

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

ABSTRACT

The present study evaluates and compares the physicochemical parameters and cost of some generic products of tadalafil as well as the innovator brand marketed in Nigeria. The six brands employed were subjected to weight uniformity, friability, hardness, disintegration and dissolution testing. 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 brands passed the disintegration time and crushing strength tests with no significant difference in values ($p < 0.05$), while all brands complied with the uniformity of weight specification except two brands. The chemical content of the brands was between 70.2 and 86.8% (weight in weight). The dissolution profile revealed that two brands could not achieve 70% drug release after the 90 min dissolution time. The average shelf price of the originator brand, 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 brand as well as the two brands that passed all the physicochemical tests can be regarded as pharmaceutically equivalent among the six brands of tadalafil drug products tested. There was an indication of high disparity in price between the innovator and the other brands 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 [1-3]. 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 [4, 5].

Across a variety of clinical populations, 5 – phosphodiesterase inhibitors form a major group of drugs employed for erectile dysfunction. Tadalafil is chemically known as hydro-2-methyl-6-[3,4-methylenedioxyphenyl]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 (PDE5) [6] .

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 [7, 8]. 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 [9]. Counterfeit and/or imitation medicines are becoming a major health problem worldwide. Multi-source production of medicines can be a cover to peddling of bio-inequivalent medications if adequate quality control measures are not in place [9].

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 tadalafil 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 4.6mm, 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) and USP dissolution apparatus (ELECTROLAB, TDT-08L Model, India).

2.2 METHOD

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 subjecting a tablet to a 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. in the drum of the friabilator was computed as the friability of the tablets. This test was not applicable to the capsule drug products.

80 2.2.5 Disintegration time test

81 The disintegration time of the tablets was determined in distilled water at $37 \pm 1^\circ\text{C}$. Six
82 tablets per sample were subjected to the disintegration test and the mean disintegration
83 time was calculated.

84

85 2.2.6 Preparation of acetate buffer

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

89 2.2.7 Determination of content of active ingredient:

90 A total of ten tablets of each brand of tadalafil were weighed into a mortar and crushed.
91 Powder equivalent to 25, 50 and 75 mg tadalafil were weighed into about 80 ml methanol
92 contained in 100ml volumetric flasks and shaken for 15 min. Each flask was made up to
93 100 ml with more methanol and shaken for 5 min. A 5 ml aliquot of each of the solutions
94 was further diluted to 100 ml with methanol and filtered before injecting into the
95 chromatographic system comprised of acetonitrile: acetate buffer pH 2.8, (45: 55, v/v) at a
96 flow rate of 1.0 ml/min. The wavelength of detection was 283 nm. The average peak area
97 for the triplicate measurement of each sample was extrapolated on the calibration curve
98 derived from the pure tadalafil powder and the equivalent weight obtained [11].

99 2.2.8 Dissolution test

100 The dissolution medium was 500 ml 0.1N HCl at $37 \pm 2^\circ\text{C}$ and stirring speed of 100 rpm. A
101 5 ml aliquot of the dissolution medium was sampled at each of 0, 5, 10, 20, 30, 60 and 90
102 min and replaced with the same volume of fresh dissolution medium after each withdrawal.

103 2.2.9 Statistical analyses

104 Statistically significant differences in the data for the different brands were considered at
105 $P < 0.05$ and analysis was done using t- test and F test.

106

107 **3. RESULTS**

108 A total of six brands of tadalafil drug products were analyzed. The details of registration
109 status, country of manufacture and labeled claims are listed in Table 1. The purity of the
110 donated tadalafil pure powder was ascertained through melting point and chemical content
111 determinations. The pure drug was thus employed to produce the calibration curve for
112 further determinations of the samples. The regression equation and calibration curve are
113 presented in Figure 1.

114 The physicochemical parameters of the drug formulation such as the friability,
115 disintegration time, chemical contents and weight uniformity are presented in Table 2.
116 Figure 2 shows the chromatogram of the analysis of the drug. The dissolution profiles of
117 the various tadalafil drug products are presented in Figure 3. The dissolution parameter
118 expressing the basis of comparing the various brands such as C_{45} , T_{70} , dissolution
119 efficiency (DE), predicted availability efficiency (PAE) for each brand are expressed in
120 Table 2.

121 **4. DISCUSSION**

122

123 All the tadalafil products studied were within their shelf life at the time of the study; each of
124 the products was legally in the market having been licensed by the national regulatory
125 body, NAFDAC. Three brands formulated as tablets were not similar in colour, shape and
126 sizes though they were sugar coated with various identification inscriptions on them. The
127 others products were capsules.

Brands TB and TD did not comply with the uniformity of weight specification of maximum deviation of 5% [12]. Brand TD however did not give twice as much deviation as compared with TB that gave a maximum deviation of over 16% (Table 2). Large tablet weight variations as found in TB may imply inconsistency of die filling during tableting. This could result from poorly flowing granules. The mean crushing strength is a measure of the degree of hardness of the tablets. Brands TB, TD and TF were presented as capsules and therefore did not require the determination of this parameter, whereas the tablet brands 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 each other. 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 brands passed the disintegration test of less than 60 min for coated tablets as specified in the B.P. (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 lately to facilitate the disintegration of tablet formulations [13].

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 brands showed that the brands did not meet the official specification of 70% dissolution after 45 min, except brand TF (Table 2).

The price of the products was generally below N2,000.00 for four capsules or tablets. However, the originator brand sold for N8,000.00. The gaping disparity in price between the innovator product and the other brands cannot be justified based on the results obtained from this study.

This investigation has shown that all the tadalafil drug products tested are officially registered with NAFDAC. The products passed all the quality assurance tests carried out

on them except the dissolution test. This development is worrisome since dissolution may be the rate limiting step in the bioavailability of the active pharmaceutical ingredients (API) from the product. The authors recommend sentinel investigation of drug products as a way of ensuring the regular availability of wholesome drug products [14]. The wide margin between the costs of the innovator product and the other brands was expected to be consistent with and justified by the physicochemical test outcomes among the brands. 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 brands as brands of lower cost were of comparable quality characteristics as the more expensive ones.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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203 polymers. *Int J Pharm* 2002; 23
204 (1) :131-44.

206 **Table 1. Identity of the tadalafil drug products tested.**

Brand Name/ Dosage form	Brand Code	Manufacturer /Country	Batch number	Date of Manufacture/ Expiry	Labeled strength (mg)	Cost of 4 tablets/capsules (N)	NAF-DAC Number
T-fil Capsule	TF	Rajat Pharm India	RA 1001	02/2011 01/2014	10	400.00	Yes
Tadakick tablet	TE	Saga Labs, India	1002	10/2010 09/2013	20	800.00	Yes
Sonagra Capsule	TD	Bond Chemical Nigeria	002	03/2010 10/2013	10	500.00	Yes
Tadalis tablet	TC	Cipla India	G14692	05/2011 04/2014	20	2 000.00	Yes
Vira Capsule	TB	Tuyil Pharm Nigeria	W002	01/2011 12/2013	20	400.00	Yes
Cialis tablet	TA	Lilly S.A. Spain	4464	05/2010 04/2013	20	8 000.00	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 six brands of tadalafil drug products

Drug 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

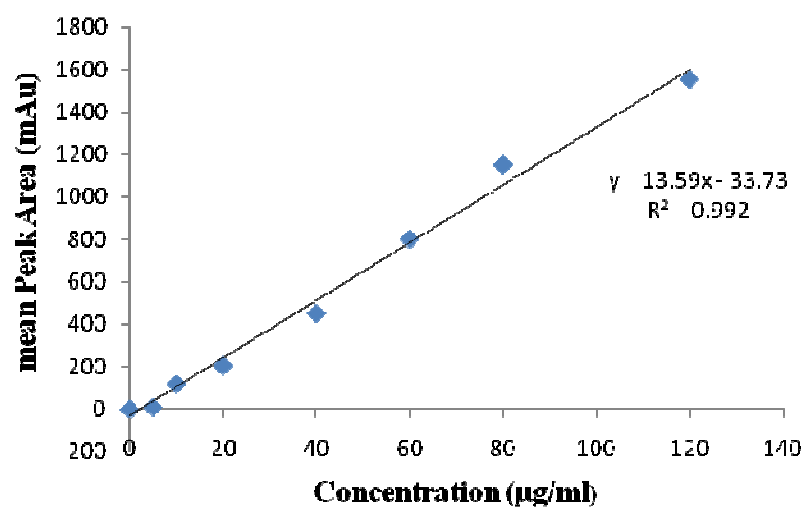
*MD %, maximum deviation percent; NA-notaplicable to the dosage form of the brand.

Table 3: dissolution indices of tadalafil tablets

Brand code	C ₄₅ (%)	T ₇₀ (min)	AUC ₍₀₋₉₀₎ (mg.min)	AUC ₍₀₋₆₀₎ (mg.min)	DE _(x)	PAE
TC	29	90	2062.50	1512.50	0.48	0.86
TE	42	-	3437.50	2012.50	0.59	1.05
TF	90	35	7629.76	4300.0	0.64	1.14
TA	67	65	4851.60	2825.0	0.56	1.0
TB	45	-	3437.50	1787.50	0.65	1.16
TD	65	48	4900.0	2650.0	0.36	0.64

*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; T₇₀ -Time to achieve 70% of drug release and C₄₅- concentration of drug in solution at 45 min.

230



231

232 **Figure 1. Calibration curve and regression equation of pure tadalafil powder**

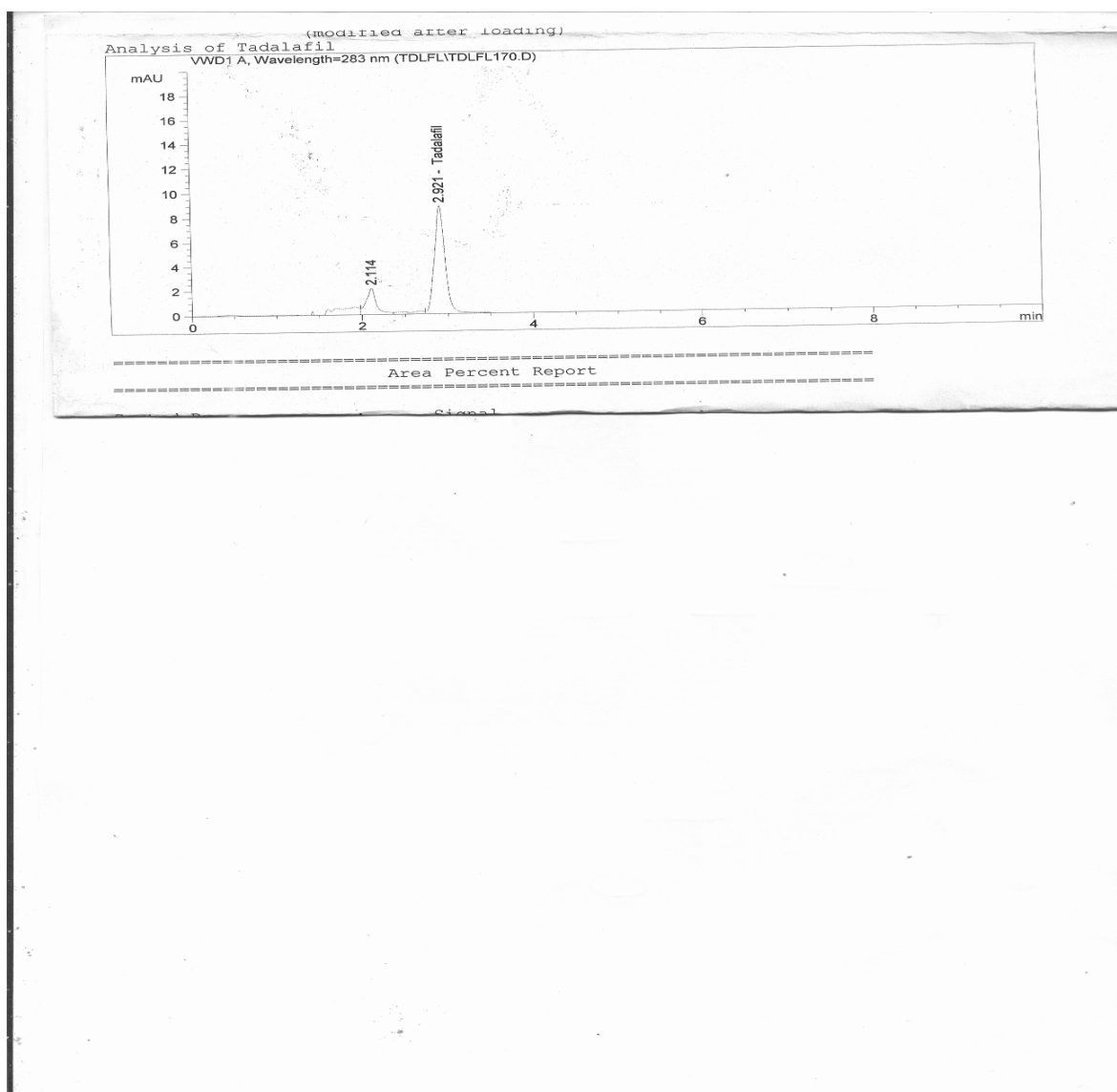


Figure 2: Chromatogram of tadalafil.

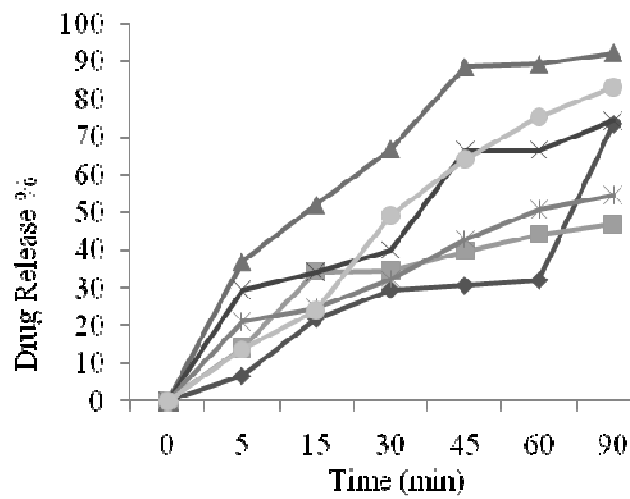


Figure 3: The dissolution profiles of the six brands of tadalafil products where TC(◆), TE (■), TF (▲), TA (x), TB (*) and TD (●).