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Evaluation of the Physicochemical Properties and Quality Indices of Multisource Tadalafil Drug Products Marketed in Nigeria

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Authors' contributions

This work was carried out in collaboration between the authors. All authors jointly designed and performed the laboratory work. Author SOA wrote up the work. Authors JAN and JIO did the data and statistical analysis and author MAI edited the write up. All authors read and approved the final manuscript.

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ABSTRACT

The present study evaluates and compares the physicochemical parameters and cost of some multisource tadalafil products marketed in Nigeria. Six randomly selected products were analyzed for weight uniformity, friability, hardness, disintegration, dissolution testing and assay. The assay for chemical content was performed using RP-HPLC method with isocratic run using acetonitrile: acetate buffer pH 2.8 (45:55, volume in volume) as mobile phase at a flow rate of 1.0 mL/min and wavelength of determination of 283 nm. All the products passed the disintegration time and crushing strength tests with no significant difference in values ($p<0.05$), while all complied with the uniformity of weight specification except two products. The chemical content of the products was between 70.2 and 86.8% (weight in weight). The dissolution profile revealed that two products

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could not achieve 70% drug release after the 90 min dissolution time. The average shelf price of the originator product, for an equivalent pack of four tablets/capsules was ₦8 000 (USD 45) while the other products were generally below ₦2 000 (USD 11). The innovator as well as the two generic products that passed all the physicochemical tests can be regarded as pharmaceutically equivalent among the tadalafil drug products tested. There was an indication of high disparity in price between the innovator and the generics that is not justified by physicochemical test outcomes.

Keywords: Tadalafil; multisource products; physicochemical characterization; RP-HPLC determination of tadalafil.

1. INTRODUCTION

The prevalence of erectile dysfunction (ED) was estimated to be over 320 million men worldwide by the year 2025 with the highest projected increases in developing countries such as Africa, Asia, and South America [1-4]. The risk factors for ED have been identified to include age, smoking, diabetes, depression, hypertension and cardiovascular disease. Age and cardiovascular disease are variables that have strong correlations with the severity of ED [5,6].

Across a variety of clinical populations, 5 – phosphodiesterase inhibitors (PDE 5) form a major group of drugs employed for erectile dysfunction. Tadalafil is chemically known as hydro-2-methyl-6-[3,4-methylenedioxy phenyl pyrazino-[11,21:1,6] pyrido [3,4-b] indole-1,4-dione and indicated for the treatment of ED. It is a selective inhibitor of cyclic guanosine monophosphate (cGMP) - specific phosphodiesterase type 5 [7,8].

Manufacturing of multi-source generic products have meant that a single API can be produced by different manufacturers employing different additives and methods. These products are required to be pharmaceutical equivalents and are further expected to be bioequivalent [9,10]. The wide differences in prices of the same labeled claim of these generic products gives some concern as to the quality, safety and efficacy of the products [11]. Counterfeit and/or imitation medicines are becoming a major health problem worldwide. Counterfeiting has been closely associated with cheaper prices relative to the genuine counterparts [12]. Multi-source production of medicines can be a cover to peddling of bio-inequivalent medications if adequate quality control measures are not in place [13]. In order to ensure the quality of drugs some simple and sensitive methods for routine analysis of drugs of interest are recommended. Some of these are physicochemical tests that include dissolution studies and assays [14].

Literature survey for tadalafil revealed some analytical methods for the determination of tadalafil by high pressure liquid chromatography (HPLC) [15,16], Flourimetry [17] and spectrophotometry [8,18,19]. Dissolution studies of drug products (*e.g.,* tadalafil and sildenafil) have been studied in the light of comparatively describing their quality characteristics [8,20].

This study seeks to compare the quality parameters of the six available tadalafil drug products vis-à-vis the disparity in cost.

2. MATERIALS AND METHODS

2.1 Materials

2.1.1 Chemicals employed in the study

Pure tadafil powder was gratefully received from Tuyil Pharmaceuticals, Ilorin, Nigeria and was certified to contain 99.65%, (w/w). Sodium acetate, glacial acetic acid, methanol and acetonitrile were purchased from Sigma Chemicals (St Louis, Mo., USA). The commercially available tadalafil drug products were purchased from reputable licensed pharmacy outfits in Benin City, southwest Nigeria and details are listed in Table 1. The dissolution medium employed was 0.1N hydrochloric acid [10], and water was double distilled.

2.1.2 Apparatus employed in the study

Equipment used included HPLC 1200 series equipped with Rheofyne manual sample injector and analytical column ODS Hypersil RP C18, 125 x 4.6 mm, 5µm, Agilent Germany; electronic balance, Adventure Ohaus, China; USP specification disintegration apparatus, COPLEY and ERWEKA, Germany; friabilator Veego VFT-1, India; tablet hardness tester, HT-30/50 Campbell Electricals, India; USP dissolution apparatus, ELECTROLAB, TDT-08L Model, India and Mel-Temp apparatus 3.0, Aldrich, Germany.

2.2 Methods

2.2.1 Visual inspection of drug products

The shape, size and colour of the tadalafil drug products were examined visually.

2.2.2 Tablet weight uniformity test

A total of ten tablets/capsules of each brand were weighed individually using a digital analytical balance and the percentage deviation of the weights of the individual tablets/capsules from the mean was determined.

2.2.3 Hardness test

The crushing strength of the tablets was determined by placing a tablet between the diametrical crushing force generated by the tablet hardness tester. A total of ten randomly selected tablets were subjected to the test and the mean hardness was computed.

2.2.4 Friability test

A total of ten tablets for each brand were weighed and subjected to abrasion using Veego tablet friabilator at 25 rev/min. The percentage weight lost after 4 min of tumblings and abrasion in the drum of the friabilator was computed as the friability of the tablets. This test was not applicable to the capsule drug products.

2.2.5 Disintegration time test

The disintegration time of the tablets was determined in distilled water at 37±1ºC. Six tablets per sample were subjected to the disintegration test and the mean disintegration time calculated.

2.2.6 Preparation of acetate buffer

A weight of 4.0 g sodium acetate was accurately taken and transferred into 1 L volumetric flask containing 500 mL distilled water. A volume of 155 mL of glacial acetic acid was added and made up to mark with distilled water.

2.2.7 Determination of content of active ingredient

The melting point of the pure tadalafil powder was determined by filling some of the powder into a pre-sealed thin-walled capillary tube and inserted into the apparatus. The melting point apparatus was heated gently at the rate of 2ºC/min while observing the temperature rise from the digital thermometer attached. The melting point was compared with the pharmacopoeia value. The assay of the pure powder was also performed to ascertain the purity of the reference powder.

Weights of 25, 50, 75 and 100 mg of pure tadalafil powder were taken and separately dissolved in 100 mL of methanol in beakers to form the stock solutions. Aliquots of the stock solutions were taken and further diluted in methanol to give concentrations of 2.5, 5.0, 10.0, 25.0, 50.0 and 100 µg/mL solutions. The solutions were filtered and injected into the chromatographic system in triplicate determinations. The mean peak area (mPA) of the determinations for each concentration was plotted against the respective concentration to get the calibration curve Fig. 1.

A total of ten tablets or capsules of each brand of tadalafil were weighed into a mortar and crushed while the capsules were uncapped and their content emptied into a mortar. Powder equivalent to 25, 50 and 75 mg tadalafil were weighed from the powder into 80 mL methanol contained in 100 mL volumetric flasks and shaken for 15 min. Each flask was made up to 100 mL with more methanol and shaken for 5 min. A 5 mL aliquot of each of the solutions was further diluted to 100 mL with methanol and filtered before injecting into the chromatographic system comprised of acetonitrile: acetate buffer pH 2.8, (45: 55, v/v) at a flow rate of 1.0 mL/min. The wavelength of detection was 283 nm. The average peak area for the triplicate measurement of each sample was extrapolated on the calibration curve derived from the pure tadalafil powder and the equivalent weight obtained [21].

2.2.8 Dissolution test

The dissolution medium was 500 mL 0.1N HCl at 37±2ºC and stirring speed of 100 rpm. A 5 mL aliquot of the dissolution medium was sampled at each of 0, 5, 10, 20, 30, 60 and 90 min and replaced with the same volume of fresh dissolution medium after each withdrawal.

2.2.9 Statistical analyses

Statistically significant differences in the data for the different brands were considered at $P<0.05$ and analysis was done using Student t- test and F test.

3. RESULTS

A total of tadalafil drug products were analyzed. The details of registration status, country of manufacture and labeled claims are listed in Table 1. The purity of the donated tadalafil pure powder was ascertained through melting point and chemical content determinations. The melting point and percentage purity values obtained for replicate determinations (n=3) for the pure powder was 280±1.41ºC and 102.83±1.15%, respectively. The pure drug was thus employed to produce the calibration curve for further determinations of the samples. The regression equation and calibration curve are presented in Fig. 1.

The physicochemical parameters of the drug formulation such as the friability, disintegration time, chemical contents and weight uniformity are presented in Table 2. The dissolution profiles of the various tadalafil drug products are presented in Fig. 2. The dissolution parameter expressing the outcome of the various brands such as C_{45}, T_{70}, dissolution efficiency (DE), predicted availability efficiency (PAE) are expressed in Table 3.

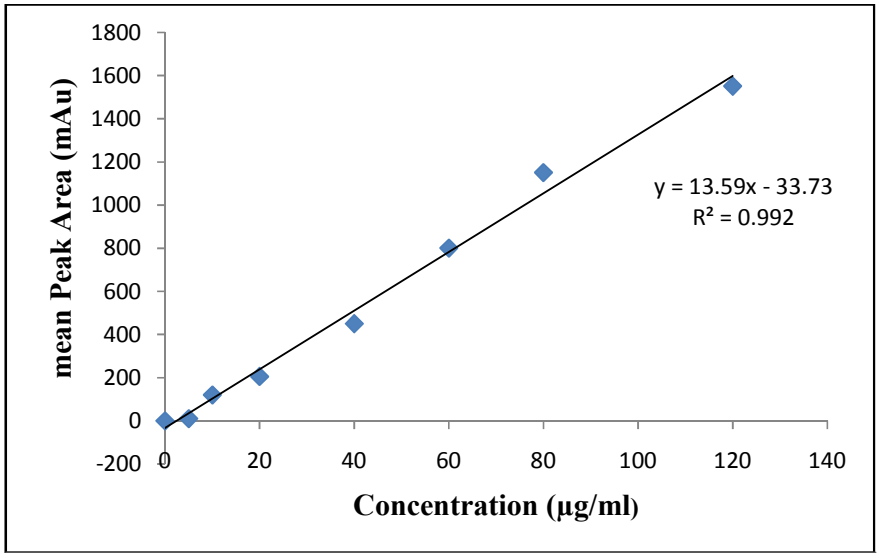

Fig. 1. Calibration curve and regression equation of pure tadalafil powder

Table 1. Identity of the tadalafil drug products tested

Product code	Name/ dosage form	Manufacturer /Country	Batch number	Date of manufacture/ expiry	Labeled strength (mg)	Cost of drug (₦)	NAF-DAC number
TA	Cialis Tablet	Lilly S.A. Spain	4464	05/2010 04/2013	20	8 000	Yes
TB	Vira capsule	Tuyil pharm Nigeria	W002	01/2011 12/2013	20	400	Yes
TC	Tadalis tablet	Cipla India	G14692	05/2011 04/2014	20	2 000	Yes
TD	Sonagra capsule	Bond chemical Nigeria	002	03/2010 10/2013	10	500	Yes
TE	Tadakick tablet	Saga labs, India	1002	10/2010 09/2013	20	800	Yes
TF	T-fil capsule	Rajat pharm India	RA 1001	02/2011 01/2014	10	400	Yes

**NAFDAC number - National Agency for Food and Drug Administration and Control number (the drug regulatory agency in the study area)*

Table 2. Some physicochemical parameters of the tadalafil drug products

Product codes	Physicochemical parameters				
	Weight uniformity MD %	Friability (%)	Hardness (kg/cm)	Chemical content (%, w/w)	Disintegration time (min)
TA	1.51	0	2.5	82.3	2.76
TB	15.20	NA	NA	86.6	5.36
TC	1.14	0	2.8	70.2	1.29
TD	6.50	NA	NA	80.8	3.61
TE	2.17	0	1.9	88.4	0.92
TF	3.92	NA	NA	80.9	4.97

**MD %, maximum deviation percent; NA-not applicable to the dosage form of the product*

Table 3. Dissolution indices of tadalafil drug products

Product code	C_{45} (%)	T_{70} (min)	AUC $_{(0-90)}$ (mg.min)	$AUC_{(0-60)}$ (mg.min)	$DE_{(x)}$	PAE
TA	67	65	4851.60	2825.0	0.56	1.0
TB	45	-	3437.50	1787.50	0.65	1.16
TC	29	90	2062.50	1512.50	0.48	0.86
TD	65	48	4900.0	2650.0	0.36	0.64
TE	42	-	3437.50	2012.50	0.59	1.05
TF	90	35	7629.76	4300.0	0.64	1.14

**Calculations of DE (Dissolution Efficiency) and PAE (Predicted Availability Equivalence) computed with reference to TA (Innovator product); AUC - Area under the drug release versus time curve; T_{70} -Time to achieve 70% of drug release and C_{45}- concentration of drug in solution at 45 min*

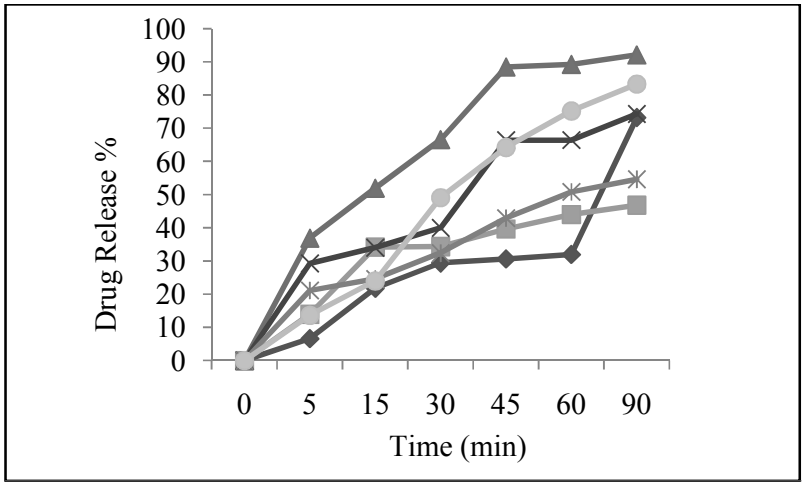

Fig. 2. The dissolution profiles of the tadalafil drug products where TC (♦), TE (▄), TF (▲), TA (×), TB (*) and TD (•)

4. DISCUSSION

All the tadalafil products studied were within their shelf life at the time of the study; each of the products was legally in the market having been licensed by National Agency for Food and Drug Administration and Control (NAFDAC), the national regulatory body. Three products formulated as tablets were not similar in colour, shape and sizes though they were sugar coated with various identification inscriptions on them. The others products were capsules.

Products TB and TD did not comply with the uniformity of weight specification of maximum deviation of 5% [22]. Product TD however did not give twice as much deviation as compared with TB that gave a maximum deviation of 15.20% (Table 2). Large tablet weight variations as found in TB may imply inconsistency of die filling during

tableting. This could also result from poorly flowing granules employed in producing the tablets. The investigated brands are majorly indigenously produced and it suffice to say that variations in tablet weight may originate from changes or differences in the properties of the raw materials used (*i.e.,* the active ingredient and the excipients). Other factors may hinge on the machine or tooling working conditions which require constant inspection and maintenance. The mean crushing strength is a measure of the degree of hardness of the tablets. Products TB, TD and TF were presented as capsules and therefore did not require the determination of this parameter, whereas the tablet products gave values within the recommended value of 4.0 Kg/cm (Table 2). The obtained values of tablet crushing strength were not statistically different from one another. Although, the crushing strength is not an official method of assessing tablet quality, it is still useful in assessing the integrity of tablet dosage forms. However, this may not be a problem with the drug products tested in this investigation since they were all blister packed.

All the products passed the disintegration test of less than 60 min for coated tablets as specified in the British Pharmacopoeia [23], Table 2. The rapid disintegration (<5 min) of the tablet formulations may suggest that superdisintegrants may have been used by the various manufacturers of the products. Superdisintegrants and other methods of facilitating the disintegration of tablets are being advocated in recent times to facilitate the disintegration of tablet formulations [24].

The dissolution rate is a measure of the amount of drug released into the system as a function of time. The dissolution profiles of the six drug products showed that they did not meet the pharmacopoeial specification of 70% dissolution after 45 min, except product TF (Table 3). Some drug products require modified dissolution media with surfactant as in the case of poorly water soluble drugs such as tadalafil. The dissolution media employed in this assessment was the pharmacopoeia method for the dissolution test for tadalafil [23].

The price of the products was generally below ₦ 2,000 for four capsules or tablets. However, the originator product sold for ₦ 8,000. The gaping disparity in price between the innovator product and the generics cannot be justified based on the results obtained from this study.

All the tadalafil drug products tested were officially registered with NAFDAC therefore the expectation was that the products should all pass the physicochemical tests. However, most of the products failed the chemical content test. This development is worrisome since the chemical content is a fundamental parameter predicting the availability of the active pharmaceutical ingredients (API) from the drug product.

In developed countries such as the United States, the drug regulatory body (*i.e*., Food and Drug Administration (FDA) has detailed guidelines for how drugs are developed and approved. Generic products are expected to fall within pre-defined specifications for pharmaceutical and bioequivalence studies comparing with the established or innovator product. Such guidelines (*i.e*., FDA-ANDA Guidelines) are available and accessible for any interested persons (*i.e*., researchers or anyone interested in generic drug production) [25]. In Nigeria, however, there is marked proliferation of generic products of almost every fast selling drug with approved or registration numbers. Such documentary protocols/specification for drug generic products approval is not accessible or may altogether be non-existent. Sentinel investigation as a way of ensuring the regular availability of wholesome drug products by independent analysts will help check the quality of drug products.

The wide margin between the costs of the innovator product and the generics was expected to be consistent with and justified by the physicochemical test outcomes among the products. There was however no significant difference in the *in vitro* test results to warrant the price disparity.

5. CONCLUSION

The study revealed that the various products of tadalafil marketed in the country have comparable quality characteristics but differing shelf prices. Some of the products were pharmaceutical equivalents while the others did not meet the criteria for equivalency. The study has revealed that there will be no need to spend more on some products as generics of lower cost were of comparable quality characteristics as the more expensive ones. There is, however need to conduct some bioequivalence and clinical pharmacological tests to determine the bioequivalence among the products.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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