ASSESSMENT OF IN-VITRO BIOEQUIVALENCE PARAMETERS OF SOME BRANDS OF PARACETAMOL TABLETS PRODUCED IN SOUTH WEST NIGERIA

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ABSTRACT

Background: Solid dosage forms, especially tablets are the commonest product lines in pharmaceutical industries. This study was therefore conducted to assess the in-vitro bioequivalence of five brands of paracetamol (500mg) tablets manufactured in South West Nigeria to ascertain its quality.

Methods: The parameters assessed were, physical properties (tablet dimensions, shape, colour, and weight variation), mechanical properties and assay (hardness, friability, and content uniformity), and release properties (disintegration, dissolution, release kinetics and mechanism).

Results: All the paracetamol brands complied with pharmacopoeia specifications for percentage weight variation and drug content uniformity while two brands A and D failed the hardness test and one brand, E failed the friability test. The disintegration times for the entire brand were within limit. Brand A had the shortest disintegration time and t_{25}%, followed by brand C. They all released at more than 80% paracetamol within 30 mins as specified by the USP in the following order A<C< D< B< E.

Conclusion: The results of most of the biopharmaceutical parameters assessed complied well with pharmacopoeia specification. So, we can conclude that the paracetamol (500mg) tablets produced in South West, Nigeria used in this study were found to be of good quality and acceptable bioequivalent properties.

Key words: Brand, bioequivalence, biopharmaceutical parameters, paracetamol, bioavailability

INTRODUCTION

Pharmacy practice is set up to ensure care and safety of the patients. This simply means the provision of safe and therapeutically effective drugs for the patients. Paracetamol tablet, an over the counter drug that is widely used and abused in Nigeria is on high demand, so it is sold everywhere and in all places in the country.[1-3] In as much as availability of medicines is important to health development, emphasis should be placed on its safety and efficacy which must not be compromised for the patient's benefit.[4] Because of the high demand of paracetamol tablet, the number of pharmaceutical companies producing it in Nigeria has increased in order to meet this growing demand. However, this has created opportunity for the production and distribution of fake and substandard products which compromised quality, especially in a completely unregulated pharmaceuticals market like Nigeria. So there is a need to carryout bioequivalence studies on some brands to ascertain their quality and to a little extent, their effectiveness and safety which thus necessitated this study.

Drug absorption after oral administration of a tablet determines bioavailability, hence therapeutic response of such drug. Bioavailability measures the rate and extent an active drug substance gets into the general circulation for therapeutic action. It determines the activity of the drug thus differences in bioavailability among brands of a given drug can have clinical significance. Bioavailability depends on the release of the drug from the tablet, its solubilization under physiological conditions and permeability across the gastrointestinal tract (GIT). Factors that could affect the release of drugs after oral administration of a tablet may include formulation variables, processing variables, storage conditions etc. To establish bioequivalence, biopharmaceutical studies including dissolution are important parameters that should be evaluated. Dissolution should give an idea of bioavailability of a drug in a patient with normal GIT conditions. Different brands of the same drug are said to be bioequivalent if they are pharmaceutically equivalent and their bioavailabilities at the same dose are similar to such a degree that their effects either desirable or undesirable, are expected to be essentially similar.[5] FDA [6] defined bioequivalence as the "absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same dose under similar conditions in an appropriately designed study". Pharmaceutical equivalence implies brands having the same amount of the same active substance, in the same dosage form, for the same route of administration and meeting the same or comparable standards, and chemical equivalence when the inactive substances in the drug products differ.

In this study, attempt was made to assess the biopharmaceutical parameters of some selected brands of paracetamol tablets produced in South West Nigeria with the intent to ascertain their quality.

MATERIALS AND METHODS

MATERIALS

Five brands (BONADOL®, DUNAMOL®, CHI Paracetamol®, Emzor Paracetamol® and M&B Paracetamol®) of 500mg paracetamol tablets manufactured in south-west Nigeria were used for this study. Pure paracetamol powder, a gift from Topway Pharmaceutical Industries Ltd, Illisan, Ogun State. Other reagents used were potassium dihydrogen phosphate and hydrochloric acid.

METHODS

Uniformity of weight

Twenty tablets from each brand were weighed individually and the mean weight and standard deviation was calculated.

Dimensions

The thickness and diameter of twenty tablets from each brand were measured using a micrometer screw gauge and the mean thickness and diameter with their standard deviation were calculated

Hardness

Hardness was determined by using a Tablet Hardness Tester (DKB instrument, Mumbai, Model EH 01). One tablet from each brand was placed between the anvil and the spindle of the tester and the tester zeroed before the knob was screwed to apply a force on the tablet. The force at which the tablet cracked or broke into halves was then recorded. Determinations were done in triplicates.

Friability

Friability was calculated as the percentage lost in weight of 10 tablets placed in a Tablet Friablity Apparatus (Veego Scientific Devices, Mumbai, India) which was operated for 4 minutes at 25 revolutions per minute. Mean of three determinations were taken.

Disintegration time determination

The disintegration test was carried out using a six station disintegration test apparatus (Shivani scientific Ind., Mumbai, India). Six tablets were placed in each basket and immersed in 900mL distilled water maintained at a temperature of 37°C±2°C as the disintegrating medium. The disintegration time was taken when no particle remained in the basket mesh.

Calibration curve

Standard dilutions of a stock solution of pure paracetamol (100µg/mL) were prepared with phosphate buffer pH 7.4 in the concentration range 2-20µg/mL. Absorbance of the of the resulting solution were taken at 247nm and plotted against the concentrations to obtain the calibration curve.[7]

Drug content determination

Drug content uniformity was done according to the United Stated Pharmacopeia. Twenty tablets from each brand were weighed and powdered. Powered tablet equivalent to 0.25 mg of Paracetamol was accurately weighed and transferred into a 100 ml volumetric flask. 10 ml of phosphate buffer pH 7.4 was added and shaken for 10 min. Thereafter, the volume was made up to the mark with phosphate buffer pH 7.4. The mixture was filtered and 1 ml of the filtrate was diluted with phosphate buffer pH 7.4 in a 10 ml volumetric flask and analyzed at 247nm using a UV/VIS Spectrophotometer (Spectrum Lab 752s, England, UK). The drug content of the each brand was obtained from the calibration curve (Figure 1).

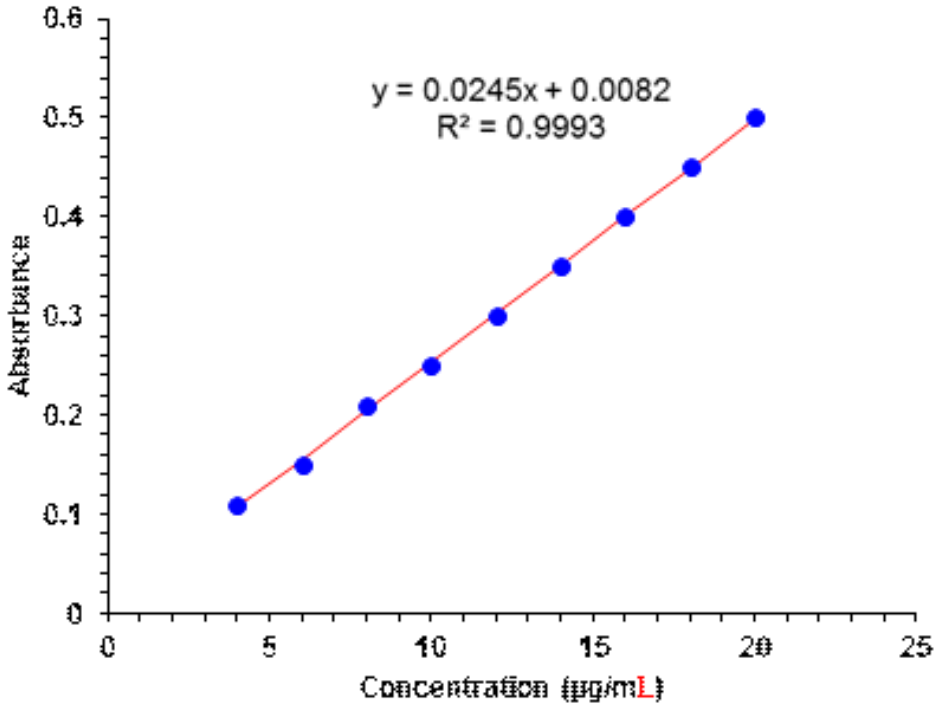

Figure 1. Standard calibration curve of paracetamol

In-vitro drug release study

The in-vitro drug release study was performed using a rotating basket USP Dissolution Apparatus (Model NE4-COPD, Copley Scientific, Nottingham, UK) operated at 100 rpm. The dissolution medium was 900 ml of phosphate buffer pH 7.4 at 372°C. Five mL samples were withdrawn at 5, 10, 15, 30, 45 and 60 mins and immediately replaced with 5 ml of fresh dissolution medium. The withdrawn sample was analysed with UV/VIS Spectrophotometer (Spectrum Lab 752s, England, UK) at 247 nm. The concentration of paracetamol released was calculated using a regression equation obtained from the calibration curve.

Analysis of dissolution data

Mean dissolution time (MDT), t_{25}% and t_{50}% (time for 25 % and 50% of drug to be released respectively) were obtained from the dissolution profile and were used to characterize the drug release rate.

Drug release kinetics

The data obtained from the dissolution profiles were fitted into different mathematical models to assess the drug release kinetics of all the batches of the paracetamol tablets. Zero-order, first order, Higuchi and Korsmeyer-Peppas were the models used.[8-10] The model that suitably fits the drug release was determined from the correlation coefficient (r^2) obtained from the regression analysis. The release mechanism was determined from the release exponential (n) obtained from Korsmeyer-Peppas equation.

Statistical analysis

The statistical analysis was performed using Microsoft excel 2010 version to obtain mean and relative standard deviation while DDsolver software was used for the release profile, mean dissolution time (MDT), t_{25} and t_{50}, and the mechanism of release.

RESULTS

Tablet dimension variation

The results of weight, thickness and diameter were expressed as mean and relative standard deviation as presented in Table 1. All the brands showed some variations in average weights, thickness and diameter. The average tablet weight ranged from 517 to 578 mg.

Table 1. Quality control parameters of the paracetamol

PARAMETERS	A(mean±SD)	B	C	D	E
Weight (mg)	578.00±0.04	561.00±0.02	553.00±0.02	536.00±0.01	517.00±0.01
Weight variation (%)	2.02 ±0.80	2.99 ±2.36	0.37 ±0.26	0.21 ±0.2 5	0.51 ±0.7 4
Thickness (mm)	4.14±0.44	4.29±0.21	4.12±0.10	4.12±0.40	3.70±0.10
Diameter (mm)	13.07±0.00	12.60±0.05	12.61±0.08	13.17±0.16	12.64±0.01
Friability (%)	0.58±1.14	0.68±0.22	0.94±0.63	0.58±0.31	2.97±2.04
Hardness (Kg/f)	12.00±1.50	7.67±1.16	6.54±1.16	12.2±1.26	5.51±1.32
Disintegration (min)	1.01±0.71	9.28±1.61	1.30±0.83	2.77±1.73	1.19±1.01
Content uniformity (%)	99.42	101.76	99.82	100.20	101.06

Mechanical properties and assay

The hardness of the five brands of paracetamol tablet revealed that three brands B, C and E complied with pharmacopeia specification (4 to 8 kgf) having values of 7.67, 6.54 and 5.51Kg/f respectively while brands A and D

with values 12.00 and 12.2 Kg/f respectively did not (Table 1). However, brands A, B, C and D met the USP specification for friability with values ranging from 0.58 to 0.94% while brand E with value of 2.97% failed. The percentage of paracetamol content for all the brands ranged from 99.42 to 101.76 (Table 1).

Release properties

All brands disintegrated between 1.01 and 9.28 mins with brand A having the shortest time and brand B having the longest time (Table 1). The release rate of paracetamol from the five brands as determined by the means dissolution time (MDT), t_{25}% and t_{50}%, obtained from the dissolution profile (Figure 2) is shown in table 2. The t_{25}%, time required for 25% of paracetamol to be released from the brands was in the order A < C < D < B < E with values 1.53, 1.62, 2.45, 4.00 and 4.95 mins while the t_{50}% and MDT followed same order as t_{25}% with values 3.69, 3.85, 4.68, 9.64 and 11.93 mins, and 6.58, 6.77, 8.79, 13.15 and 14.17 respectively. The correlation coefficient (r^2) from the release rate kinetic modeling in Table 3 was between 0.9808 and 0.9145 and the diffusion exponential n, for all the brands was observed to be between 0.157 and 0.397.

Table 2. Dissolution times of the paracetamol tablets

BRAND	t_{25}% (mins)	t_{50}% (mins)	MDT (mins)
A	1.53	3.69	6.58
B	4.00	9.64	13.15
C	1.62	3.85	6.77
D	2.45	4.68	8.79
E	4.95	11.93	14.19

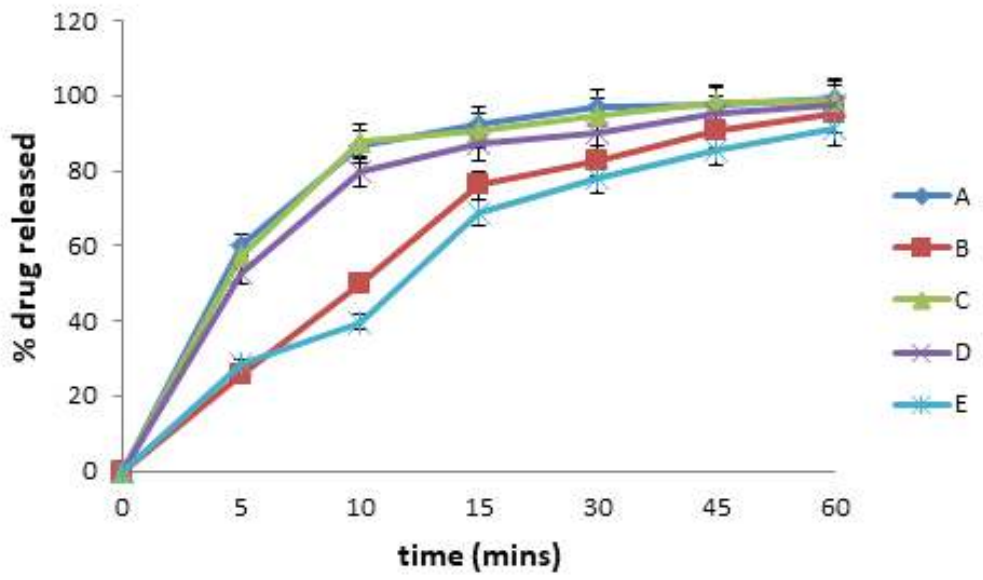

Figure 2. Release profiles of the paracetamol tablets

BRANDS	KH	r2	KKP	r2	N
A	0.188	0.9808	56.439	0.7466	0.149
B	0.072	0.9456	21.900	0.8577	0.374
C	0.180	0.9534	54.535	0.7224	0.157
D	0.148	0.9145	47.638	0.8004	0.185
E	0.058	0.9242	18.920	0.8934	0.397

r^2 = correlation coefficient, n = exponential, K_H = higuchi release rate constant, K_{KP} = korsemeyerpeppas release rate constant

DISCUSSION

All the brands of paracetamol 500mg used in this study were well within their shelf life as at the time the study was conducted. They are all white and round in shape without any physical abnormalities. All brands had manufacturing and expiration dates, batch numbers and NAFDAC (National Agency for Food, Administration and Control) registration numbers.

The variation shown in average weights is probably an indication that different excipients were used in the formulation of the brands. Also, there were variations in average thickness. Generally, variation in tablet thickness could be due to the volume of powder blend of formulation filled into the die from the hopper during tableting, compression pressure employed and the size of the die used.[11, 12] In this case, tablet thickness was found to be partly related to the weight/volume of the tablets as brand E with the least weight had the smallest thickness. The percentage weight variation analysis of all the brands showed compliance with the British Pharmacopeia (BP) specification since none of the brands deviated from the official specification. The implication of this is that drug content uniformity is most likely to be satisfactory. Weight variation outside specification limit is an indication of less or more dose of the drug per tablet which could compromise the efficacy and safety of the drug. All the brands had fairly similar tablet diameter.

Hardness is a measure of tablets strength while friability is a measure of tablets weakness, both indicates the ability of a tablet to withstand mechanical shocks during manufacturing, packaging, shipping and handling by consumers.[13] Hardness (tablet breaking force) and friability are non-official quality control test. However, they are now included in the United States Pharmacopeia (USP) since 2007. The USP specification for hardness of uncoated tablet is 4 to 8 kgf.[14] The hardness of the five brands of paracetamol revealed that three brands B, C and E complied with specification while brands A and D did not. However, brands A, B, C and D met the USP specification for friability while brand E failed. Convectional tablets which loose more than 1% of their weight during the friability test are rejected. The brands that failed the hardness test could be as a result of the concentration of the binder used being too high in the formulation[15] or due to high compression force.[16]Ordu et al.; Odeku and Itiola; Rahul et al.; Meena et al.[17-20]and others have established that increase in binder concentration has a direct relationship with tablet hardness which has an impact on disintegration as excess compression pressure and binder concentration could make tablet to be too hard, delaying or preventing disintegration in some instances.
All the brands had drug content within the USP specification (95–105%). This is in line with the results of weight uniformity.

Disintegration and dissolution test were used to assess the release properties of the five brands of paracetamol used in this study. The

USP specification for disintegration time for uncoated tablet is 5 to 30 minutes.[14]All the brands complied with USP limit despite some failing the hardness test. There should generally be a strong correlation between hardness and disintegration as reported in literatures.[15, 17-20]This was also observed with some brands (B, C and E) in this study except for brands A and D which do not show correlation when compared with other brands. The difference observed with the relationship between hardness and disintegration in this study could probably be due to the inclusion or non-inclusion of disintegrant in the formulation, and also type, nature and concentration of the disintegrant used.

The drug release study gives an idea of amount of the drug released from the drug delivery design for onward absorption and availability for therapeutic activity. The onset of action of a drug is determined by how fast the drug is released for absorption. The use of paracetamol by patients requires a fast action so they could be relieved of fever and pain in a short time. The time required for 25% (t25%) of paracetamol to be released from the brands was in the following order A<C< D< B< E. Brand A which released 25% of paracetamol in the shortest time, followed closely is Brand C would give a faster onset of action than other brands, so they are the most preferred brands for fast relieve of fever and pains. The time required for 50% of paracetamol to be released from the brands was satisfactory. They all released more than 80% paracetamol within 30 mins as specified by the USP in the following order A<C< D< B< E. The MDT also followed the same order. The release kinetic modeling fits the Higuchi model which showed the highest linearity for all the brands. The diffusion exponential (n) obtained from KorsemeyerPeppas equation, for all the brands was observed to be below 0.45 indicating that mechanism of drug release is Fickian diffusion.

Conclusion

The biopharmaceutical parameters of some brands of paracetamol tablets produced in South West Nigeria have been assessed to ascertain their quality. The tablets possess properties that complied well with pharmacopoeia specification and could be described to be of acceptable quality.

Limitations

The number of brands of paracetamol tablet selected for this study was small compared to the number of companies producing paracetamol tablet in the south west. This is not enough to be used to generalize the conclusion of this study.

REFERENCES

1.Akande TM and Ologe MO (2007). Prescription pattern at a secondary health care facility in Ilorin, Nigeria. Ann Afr Med 6(4):186-189

2.Oshikoya KA, Njokanma OF, Bello JA and Ayorinde EO (2008). The use of prescribed and non-prescribed drugs in infants in Lagos, Nigeria. Journal of Medical Science 8(2): 111-117

3.Oladimeji and Iranloye (1990). Survey of analgesics/antipyretics and antimalarial drugs used in Nigeria. Pharmacy world Journal 7: 123-128

4.Yamato S, Sakai M and Shimada K (1996). Quantitative analysis of chlorpheniramine maleate in cough and cold medicines by ion-pair high-performance liquid chromatography for the simultaneous determination of chlorpheniramine and maleate. Yakugakuzasshi 116(4): 329-334

5. Birkett DJ. (2003). "Generics - equal or not?" AustPrescr 26: 85-7

6.FDA (2003). Guidance for Industry: "Bioavailability and bioequivalence studies for orally administered drug products—general considerations". Food and Drug Administration, Rockville, 1-23.

7. Yasmeen Z, Mamatha T, Farheen H and Qureshi HK (2013). Dissolution method development and validation for combination of ibuprofen and paracetamol tablets. Asian Journal of Pharmaceutical and Clinical Research 6(2): 162-166

8. Costa PJ and Lobo MS (2001). Modeling and comparison of dissolution profiles. European Journal Pharmaceutical Science 13(2): 123-33

9.Korsmeyer RW, Gurny R and Peppas NA (1983). Mechanisms of solute release from porous hydrophilic polymers. International Journal of Pharmaceutics 15(1): 25-35

10. Higuchi T (1963). Mechanism of sustained - action medication: Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. Journal of Pharmaceutical Science 521: 138-145

11.Bendari A, Al-Shehi B and Ahuja A (2015). Comparison of pharmaceutical properties of different marketed brands of metronidazole tablets available in Oman. International Journal of Pharmaceutical Archives 4(2): 9-21

12.Ayorinde JO, Odeniyi MA and Itiola OA (2012). Evaluation of pharmaceutical and chemical equivalence of selected brands of diclofenac sodium tablets. East Central African Journal of Pharmaceutical Science 15(1): 3-9

13. Lachman L and Lieberman HA (2015). In: Khar RK, Vyas SP, Ahmad JF, Jain KG, (eds).
The theory and practice of industrial pharmacy. 4th edn. Delhi: CBS Publishers, 481-483.

14. The United States Pharmacopeia and National Formulary USP29–NF24. Rockville: The United States Pharmacopeial Convention, Inc.; 2009. p. 2778.

15.Adeleye AO, Odeniyi MA and Jaiyeoba KT (2011). Evaluation of cissus gum as binder in a paracetamol tablet formulation. Farmacia 59(1): 85-96