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Computational prediction of pharmacokinetic parameters as an *in vitro* approach for assessing paracetamol tablets for IVIVC; a strategy in COVID-19 disruptive times.

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ABSTRACT

In vitro-in vivo correlation (IVIVC) is a desirable attribute for any drug dissolution test to establish relevance and confidence in evaluating the quality and safety of products. The pharmacokinetic parameters of paracetamol have been studied extensively but information about the IVIVC is scanty and mostly controversial; this justifies its choice as a model drug for this study. This work is aimed to evaluate and compare the IVIVC dissolution profile of different brands of paracetamol tablets using authentic pharmacokinetic parameters such as; maximum observed dug concentration (C_{max}), time to reach C_{max} (T_{max}) and Area under Curve concentration-time curve (AUC) obtained from literature. *In vitro* release data were obtained for each brand (n=12) using the USP II apparatus at 50 rpm in 900 ml phosphate buffer of pH 5.8, maintained at 37±0.5 °C and the results were mathematically extrapolated to predict *in vivo* data. The percent predicted error (% PE) for C_{max} ranges from 1.70 to 6.52 % across the brands, while those for T_{max} and AUC were < 0 % and > 20 % respectively. The observed low prediction error for C_{max} and T_{max} (<10 %) demonstrated that the paracetamol IVIVC model was valid based on FDA guidelines. While a satisfactory result could not be achieved for AUC, promising results were obtained exploiting the convolution based IVIVC model.

Key words: In vitro-in vivo correlation, paracetamol, dissolution, pharmacokinetics

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INTRODUCTION

In vivo-in vitro correlation (IVIVC) is a mathematical concept that reveals the relationship between an *in vitro* property (extent of drug release) of a dosage form and a key *in vivo* response (amount of drug absorbed) [1]. The primary objective of developing an IVIVC is to establish the *in vitro* test as a surrogate for human bioequivalence studies [1]. The IVIVC can also be used to support and/or validate the use of dissolution method and set dissolution specifications as to whether the two pharmaceutical products are equivalent or not. It can be utilized to predict bioavailability of some drug substances thereby minimizing the high cost of bioequivalence studies and also decrease the lead time of generic product development [1].

Convolution IVIVC is the process of extrapolating drug profile from in vitro dissolution result, whereas getting dissolution profile from a blood profile is known as deconvolution IVIVC [2]. Convolution process utilizes *in vitro* dissolution data to achieve blood drug levels by employing pharmacokinetic parameters gotten from literature of a test product-hence it does not require human study; and there is no need to define experimental conditions of an appropriate dissolution test for multiple products with different *in vivo* release properties unlike deconvolution method [2]. Convolution technique is now even more relevant in a COVID-19 era since contact with human subject is absent.

Paracetamol is a nonsteroidal analgesic without anti-inflammatory property [3]. It is on a borderline between Biopharmaceutics Classification System (BCS) class I and III [2]. Both class I and III drugs are considered eligible for biowaiver especially if their margin of safety is broad [4]. The pharmacokinetic properties of this drug have been evaluated to a large extent but information concerning its *in vivo–in vitro* correlation is few and also discriminatory; and this has made most countries not to adopt paracetamol biowaiver monograph despite its availability [3]. Hence, it's choice for this study. It has been recommended by some authors that biowaiver for immediate release paracetamol tablet should be accepted if the test product contains the same number of excipients in the right amount, and dissolves rapidly; and also possess similarity value of dissolution profiles in comparison to that of reference product [4]. However, in-equivalency have been recorded in some commercial paracetamol formulations by several authors [2]. It is also on report that absorption of paracetamol from oral tablet preparations could affect its dissolution rate negatively [5]; and two controlled-released paracetamol preparations which differs in release profiles could showed different plasma concentration profiles [5], just as USP dissolution test for paracetamol tablets has failed for some formulations that are bioequivalent, and alternative dissolution methods have been proposed by some authors [2].

In this work, we evaluate and compare the IVIVC dissolution profile of different brands of paracetamol tablets using authentic pharmacokinetic parameters obtained from literature to reveal the relationship between extent of drug release and their amount of drug absorbed via convolution procedure, and also checked if there is any variation between the pharmacokinetic parameters obtained from dissolution data for generics versus the reference tablets under identical test conditions.

MATERIALS AND METHODS

Three brands of paracetamol immediate release tablets (500 mg) were sourced from retailed pharmacy outlet in Abuja metropolis of Nigeria. Brand A was manufactured in Nigeria, while brand B was made in the UK. Both brands were compared to an Innovative Brand-Panadol® (IB).

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

Physicochemical evaluations of various batches

Identification test, weight variation, crush strength, friability, disintegration, and assay test were all determined by methods described elsewhere [5,6,7].

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. Samples (10 mL) were withdrawn and replaced at 0.08, 0.17, 0.33 and 0.5 h. The withdrawn samples were filtered with the aid of 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 [7].

Pharmacokinetic parameters.

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

Bioavailability (F)=0.76; Volume of distribution (V_d)= 0.85 L/Kg; Half-life ($T_{1/2}$) =7h; 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 [5].

Mathematical expression.

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

$$f1 = \frac{\{\sum_{t=1}^{n} Rt - Tt\}}{\{\sum_{t=1}^{n} Rt\}} \times 100$$

$$f2 = 50 \times log\left\{1 + \frac{1}{n}\sum_{t-1}^{n}(Rt - Tt)^2\right\}^{-½} \times 100$$

Where Rt is the percentage of dissolved reference or innovative brand at a given time t,

Tt is the percentage of dissolved generic product, while n is the number of time point.

Discrete amount in (mg) were calculated from the percentage of drug release obtained from dissolution test[6].

Elimination rate was computed using:

$$ke = (In\ C1 - In\ C2/(t2 - t1)$$

Where predicted drug amount in blood at time t1 and t2 are C1 and C2, and Ke represent first order elimination rate constant [8].

The expected profile in blood level was extrapolated using:

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

F and Vd represent bioavailability and volume of distribution respectively [8].

$$\%\ PE = Observed\ parameter - Predicted\ parameter \times 100/Observed\ parameter$$

And PE depicts predicted error [8].

RESULTS

Physicochemical studies of paracetamol tablets

A violet colour confirmed the presence of paracetamol in all batches [7]. Weight variation values were ideal for tablets weighing 250 mg or more [7]. Only IB met specification for hardness test (4-10 kgF) [6]. All batches met ≤1 % specification for friability [5]. Drug content for all brands were within 100 ± 5 % specification [7]. All tablets disintegrate within 15 min specified for conventional tablets [7]. (Table 1).

In vitro release study of paracetamol tablets

The indifference in the physicochemical parameters evaluated for A and B when compared to IB laid the foundation for conducting in vitro dissolution study [8]. Results show that all brands release over 80 % of paracetamol within 30 min as stipulated in USP (figure 1). Comparison between the dissolution profiles was achieved using f1 and f2; and the apparent dissimilarity between A and B (f1 values were ≤15 and those for f2 ≥50) in comparison to IB is the criteria for the follow-up IVIVC model development (table 1) [8].

In vitro-in vivo study

The calculated drug levels for all brands are shown in Table 2a, 2b and 2c. Figure 2 depict the calculated drug levels of the products in blood at various time intervals which helps in determining C_{max}, T_{max} and AUC for all brands. Results obtained from the *in vitro* dissolution study which eventually were converted to AUC, C_{max} and T_{max} with their respective predicted error for all brands are presented in table 3. The percent predicted error (table 3) to determine the predictability of the model for C_{max} and T_{max} were less than 10 % which is within the acceptable limit, where as those of AUC were greater than 20 % suggesting lack of predictability [9].

DISCUSSION

The physicochemical results showed that all samples had acceptable quality. The tablets were satisfactory in appearance, content, disintegration, friability and in weight [2]. This is a measure of good manufacturing practices (GMP) employed by the particular companies involved.

Dissolution test evaluates the rate and extent of absorption and subsequent therapeutic outcome of a drug. This test is key in predicting in vivo

bioavailability of most oral drugs. Drug absorption precede elimination phase, making release of drug within sampling interval to have its unique profile for first order elimination kinetics [9]. This profile when extrapolated gives drug levels at various time following absorption. The similarity in C_{max} value reported in literature for paracetamol tablet when compared to those observed in this study validates this approach (table 3). Comparable values for C_{max} and AUC have been predicted between test and reference paracetamol tablets in a similar study [4]. IVIVC of a drug product can be established if an *in vitro* dissolution test appears to be predictive of *in vivo* absorption [2]. Our findings however suggested that evaluating dissolution characteristics of paracetamol tablets could play an integral role in calculating their corresponding blood drug levels.

Variations in C_{max} T_{max} and AUC across the brands could be attributed to the type and quantity of excipients used. For instance, formulations with larger amount of sodium bicarbonate have been shown to have faster drug absorption [8]. Type of dissolution apparatus used could play a part. Dissolution has been shown to be faster with crescent- shaped spindle than with paddle. The former could reflect in vivo release across gastro intestinal tract producing in vivo hydrodynamics; whereas with the later, only a limited release could take place from the surface of the tablet that is in contact with the surface of the vessel [10]. Discriminatory nature of dissolution media may be another reason. When dissolution conditions are altered to reflect in vivo performance of drug by developing biorelevant and biopredictive media such as dissolution-absorption or permeation stimulating system IVIVC performance could be improved [11].

CONCLUSION.

Today, computational techniques are increasingly been employed in developing pharmaceuticals and there is need to expand the translation of in vitro data into in vivo performance to aid Research and Development in providing reliable predictions. Our work employed a simple convolution technique and suggested that data from *in vitro* release of paracetamol tablet could give scientific information about the predicted *in vivo* plasma drug profile. Furthermore, pharmacokinetic data from studies involving human volunteers can be utilize to establish and cross validate the model.

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Table 1. Physicochemical parameters, f1 and f2 values of IB, A and B of paracetamol.

	H (kgF)	F (%)	WV (g)	DT (min)	A	f1	f2
IB	6.83±0.73	0.37	0.67±5.20	0.40±0.32	96.13		
A	16.00±5.29	0.50	0.65±3.14	1.22±0.57	101.01	3	82
B	10.80±0.53	0.17	0.58±2.52	6.31±0.01	96.40	3	84

H=Hardness (n=6), F=Friability (n=10), WV=weight variation (n=20), DT=Disintegration time (n=6), A=Assay

Table 2a. Discrete amount release and their corresponding predicted blood amount obtained within sampling intervals for IB.

Dissolution sampling time (h)			0.08	0.17	0.33	0.5
Discrete amt. (mg) released			346.5	92.85	29.3	0.45
TA (h)	**PBA (mg)**				**PTA (mg)**	**PC (µg/mL)**
0					0	0
0.08	346.5				346.5	4.43
0.17	343.09	92.85			435.94	5.57
0.33	337.1	91.13	29.3		457.53	5.84
0.5	330.85	89.44	28.76	0.45	449.5	5.74
1	313.14	84.65	27.22	0.43	425.44	5.43
2	280.52	75.83	24.39	0.38	381.12	4.87
3	251.3	67.93	21.85	0.34	341.42	4.36
4	225.12	60.86	19.57	0.31	305.86	3.91
5	201.67	54.52	17.53	0.27	273.99	3.50
6	180.66	48.84	15.71	0.23	245.44	3.14
7	161.84	43.75	14.07	0.22	219.88	2.81
8	144.98	39.19	12.6	0.2	196.97	2.52
9	129.88	35.11	11.29	0.18	176.46	2.25
10	116.35	31.45	10.11	0.16	158.07	2.02
11	104.23	28.18	9.06	0.14	141.61	1.81
12	93.17	25.24	8.12	0.13	126.66	1.62
13	83.46	22.61	7.27	0.11	113.45	1.45
14	74.77	20.26	6.51	0.1	101.64	1.30
15	66.98	18.15	5.84	0.09	91.06	1.16
16	60	16.23	5.23	0.08	81.54	1.04
17	53.75	14.56	4.68	0.07	73.06	0.93
18	48.15	13.05	4.2	0.07	65.47	0.84
19	43.14	11.69	3.7	0.06	58.59	0.75
20	38.64	10.47	3.37	0.05	52.53	0.67
21	34.62	9.38	3.02	0.05	47.07	0.60
22	31.02	8.4	2.7	0.04	42.16	0.54
23	27.78	7.53	2.42	0.04	37.77	0.48
24	24.89	6.74	2.17	0.03	33.83	0.43

TA = time after absorption, PBA=predicted blood amount after absorption, PTA = predicted total blood amount after absorption, PC = predicted concentration at times.

Table 2b. Discrete amount release and their corresponding predicted blood amount obtained within sampling intervals for A.

Dissolution sampling time (h)	0.08	0.17	0.33	0.50
Discrete amt. released (mg)	337.50	84.20	21.21	20.55

TA (h)	**PBA (mg)**				**PTA (mg)**	**PC (µg/mL)**
0.08	337.5				337.5	4.31
0.17	334.18	84.2			418.38	5.34
0.33	328.35	82.73	21.2		432.28	5.52
0.5	322.27	81.2	20.81	20.55	444.83	5.68
1	305.02	76.85	19.69	19.45	421.01	5.38
2	273.25	68.84	17.64	17.42	377.15	4.82
3	244.78	61.67	15.81	15.61	337.87	4.32
4	219.29	55.25	14.16	13.98	302.68	3.87
5	196.44	49.49	12.68	12.53	271.14	3.46
6	175.98	44.34	11.36	11.22	242.9	3.10
7	157.65	39.72	10.18	10.05	217.6	2.78
8	141.23	35.58	9.12	9.01	194.94	2.49
9	126.52	31.88	8.17	8.07	174.64	2.23
10	133.33	28.56	7.32	7.23	176.44	2.25
11	101.53	22.92	6.55	6.47	137.47	1.76
12	90.96	20.53	5.87	5.86	123.22	1.57
13	81.48	18.39	5.26	5.25	110.38	1.41
14	72.99	16.48	4.71	4.7	98.88	1.26
15	65.39	14.76	4.22	4.21	88.58	1.13
16	58.58	13.22	3.78	1.33	76.91	0.98
17	52.48	11.84	3.39	1.19	68.9	0.88
18	47.01	10.61	3.03	1.07	61.72	0.79
19	42.11	9.51	2.72	0.95	55.29	0.71
20	37.73	8.52	2.22	0.86	49.33	0.63
21	33.8	7.63	2.18	0.77	44.38	0.57
22	30.28	6.83	1.95	0.69	39.75	0.51
23	27.12	6.12	1.75	0.61	35.6	0.45
24	24.3	5.48	1.57	0.55	31.9	0.41

TA = time after absorption, PBA=predicted blood amount after absorption, PTA = predicted total blood amount after absorption, PC = predicted concentration at times

Table 2c. Discrete amount release and their corresponding predicted blood amount obtained within sampling intervals for B.

Dissolution sampling time (h)	0.88	0.17	0.33	0.50
Discrete amt. released (mg)	346.9	83.6	15.3	8.75

TA (h)	**PBA (mg)**				**PTA (mg)**	**PC (µg/mL)**
0	0				0	0
0.08	346.9				346.9	4.43
0.17	343.48	83.6			427.08	5.46
0.33	337.49	82.14	15.3		434.93	5.56
0.5	331.24	80.62	15.02	8.75	435.63	5.56
1	313.51	76.31	14.21	8.28	412.31	5.27
2	280.85	68.36	12.73	7.42	369.36	4.72
3	251.6	61.24	11.4	6.64	330.88	4.23
4	225.39	54.86	10.22	5.95	296.42	3.79
5	201.91	49.15	9.15	5.33	265.54	3.39
6	180.88	44.03	8.2	4.78	237.89	3.04
7	162.04	39.44	7.34	4.28	213.1	2.72
8	145.16	35.33	6.58	3.83	190.9	2.44
9	130.04	31.65	5.89	3.43	171.01	2.18
10	116.49	28.36	5.28	3.08	153.21	1.96
11	104.36	25.4	4.73	2.76	137.25	1.75
12	93.49	22.76	4.24	2.47	122.96	1.57
13	83.75	20.39	3.8	2.21	110.15	1.41
14	75.03	18.26	3.4	1.98	98.67	1.26
15	67.21	16.36	3.05	1.76	88.38	1.13
16	60.21	14.66	2.73	1.59	79.19	1.01
17	53.94	13.13	2.44	1.42	70.93	0.91
18	48.32	11.76	2.19	1.28	63.55	0.81
19	43.29	10.54	1.96	1.14	56.93	0.73
20	38.78	9.44	1.76	1.02	51	0.65
21	34.74	8.46	1.57	0.92	45.69	0.58
22	31.12	7.57	1.41	0.82	40.92	0.52
23	27.88	6.79	1.26	0.74	36.67	0.47
24	24.98	6.08	1.13	0.9	33.09	0.42

TA = time after absorption, PBA=predicted blood amount after absorption, PTA = predicted total blood amount after absorption, PC = predicted concentration at times

Table 3. Predicted and observed pharmacokinetic parameters for IB, A and B with corresponding percentage prediction error for C_{max}, T_{max} and AUC.

		PV	IB (OV)	A (OV)	B (OV)	IB (PPE)	A (PPE)	B (PPE)
1	C_{max}	6.17	6.60	6.42	6.28	6.52	3.89	1.75
2	AUC	31.2	57.17	56.32	55.42	45.43	44.60	43.44
3	T_{max}	1.06	0.33	0.5	0.5	-221	-112	-112

PV= predicted values, OV = observed values, PPE = percent prediction error

Figures

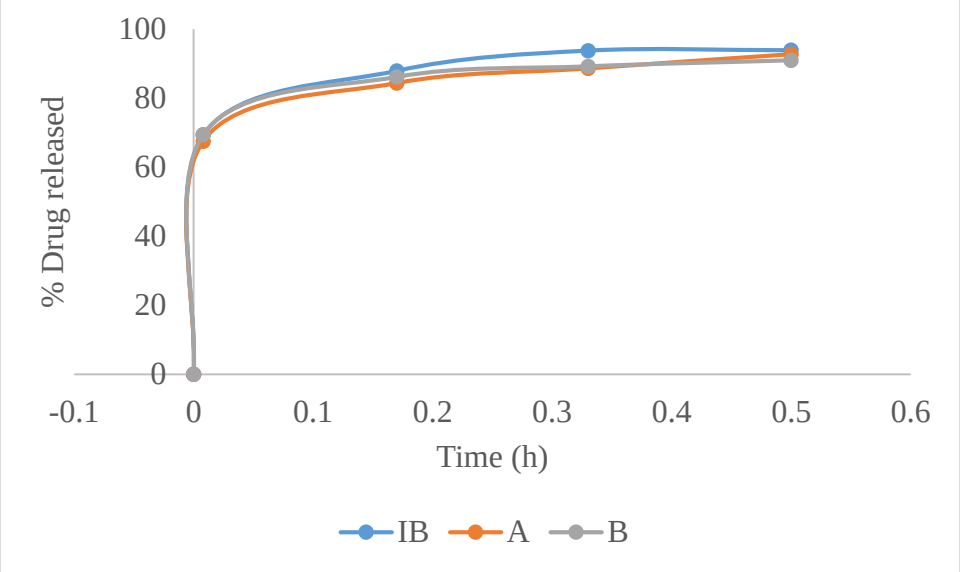

Figure 1. In vitro drug release for A, B and IB (n=12).

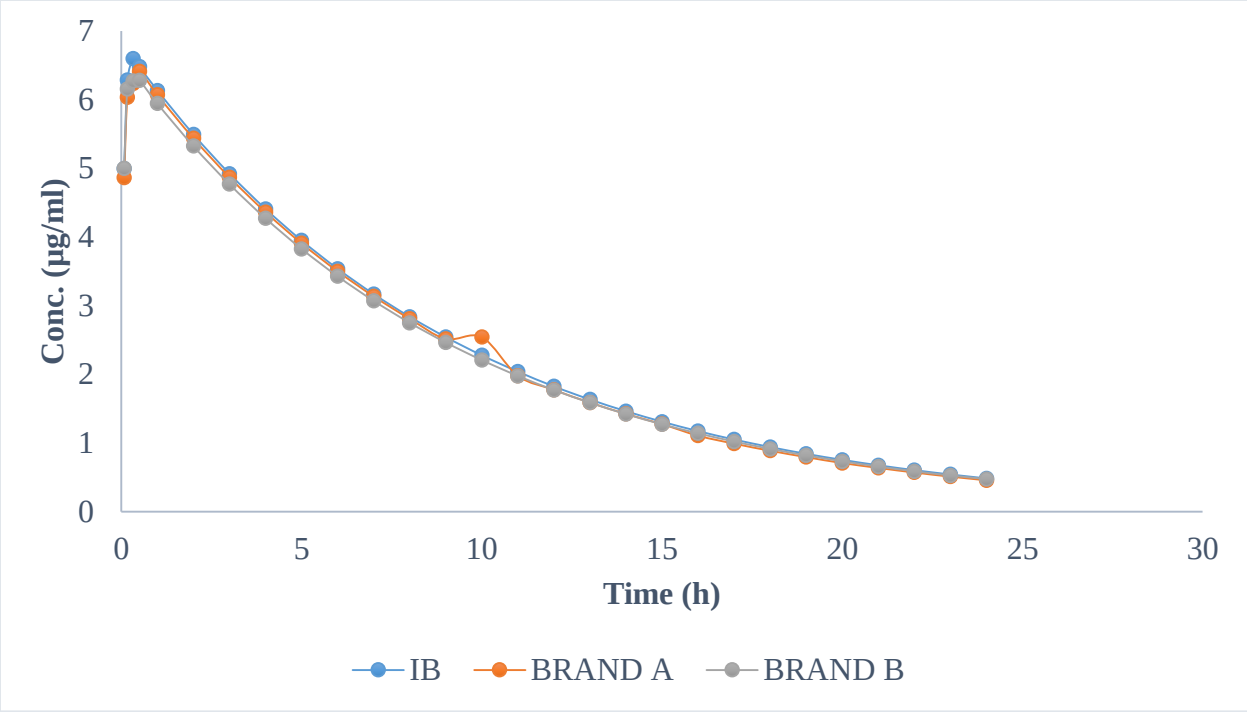

Figure 2. Plasma drug concentration time profiles derived from in vitro dissolution profiles for A, B and C (n=12).