Product Evaluation of Carbamazepine 200mg Controlled Release Tablets using an *in vitro-in vivo* Correlation Simulation Model

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Evaluation of the dissolution characteristics of drugs and their bioavailability can be conducted using an *in vitro-in vivo* correlation model. This can help in assessing the products available in the market for quality. Random testing in post-marketing surveillance would gauge the quality of the drug products. This study involved evaluation of three batches of controlled-release carbamazepine, Tegretol 200mg CR® tablets through dissolution tests from which a dissolution profile and blood concentration-time profile were derived. The *in vitro-in vivo* correlation simulation model was used to determine the Area Under Curve and Maximum Plasma Concentration and demonstrate bioequivalence of the product batches. The three batches exhibited similarity upon statistical analysis. The results also correspond to the values obtained in literature from bioequivalence studies. *In vitro-in vivo* correlation can thus be a useful instrument in pharmacovigilance for marketed drug products.

Keywords: IVIVC, carbamazepine, bioavailability, pharmacokinetic parameters, dissolution

INTRODUCTION

Pharmaceutical products should exhibit efficacy and safety during their active shelf life. Different brands should demonstrate interchangeability through pharmacodynamics studies, clinical trials and/ or *in vivo* bioequivalence studies. The method chosen depends on the properties of the drug substance and the drug product [1].

In vitro-in vivo correlation (IVIVC) is defined by the US FDA as "a predictive mathematical model describing the relationship between an *in vitro* property of a dosage form and an *in vivo* response"[2]. This relates to dissolution and absorption [3]. It is used as a surrogate in bioequivalence testing for biowaivers, validation of dissolution methods and in quality control during formulation development [4]. The method has been considered useful for estimating bioequivalence for carbamazepine (CBZ) tablets. Bioequivalence of CBZ tablets is assured through this method in the USP specifications of 'not less than 75% dissolved after 1 h' [5].

IVIVC provides an avenue of predicting plasma levels from dissolution studies or vice versa. This is through convolution and deconvolution methods. In convolution, the products of interest are dissolved in appropriate media, samples taken at specific time points, analyzed and a dissolution profile developed. The plasma drug concentration-time curve is then obtained. Using these results and literature values, the expected plasma levels can be compared to authenticate the appropriateness of the drug levels in the formulation.

Bioavailability is defined as the proportion of active drug or its active metabolite that reaches the site of action. This is assessed using Maximum Plasma Concentration **(**C_{max}), time to peak concentration (T_{max}) and Area under curve (AUC). Two drug products are said to be bioequivalent if they provide the same therapeutic effect. Bioequivalence is assumed if a generic test product is within 80-125% match of the reference or innovator product. Single doses are generally accepted for Controlled-Release [CR] products' bioequivalence [BE] testing by the US FDA[6]. For orally administered drugs, similar plasma concentrations of two drugs or two

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batches of the same drug is an indicator of bioequivalence [7].

The Biopharmaceutics Classification System [BCS] classifies drugs based on their solubility and permeability upon oral administration. It enables use of *in vitro* dissolution studies in place of bioequivalence studies. The characteristics of the drug substance are used to classify drugs in the Biopharmaceutical Classification System (BCS) [8]. Carbamazepine is a BCS Class II drug that shows high permeability and low solubility.

Controlled release dosage forms release the drug at a slower rate than the conventional dosage form. This is to attain therapeutic effect with a lower frequency of administration. The drug particles are covered with a material which is resistant to degradation in the stomach/intestine for a period of time. The drug is released via diffusion, erosion, leeching or rupture of the coating material based on the type and thickness of the coat [9]. In oral controlled release formulations, matrix systems are employed as they are cost effective, flexible, are minimally affected by physiological changes in the GIT and are accepted by regulatory authorities [10]. Various kinetic models are employed to define the release mechanism. These include; Zero Order, First Order, Hixson- Crowell, Higuchi, Korsmeyer-Peppas, Hopfenberg, Baker-Lonsdale, Weibull and Quadratic, among others. The best fitting model is then used to determine pharmacokinetic parameters [5].

The aim of this study was to use an IVIVC simulation model to evaluate the bioequivalence of three batches of Tegretol 200mg CR® tablets.

MATERIALS AND METHODS

MATERIALS:

Three batches (A, B and C) of Tegretol® 200mg CR tablets manufactured by Novartis Pharma; Switzerland were purchased from Nairobi Central Business District pharmacies. The Carbamazepine standard was obtained from the Drug Analysis Research Unit (DARU) of the University of Nairobi.
Absorbance was measured on a GENESYS 10S-VIS Spectrophotometer manufactured by ThermoScientific (Waltham, MA, USA). Dissolution testing was carried out on an ERWEKA DT6 Dissolution Apparatus Type I (ERWEKA, Heusenstamm, Germany). Ms Excel and DDSolver software were used for data analysis.

METHODS

The USP 30, 2007 dissolution test method for Carbamazepine CR formulations was used. Dissolution Apparatus Type I (basket type) was used at a speed of 100 rpm. The dissolution medium used was distilled water at 37 ± 0.5 °C. The medium was equilibrated overnight prior to every test to allow for de-aeration.

Different concentrations, 2.3, 4.6, 9.2 and 18.4µg/ml of the carbamazepine standard dissolved in distilled water at 37 ± 0.5 ^{0}C were prepared as per the USP method with sonication. The absorbance values of the solutions at 284 nm were used to obtain the standard dissolution curve.

Six tablets from each batch of Tegretol® 200mg CR tablets were dissolved in 900ml of distilled water at 37 ± 0.5 ^{0}C over a 24- hour period. Aliquots were taken at 1, 3,6,12 and 24 hours with replacement. They were appropriately diluted and their absorbance measured at 284 nm. The absorbance was then compared with the standard curve and the drug concentration obtained.

Data Analysis

Data analysis was carried out using MS Excel Spreadsheet and DDSolver software.

Pharmacokinetic Parameters

The apparent volume of distribution (V_d), bioavailability factor (F), elimination constant (k_{el}) and body weight were obtained from literature [11].

Dissolution Profiles Assessment

The similarity factor, f_2, difference factor, f_1 [12] and ANOVA were used to compare the dissolution profiles of the different batches. Equations 1 to 4 were used in computing various release parameters:

$$D_{rel} = \frac{\%\ \text{drug released} \times \text{product strength}}{100}$$ equation 1

Where D_{rel} = amount of drug released

$$D_{abs} = D_{rel} \times F$$ equation 2

Where D_{abs} = Amount of drug absorbed, F = bioavailability factor

$$C_t = C_0.e^{-kt}$$ equation 3

Where C_t = plasma concentration at time t, C_0 = initial plasma concentration, k = elimination rate constant

$$C_p = \frac{\text{Amount of drug in blood} \times F}{Vd \times \text{Body weight}}$$ equation 4

Where C_p = blood drug concentration, F = bioavailability factor,
V_d = apparent volume of distribution

RESULTS

Dissolution

The dissolution results of the % CBZ released at various sampling time points from the 3 batches are summarized in Table 1.

Dissolution profiles

Dissolution profiles from 3 batches of Tegretol® 200 CR tablets were obtained as shown in figure 1. They were analyzed statistically to determine any inter-batch variation.

Release Kinetics

Zero order, first order, Higuchi release, Korsmeyer-Peppas and Hixon-Crowell models were fitted for the release kinetics. The best-fit was Higuchi release which showed the best linearity upon regression analysis.

Pharmacokinetic profile determination

The discrete amount of drug absorbed was predicted using the dissolved amount per time segment as shown on Table 2 for each batch of the product. Using Microsoft Excel, the concentration of the drug in blood was calculated as shown in Table 3. These concentrations were then plotted against time to obtain the profiles shown in figure 2.

Table 1: Dissolution data of average % CBZ Released per tablet Tested

	% CBZ Released (SD)					
Time (hr)	**0**	**1**	**3**	**6**	**12**	**24**
Batch						
A	0.00	11.05 (2.07)	22.24 (4.28)	40.95 (5.43)	58.10 (7.54)	78.05 (7.43)
B	0.00	10.72 (2.51)	20.14 (3.35)	37.17 (6.36)	58.46 (7.23)	77.89 (8.02)
C	0.00	14.18 (2.07)	30.23 (3.34)	50.71 (5.12)	74.65 (5.23)	88.67 (6.50)

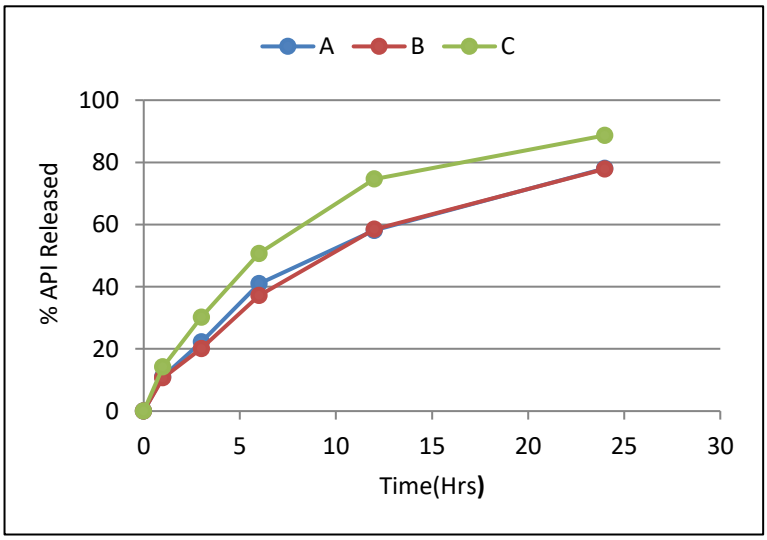

Figure 1: Percentage API release of batches A, B and C over time

Table 2: Drug amount released and absorbed within sampling times

Time (h)	Batch	% Released (Cumulative)	% Released (within sampling interval)	Amt (mg) released (within sampling interval)	Amt (mg) absorbed corrected for bioavailability (F)
0	A	0.00	0.00	0.00	0.00
	B	0.00	0.00	0.00	0.00
	C	0.00	0.00	0.00	0.00
1	A	11.10	11.05	22.10	22.10
	B	10.72	10.72	21.44	21.44
	C	14.18	14.18	28.36	28.36
3	A	22.20	11.19	22.38	22.38
	B	20.14	9.42	18.84	18.84
	C	30.23	16.05	32.10	32.10
6	A	41.00	18.71	37.42	37.42
	B	37.17	17.03	34.06	34.06
	C	50.71	20.48	40.96	40.96
12	A	58.10	17.15	34.31	34.31
	B	58.46	21.29	42.58	42.58
	C	74.65	23.94	47.88	47.88
24	A	78.00	19.94	39.89	39.89
	B	77.89	19.43	38.86	38.86
	C	88.67	14.02	28.04	28.04

Table 3: Predicted Pharmacokinetic profile

	Batch	**Blood Amount after Absorption(mg)**						**Total Blood Amt. after Absorption(mg)**	**Conc. (ng/mL) at Times**	**AUC (ng.h/ml)**
Dissolution Sampling Time (hr)		0	1	3	6	12	24			
0	A	0.00						0.00	0.00	0.00
	B	0.00						0.00	0.00	0.00
	C	0.00						0.00	0.00	0.00
1	A	0.00	22.10					22.10	250.57	125.28
	B	0.00	21.44					21.44	243.08	121.54
	C	0.00	28.36					28.36	321.54	160.77
3	A	0.00	21.27	22.38				43.65	494.92	745.48
	B	0.00	20.64	18.84				39.48	447.61	690.69
	C	0.00	27.30	32.10				59.40	673.47	995.01
6	A	0.00	20.09	21.13	37.42			78.65	891.74	2079.98
	B	0.00	19.49	17.79	34.06			71.35	808.92	1884.78
	C	0.00	25.78	30.32	40.96			97.06	1100.47	2660.92
12	A	0.00	17.92	18.85	33.38	34.31		104.47	1184.41	6228.46
	B	0.00	17.39	15.87	30.38	42.58		106.22	1204.34	6039.78
	C	0.00	23.00	27.04	36.54	47.88		134.46	1524.51	7874.93
24	A	0.00	14.26	15.00	26.56	27.30	39.89	123.01	1394.69	15474.62
	B	0.00	13.84	12.63	24.18	33.88	38.86	123.38	1398.89	15619.39
	C	0.00	18.30	21.52	29.07	38.10	28.04	135.03	1530.97	18332.87
Total	A								**1394.69**	**24528.54**
	B								**1398.89**	**24234.64**
	C								**1530.97**	**29863.73**

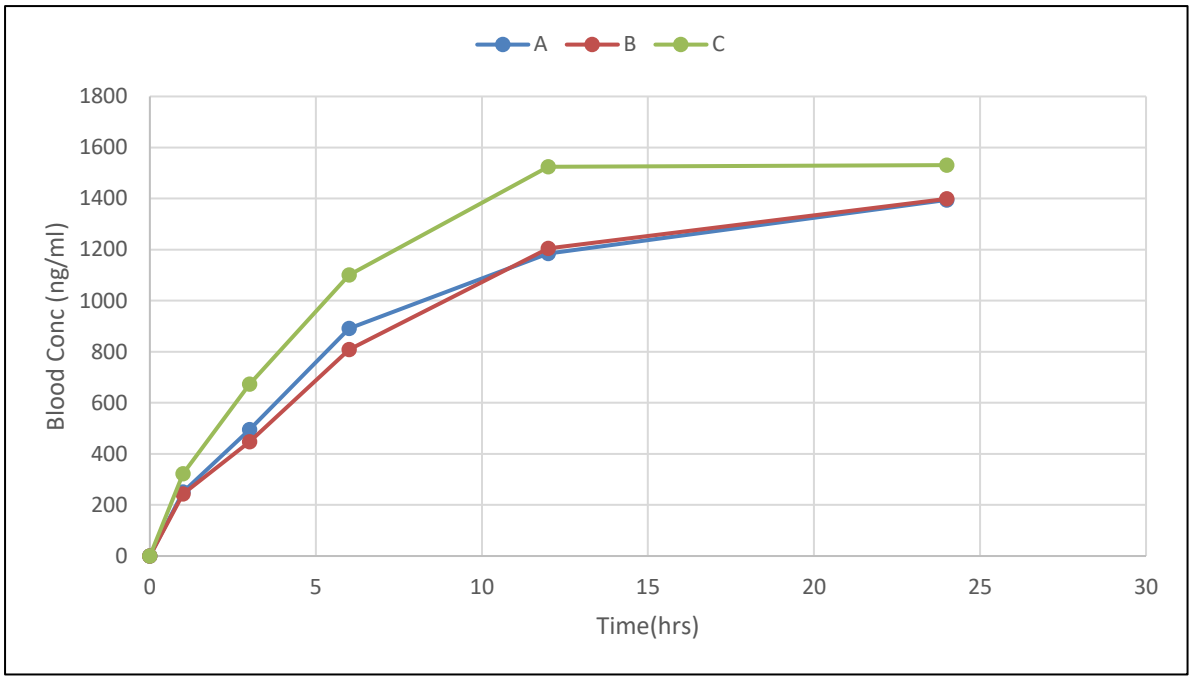

Figure 21: Predicted Blood concentration–time profile

ANALYSIS OF DISSOLUTION DATA

The results for the computation of the selected fit factors are shown in Table 4. ANOVA was carried out on C_{max} and AUC values and the results are displayed in Tables 5 and 6 respectively.

Table 4: Fit factors for the dissolution profiles

Batch	A/B	B/C	A/C
f_1 value	3.1958	26.45	22.84
f_2 value	84.52	50.72	48.62

Table 5: Predicted C_{max} values ANOVA

Summary						
Groups	**Count**	**Sum**	**Average**	**Variance**		
Batch A	6	4216.37	702.72	297604		
Batch B	6	4102.84	683.81	303114.7		
Batch C	6	5150.97	858.5	402783.1		
ANOVA						
Source of Variation	**SS**	**Df**	**MS**	**F**	**p-value**	**f crit**
Between Groups	110277.5	2	55138.76	0.17	**0.85**	**3.69**
Within Groups	5017509	15	334500.6			
Total	**5127787**	**17**				

Table 6: Predicted AUC values ANOVA

Summary				
Groups	**Count**	**Sum**	**Average**	**Variance**
Batch A	5	4216.33	843.27	223859.94
Batch B	5	4102.84	820.57	238616.05
Batch C	5	5150.96	1030.19	282375.32
ANOVA				

Table 6 cont'd

Source of Variation	SS	df	MS	F	p-value	f_{crit}
Between Groups	132333	2	66166.51	**0.266**	**0.77**	**3.89**
Within Groups	2979405	12	248283.77			
Total	3111738	14				
Within Groups	2979405	12	248283.77			
Total	**3111738**	**14**				

DISCUSSION

The FDA guidelines dictate an f_1 range of 0-15 and an f_2 range of 50-100 for an inference of similarity of the dissolution curves. The f_1 values obtained show dissimilar dissolution curves between batches A/C and B/C as the f_1-value is > 15. However, batches A/B have an f_1 value of 3.2 which is < 15 indicating their dissolution curves are similar.

For dissolution profiles comparison, the FDA has adopted the f_2 factor as per the guidelines [6].The obtained f_2 values for A/B and A/C were within the prescribed limits indicating similarity of the dissolution profiles. However, B/C f_2 value of 48% was below the acceptable range. This showed dissimilarity of their dissolution curves. This indicates a difference in the release of the API between the two batches of the products.

With a p-value of 0.85 ($p>0.05$) the C_{max} values of the three batches of product are similar and the differences are not statistically significant. The obtained p-value of 0.77 ($p > 0.05$) implies that the AUC values for the all the batches are similar and the differences are not statistically significant. The calculated F-value is less than F_{crit} , also indicating similarity of the AUC values. The predicted AUC and C_{max} values obtained showed similarity between the three batches of the product tested. This indicates that the differences in the dissolution profiles of B/C batches may not impact on the overall blood concentration-time profile of the product.

From the results, a Multiple Level C IVIVC which indicates the relationship between a PK parameter and dissolved drug at several time points on the dissolution profile [13] was established in this study. In this study, the different batches showed similar dissolution profiles as per the p-values ($p > 0.05$) at all sampling points. From USP limits, the percentage dissolution and release fall within the prescribed limits for all batches. This is important as CBZ has a narrow therapeutic index and whose plasma fluctuations may impact on the patients negatively. Use of IVIVC is therefore useful in comparing batches of a product in the market for consistency without undertaking fresh *in vivo* studies for bioequivalence.

CONCLUSION

The results of the study demonstrate that of the three batches tested, the drug blood concentrations are similar. This indicates that expected therapeutic dosages are obtained from the three batches of the drug. This study demonstrates the utility of IVIVC models for continuous monitoring of the drug product in the market especially in case of one product from different manufacturing sites.

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