



INTER-BATCH QUALITY CONTROL (QC) AND BIOAVAILABILITY VARIABILITY OF A BRANDED ARTESUNATE TABLET IN NIGERIA

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ABSTRACT

To evaluate the inter-batch quality control and bioavailability variability of a branded artesunate tablet in Nigeria. The weight uniformity, tablet thickness and diameter, hardness, friability, disintegration time, dissolution rate, dissolution efficiency and content of active ingredient of five batches of a branded artesunate tablet in Nigeria were evaluated using standard methods. All batches passed the weight uniformity, tablet thickness, friability, and disintegration tests. Tablet hardness among the batches was unacceptable, as their hardness range of 2.88–3.97 kgf was grossly below the approved limit of 5–7 kgf. Also, tablet diameter was inconsistent and each batch indicated a coefficient of variation (CV), 3.36–11.00 %, above 2.00 %. The percentage drug release of the batches within 30 min (27.50–48.80 %) was inadequate; since a good drug is expected to release not less than 70.00 % of its label claim within 30 min. The average drug content of four batches (B–E) was less than 89.00 % (58.36–88.64 %), while batch A had an average drug content of 116.12 %. With respect to the recommended BP content of active ingredient (90–110 %), all the batches failed the average drug content test. There were variations among the quality control parameters and bioavailability of the five batches of the branded artesunate tablet. None of the batches, evaluated, met fully the BP or USP requirements for tablets.

Keywords: Artesunate tablets, Quality control, Bioavailability, Inter-batch variability.

INTRODUCTION

About 14–17 million people die each year of infectious diseases and nearly all live in developing countries.¹⁻⁴ Malaria, a vector-borne infectious disease caused by *Plasmodium falciparum*, is wide spread in tropical and subtropical regions;⁵ and has an incidence of about 515 million cases annually, killing 1-3 million people - majority of whom are children and pregnant women in sub-Saharan Africa.⁶ The control of malaria, which is dependent upon effective anti-malarials, has been severely hampered by a persistent increase in the prevalence of drug resistant malaria parasite.^{7,8}

Artesunate, dihydroartemisinin -10 α – hemisuccinate, is a semi-synthetic derivative of artemisinin that is widely and increasingly used in the treatment of *P. falciparum* malaria in many southeast asian and African countries; and is vital for the therapy of drug resistant malaria.^{8,9} Due to the very high efficacy of artesunate in controlling malaria, the high incidence rate of malaria in Nigeria as well as economic factors; lots of branded artesunate tablets and its other dosage forms have infiltrated the Nigerian health care system. The efficacy of these various brands and consistency in quality after initial registration by the regulatory agency, in Nigeria, is a growing concern to health care professionals and consumers.

Existing literatures, have highlighted the bioequivalence/bio-equivalence of some brands of artesunate tablets and other pharmaceuticals in the Nigerian market.¹⁰⁻¹² But no study has focused on the determination of active pharmaceutical ingredient (API) consistency, bioavailability and other QC indices

variability among various batches of a particular product. If a significant batch-to-batch bioavailability and quality variations exist, such that the absolute API content, bioavailability and other quality indices do not meet the label claim and/or BP requirements; there could be cases of therapeutic failure and development of drug resistance.

Thus, the present study accessed the intra-batch QC bioavailability variability of a branded artesunate tablet in Nigeria. The obtained information will be indispensable in the discourse of the public health risk risks associated with the manufacture, distribution, sales and consumption of products of inconsistent quality.

MATERIALS AND METHODS

Sample collection

Five batches (coded A–E) of a particular brand of artesunate tablet approved for use in Nigeria, and manufactured six months prior to the study were obtained commercially from pharmacies in Nsukka, Enugu State – Nigeria. Chemical reference sample (pure sample) of artesunate was obtained free, from Kunimed Pharmaceutical Company Ltd., Lagos, Nigeria; and used as supplied. All the drugs were stored in their packs under conditions specified by the manufacturer prior to assay, which was done before their expiry dates.

Reagents and equipment

Sodium hydroxide pellets (Avondale Laboratories, UK), monobasic potassium phosphate (May and Baker, UK) and hydrochloric acid (BDH, Poole, England) were



obtained from local dealers and used as supplied. Equipment used for the experiment was UV-visible spectrophotometer (Unico 2101, USA), Erwerka DT-D dissolution apparatus (Erwerka, UK) and Erwerka tablet hardness tester (TBH 100, UK).

Content of active ingredient test

Based on the label claim, the equivalent mass of each batch of artesunate tablet containing 100.00 mg of the active ingredient was weighed from a pool of 20 crushed tablets using an analytical balance and dissolved in 1.00 L volumetric flask with distilled water to mark. This is to obtain an equivalent API concentration of 100 ppm. After filtration, 1.5 ml of stock solution was drawn into a 100 ml volumetric flask using a 5 ml capacity pipette and made up to mark with distilled water to obtain an equivalent API concentration of 1.5 ppm. This was used for absorbance measurement at 287 nm. The absorbance of five different concentrations (0.5, 1.0, 1.5, 2.0 and 2.5 ppm) of artesunate CRS solution were used for the Beer-Lamberts plot. The content of active ingredient for each of the five batches of the branded artesunate tablet was extrapolated from the standard Beer-Lamberts plot for the pure artesunate sample (CRS).

Disintegration time test

The disintegration time of randomly selected tablet of each of the five batches was determined in distilled water using a multi-unit disintegration time test apparatus set at 50 rpm. The time taken for the last tablet to break up into small aggregates was noted as the disintegration time.^{13,14}

Weight uniformity test

Twenty tablets were selected randomly and weighed singly using an analytical balance (Mettler UK).¹³ Average tablet weight, standard deviation and coefficient of variation (CV) for each of the five batches was evaluated. Permitted coefficient of variation of 5 % for tablet weight ≥ 250 mg was taken as the acceptable limit.¹⁵

Hardness test

Five tablets of each brand were randomly chosen. The hardness of each tablet was determined using Erwerka hardness tester and the average hardness of 5–7 kgf was considered acceptable for coated tablets.^{12,15}

Friability test

Friability is a measure of the resistance of tablet and granule formulations of pharmaceutical products to abrasion.¹⁵ Twenty tablets, of each batch, were dusted, weighed and agitated in an Erwerka friabilator set at 25 rpm for 4 min. After which the tablets were removed, de-dusted and re-weighed. The measure of abrasion B calculated as the per cent loss in weight was done using the expression:

$$B = [(W_o - W) / W_o] * 100$$

Where B = measure of abrasion (% loss in weight)

W_o = original weight before agitation

W = weight after agitation and de-dusting

Values of B not exceeding the upper limit of 0.8–1.0 % were considered to be acceptable.¹⁵

Dissolution rate test

The paddle method was used. A representative tablet from each of the batches was placed in the suspended sample porch of Erwerka dissolution test apparatus containing 900 ml of simulated intestinal fluid (SIF) maintained at 37 ± 1 °C. The speed was fixed at 50 rpm, and 2-ml aliquot was withdrawn from the setup at various time intervals (5, 10, 15, 20, 30, 40, 60, 80, 100 and 120 min). At each withdrawal, fresh 2-ml portion of SIF was added to the system to maintain sink conditions. Each of the withdrawn sample was filtered, the filtrate diluted and its absorbance at 287 nm determined in Unico 2102 UV-visible spectrophotometer against blank SIF. The concentration of artesunate in the samples was estimated from the standard Beer-Lamberts curve, similarly obtained with artesunate CRS. A plot of per cent drug release against time, gave the dissolution rate. While the proportion of drug released (% drug release) at 30 min, was reported as dissolution profile.

Thickness and diameter test

Twenty tablets were randomly selected from each batch and micrometer screw gauge was used to measure the thickness and diameter of each tablet. The mean values as well as standard deviations and coefficient of variations were evaluated, for each of the batches.

RESULTS

The quality control parameters of the batches were presented in Table 1. It revealed that all the batches possessed unacceptable absolute drug content, but with excellent friability index. Table 1, also indicated that the dissolution profiles of the various batches were defective; as none of the batches released up to 70 % of its drug content within 30 min. The *in vitro* bioavailability of the batches is presented in Fig. 1. From the figure, batch B released 100 % of its drug content at 80 min after dissolution, while batch D did not attain 100 % drug release at 120 min.

DISCUSSION

The hardness test of the batches indicated that none of the tablet batches possessed adequate hardness. A hardness range of 5–7 kgf has been documented as the acceptable limit for film coated tablets.^{12,15,16} Tablets with poor hardness profile are liable to powdering during transportation and distribution. Very hard tablets may possess poor bioavailability, as it may fail to disintegrate in the gastrointestinal tract (GIT) to release the drug into the bio-system. Weight uniformity CV in excess of 5 % indicates uneven dosing of pharmaceuticals.¹³ However, all the passed the weight uniformity test; their weight CV



was generally below 1.30 %. The resistance of the batches to abrasion, expressed B values was excellent. Because, the observed B values were below the upper abrasion limit of 0.8 %.

The result of the disintegration time test in Table 1, showed that all the five batches have a disintegration time ranging from 180.6–184.8 sec compared to the acceptable upper limit of 900 sec for film coated tablets/caplets.¹³ They could therefore be considered as satisfactory with respect to tablet friability. Disintegration time determination is one of the two pharmacopeia tests for measuring *in vitro*, the ability of the incorporated active ingredient to be released from the tablet. The results of the active ingredient (absolute drug content) assay revealed that four batches (B–E) fell outside the BP acceptable limit of 90–110 % absolute drug content for artesunate tablets. On the other hand, drug content of batch A (116.12 %) was in excess of the upper limit of 110 %. Thus administration of the batches may either lead to

under or dosage; since none expressed absolute drug content within the acceptable range.

According to British Pharmacopeia,¹³ a good pharmaceutical should release 70 % of its drug content within 30 min, in an *in vitro* per cent drug release test. None of the evaluated batches achieved this standard. Thus they are suspected to possess poor bioavailability. Their corresponding dissolution efficiency, equally, confirmed the expected inadequate bioavailability. As the maximum dissolution efficiency at 30 min was 62.44 %, against 100 %. Also, the drug release profile of the batches was variable; with batches D and E releasing about 50 % of their label claim at 1 h after administration. Batch B released nearly all its drug content at the 60 min mark. Generally, the *in vitro* bioavailability of the drug batches was poor and as such, is unacceptable. This will definitely translate to inadequate bioavailability in the bio-phase and the attendant dangers of therapeutic failure and evolution of drug resistant strains of malaria parasites.

Table 1: Quality control parameters of batches of the branded artesunate tablet

QUALITY CONTROL INDICES	DRUG PRODUCT BATCHES				
	A	B	C	D	E
Weight uniformity (g)	0.32 ± 0.00 (0.62) *	0.32 ± 0.00 (0.94)	0.32 ± 1.24 (1.24)	0.32 ± 0.00 (1.24)	0.32 ± 0.00 (0.93)
Tablet thickness (cm)	0.34 ± 0.01 (1.49)	0.33 ± 0.01 (1.53)	0.34 ± 0.01 (1.49)	0.34 ± 0.00 (1.18)	0.33 ± 0.01 (1.50)
Tablet diameter (cm)	1.08 ± 0.12 (11.00)	1.16 ± 0.05 (4.31)	1.23 ± 0.04 (3.36)	1.23 ± 0.04 (3.59)	1.24 ± 0.05 (3.97)
Hardness (kgf)	2.88 ± 0.23	3.89 ± 0.38	3.74 ± 0.32	3.97 ± 0.18	3.85 ± 0.13
Friability (% weight loss)	0.37 ± 0.01	0.14 ± 0.00	0.19 ± 0.01	0.20 ± 0.01	0.20 ± 0.00
Disintegration time (min)	3.03 ± 0.01	3.01 ± 0.00	3.07 ± 0.00	3.08 ± 0.01	3.08 ± 0.00
Dissolution profile (% release @ 30 min)	34.50 ± 0.12	48.80 ± 0.15	46.10 ± 0.17	27.50 ± 0.16	28.00 ± 0.01
Dissolution efficiency (% DE @ 30 min)	62.44 ± 0.11	48.70 ± 0.17	40.87 ± 0.15	47.76 ± 0.12	48.36 ± 0.01
Absolute drug content (% label claim)	116.12 ± 0.12	67.29 ± 0.15	88.64 ± 0.89	71.15 ± 0.65	58.36 ± 0.76

*Values in parenthesis refer to coefficient of variation (CV).

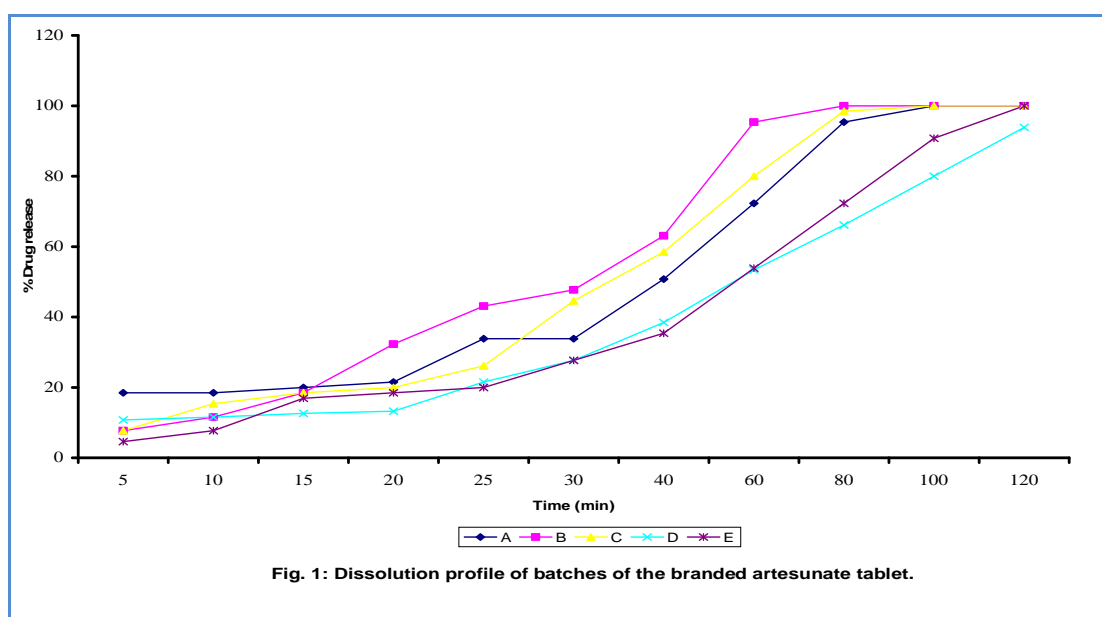


Fig. 1: Dissolution profile of batches of the branded artesunate tablet.

CONCLUSION

This study showed that there were variations in the hardness, absolute drug content, dissolution and drug release profiles of the five selected batches of a branded artesunate tablet in Nigeria. All the batches passed the weight uniformity, tablet thickness and diameter, friability and disintegration tests. Based on these parameters, the batches are acceptable; however their hardness, absolute drug content, dissolution and drug release profiles were unacceptable. Thus, none of the batches fully met the BP requirements for tablet dosage form. Consequently, they will express inadequate and variable bioavailability in the bio-phase; which may lead to therapeutic failure and emergence of artesunate resistant strain of *P. falciparum*.

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