EZ tablet and syrup in various simulated GIT media

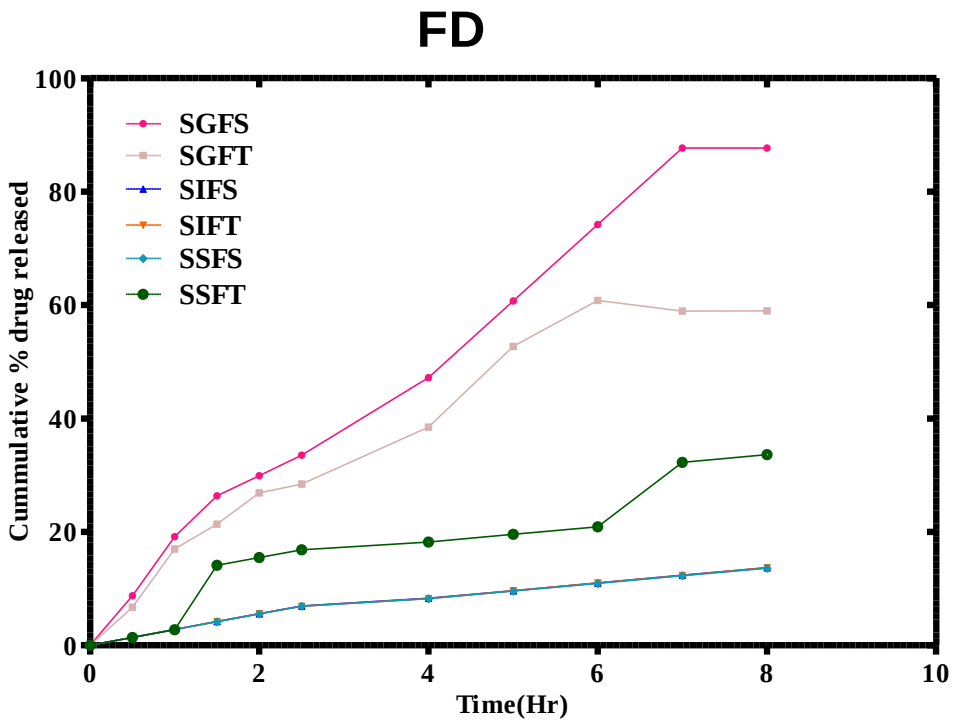


a

	Area under curve (AUC)					
	SGFS	**SGFT**	**SIFS**	**SIFT**	**SSFS**	**SSFT**
Baseline	0.0	0.0	0.0	0.0	0.0	0.0
Total Area	195.3	133.7	68.96	68.40	68.38	67.94
Number of Peaks	1.000	1.000	1.000	1.000	1.000	1.000

b

Fig. 3. (a) *In vitro* release profile (b) AUC of BM tablet and syrup in various simulated GIT media

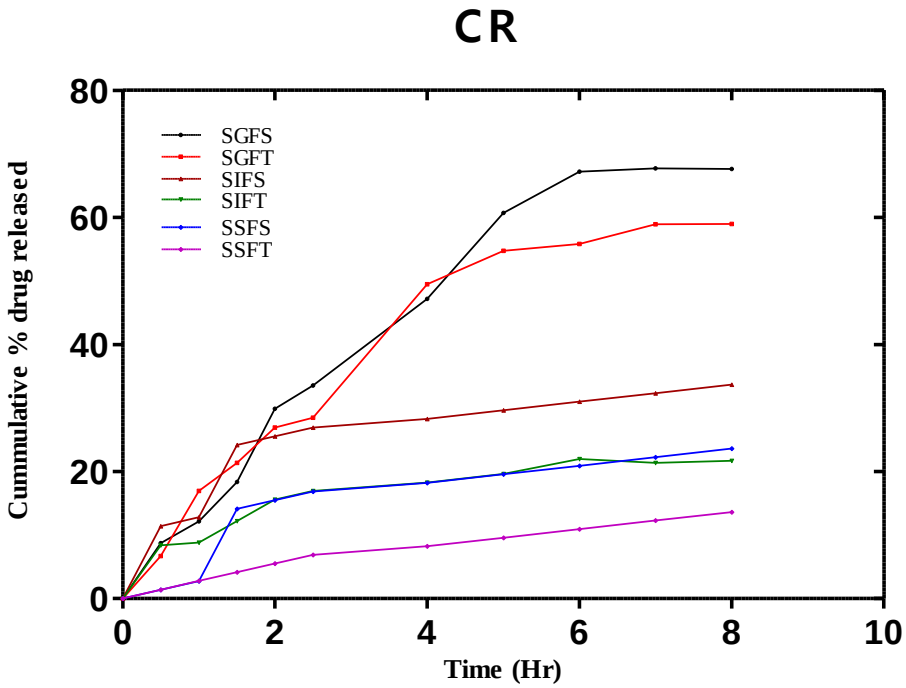


a

	Area under curve (AUC)					
	SGFS	**SGFT**	**SIFS**	**SIFT**	**SSFS**	**SSFT**
Baseline	0.0	0.0	0.0	0.0	0.0	0.0
Total Area	401.0	314.5	64.15	64.07	63.69	146.0
Number of Peaks	1.000	1.000	1.000	1.000	1.000	1.000

b

Fig. 4. (a) *In vitro* release profile (b) AUC of FD tablet and syrup in various simulated GIT media

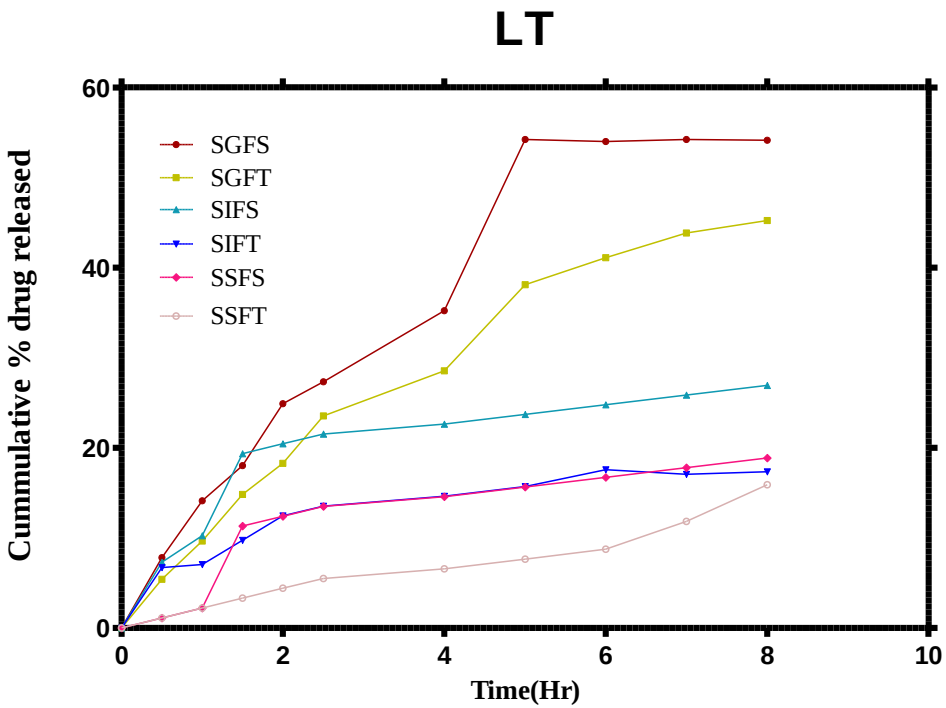


a

	Area under curve (AUC)					
	SGFS	**SGFT**	**SIFS**	**SIFT**	**SSFS**	**SSFT**
Baseline	0.0	0.0	0.0	0.0	0.0	0.0
Total Area	356.5	325.3	209.0	136.1	131.1	63.66
Number of Peaks	1.000	1.000	1.000	1.000	1.000	1.000

b

Fig. 5. (a) *In vitro* release profile (b) AUC of CR tablet and syrup in various simulated GIT media



a

	Area under curve (AUC)					
	SGFS	**SGFT**	**SIFS**	**SIFT**	**SSFS**	**SSFT**
Baseline	0.0	0.0	0.0	0.0	0.0	0.0
Total Area	293.2	229.0	166.3	108.8	104.9	55.43
Number of Peaks	1.000	1.000	1.000	1.000	1.000	1.000

b

Fig. 6. (a) *In vitro* release profile (b) AUC of LT tablet and syrup in various simulated GIT media

Table 5. Kinetic parameters obtained from the linear regression analysis of paracetamol syrup and tablet dosage forms

Brand code	SGFS		SGFT		SIFS		SIFT		SSFS		SSFT	
	K_0	R^2	K_0	R^2	K_0	R^2	K_0	R^2	K_0	R^2	K_0	R^2
EZ	6.241	0.9875	4.846	0.9281	1.617	0.9677	1.619	0.9678	1.610	0.9683	1.612	0.9683
BM	5.028	0.9526	3.817	0.9442	1.529	0.9525	1.529	0.9528	1.523	0.9536	1.528	0.9533
FD	11.06	0.9851	7.663	0.9351	1.619	0.9676	1.618	0.9677	1.610	0.9678	3.837	0.8837
CR	9.087	0.9426	7.620	0.9141	3.216	0.6969	2.226	0.7758	2.759	0.7721	1.612	0.9683
LT	7.100	0.9198	5.725	0.9574	2.643	0.6988	1.781	0.7758	2.207	0.7721	1.687	0.9535

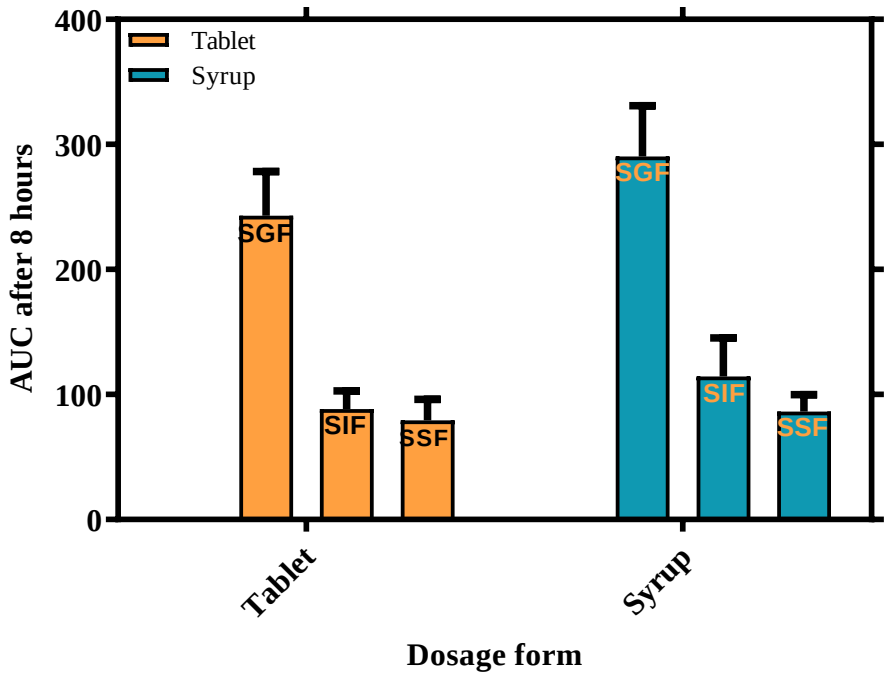


Fig. 7. Two-way ANOVA of the area under curve of drug release from tablets and syrup in SGF, SIF and SSF

4. DISCUSSION

Biopharmaceutics examines the interrelationship of the physical/chemical properties of the drug, the dosage form (drug product) in which the drug is given, and the route of administration on the rate and extent of systemic drug absorption. In this study two dosage forms were used: syrup (liquid) and tablets (solid). All of the paracetamol products used were certified by the National Agency for Food and Drug Administration and Control (NAFDAC). Hence, irrespective of their dosage forms, it is believed they had same chemical property. Five millilitres of syrup contained 125 mg of paracetamol while a tablet contained 500 mg of paracetamol. Since it is the practice of some nursing parents or legal guardians to administer a quarter of the 500 mg adult dose (¼ × 500 mg) to children (Nwafor *et al.,* 2024), in this study an attempt was made to replicate that. The aim of the present study was to conduct a systematic comparative *in vitro* pharmacokinetic study of commercially available brands of paracetamol syrups and dispersible tablets, vis-a-vis paediatric population.

The route of oral administration of drugs is through the gastrointestinal tract (GIT). Hence, the various media SSF, SGF and SIF (without enzymes) were used to study the rate of release of the dosage forms *in vitro*. The release profile of the samples were determined (Figs. 2a—6a). It could be observed that the *in vitro* release profile of paracetamol in SGF, irrespective of dosage forms presented a better *in vitro* release index than those in SIF and SSF respectively. The variations in the biopharmaceutical parameters of the brands in SGF, SIF and SSF are expected due to the difference in pH and compositions of the media (Uzochukwu *et al.,* 2008; He and Mu, 2023). Paracetamol being a weakly basic drug will be more soluble in SGF (acidic medium) than in SIF and SSF (alkaline media). In other words, theoretically, decreasing the pH could improve the solubility of a weakly basic drug such as paracetamol.

Area under the curve (AUC) of concentration of drug released from the two dosage forms with respect to time were measured (Fig. 2b – 6b) using the GraphPad Prism5 tool-pack. In pharmacology, the area under the plot of plasma concentration of a drug *versus* time after dosage (called “area under the curve” or AUC) gives insight into the extent of exposure to a drug and its clearance rate from the body (Scheff *et al.,* 2011). This simply means that by integrating over time rather than looking at individual concentration measurements, a more accurate estimate of the overall exposure to the drug is

obtained. In this study, the AUC tool was used to understand what the net pharmacologic response to a given dose of paracetamol dosage form would be. Generally, the AUC of drug amount measured in the syrup—dosage system were relatively higher than those obtained from the tablet.

Kinetic parameters obtained from the linear regression analysis of the *in vitro* release profile paracetamol of syrup and tablet dosage forms are presented (Table 5). For all categories of the kinetic study, the syrup formulation comparatively showed an increased rate of paracetamol release to the crushed tablet-dosage form. To study the release kinetics, data obtained from *in vitro* release studies were plotted as the cumulative amount of drug released versus time. This resulted in a zero-order release kinetics, thus:

$$Q_t = Q_0 + K_o t, \ldots\ldots\ldots\ldots\ldots\ldots \quad equation\ 1$$

$$Q_t = K_o t, \ldots\ldots\ldots\ldots\ldots\ldots \quad equation\ 2,$$

because, the amount of drug released at

$t = 0$, i.e. $Q_0 = 0$

Here, K_o is the zero–order release constant (Concentration/time), and Q_t is the amount drug released at time, t.

The value K_0 was obtained from the slope of the linear plot of cumulative % drug release versus time.
Mathematically, $K_0 = \frac{Q_t}{t}$.

The implication of this is a higher K_0 translates to an increase in the amount of drug released, and *vice versa.* Hence, the study revealed that syrup dosage forms presented relatively higher values of K_0 than tablet crushed in water.

Even if there may not be any statistical difference in the antipyretic effects of syrup and crushed-in-water dispersible tablets when they are administered exclusively as Okereke *et al.* (2021) had opined, findings from the present study proves that the former elicits relatively faster therapeutic response than would the latter.

Two-way ANOVA test of the AUCs of the dosage forms studied is presented in Fig. 7. To arrive at a reasonable conclusion, three questions were asked. First, does drug dosage form (syrup and tablet) have the same effect at all values of time? Here, the interaction accounted for 0.72% of the total variance (F = 0.40, DFn = 3, DFd = 32 and *P*-value = 0.7532). The interaction is considered not significant, on the basis that there is a 75% chance of randomly observing so much interaction in an experiment of this size, if there is no interaction at all. This finding agrees with the position of Okereke *et al.* (2021). The second question asked was, “does drug dosage form (syrup and tablet) affect the pharmacologic response?” Well, in this study, drug dosage form accounted for 0.86% of the total variance (F = 1.44, DFn = 1, DFd = 32, and *P*-value = 0.2389). Again, if drug dosage form has no effect at all, there is 24% chance of randomly observing an effect this big in an experiment of this size. Hence, the effect is considered not significant. Finally, “does time affect the pharmacologic response?” Time accounted for 79.35% of the total variance (F=44.37, DFn=3, DFd= 32 and *P*-value < 0.0001). If time has no effect overall, there is a less than 0.01% chance of randomly observing an effect this big in an experiment of this size. Thus, the effect is considered extremely significant.

Consequently, the argument is not about whether scaled-down adult dose paracetamol tablets can elicit therapeutic response as much as it is about the age-appropriateness of it. The time taken to elicit therapeutic response is shorter when paediatric syrup formula of paracetamol is used than the adult dosage within the paediatric population. By implication, therefore, the *in vivo* bioavailability of the paediatric syrup formula of paracetamol will elicit a faster therapeutic effect than the adult dosage form in paediatric patients (Rojas and Restrepo, 2015; Bouhaddou *et al.,* 2020; Varela-Moreira *et al.,* 2022).

Thus, child caregivers who practice or hold the notion that scaled-down, adult-dose-crushed paracetamol tablet reconstituted in water elicits better therapeutic outcome to the paediatric syrup dosage form is by the findings of this study unfounded. If anything, crushing adult-dose paracetamol tablet for paediatric use can release all of the drug at once and predispose the child to the risk of the side effects such as liver failure, renal failure, and metabolic acidosis (de Bont *et al.,* 2014). There is a reason that there are pain relief options that are developed specifically for little ones. Accuracy when giving medication to a child is indispensable; it is crucial to constantly measure the dose given to children, and this is not possible when administering a medicine not made specifically for paediatrics. Manipulating

and crushing adult paracetamol also means that the parent or carer are unable to know the dose that they are administering to the child–especially in relation to their size, age, and weight. Succinctly, adult paracetamol is not made to correctly dose children or babies.

5. CONCLUSION

The comparative *in vitro* pharmacokinetic study of commercially available brands of paracetamol syrups and dispersible tablets, vis-a-vis paediatric population revealed that the paediatric syrup formula has a better release kinetics than the scaled down adult formula.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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