Comparative quality assessment of selected fluconazole brands in Ibadan, Nigeria

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ABSTRACT

Background: Drug therapeutic failure is a significant challenge currently ravaging the healthcare system of developing countries like Nigeria. This is often linked to the variable quality of generic drug brands. Fluconazole, a triazole antifungal agent, is of clinical importance due to its excellent penetrability in the CSF.

Objective: To evaluate the quality and pharmaceutical equivalence between generic brands of fluconazole and the innovator brand that might affect its performance and interchangeability within Ibadan, Nigeria.

Methods: Seventeen brands of fluconazole including the innovator brand were evaluated for their physicochemical properties (weight uniformity), mechanical properties (crushing strength and friability), release properties (disintegration and dissolution time tests), content assay, and antifungal activity. Statistical analysis was conducted using ANOVA ($p < 0.05$) to assess significant differences.

Results: All brands passed the weight uniformity test, but only three passed the friability test. One brand from the tablets and the capsules failed the disintegration time test. Notably, only one brand passed the content assay test. The tablets released > 80 % of fluconazole within 30 min while all the capsules including the innovator brand exhibited a burst release. Two brands showed no activity against *Candida albicans*. The innovator brand had a significantly higher antifungal activity ($p < 0.05$) than the generics.

Conclusion: The differences in quality among the brands suggest that none would adequately substitute the innovator brand.

Keywords: Antifungal, Fluconazole, Generic drugs, Pharmaceutical equivalence, Ibadan

Évaluation comparative de la qualité de certaines marques de fluconazole à Ibadan, au Nigéria.

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RÉSUMÉ

Contexte: L'échec thérapeutique des médicaments est un défi important qui ravage actuellement le système de santé des pays en développement comme le Nigéria. Ce problème est souvent lié à la qualité variable des marques de médicaments génériques. Le fluconazole, un agent antifongique triazole, est d'une importance clinique en raison de son excellente pénétration dans le LCR.

Objectif: Évaluer la qualité et l'équivalence pharmaceutique entre les marques génériques de fluconazole et la marque innovante qui pourraient affecter ses performances et son interchangeabilité à Ibadan, au Nigéria.

Méthodes: Dix-sept marques de fluconazole, dont la marque innovante, ont été évaluées pour leurs propriétés physicochimiques (uniformité du poids), leurs propriétés mécaniques (résistance à l'écrasement et friabilité), leurs propriétés de libération (tests de désintégration et de temps de dissolution), leur dosage et leur activité antifongique. Une analyse statistique a été réalisée à l'aide de l'ANOVA ($p < 0,05$) pour évaluer les différences significatives.

Résultats: Toutes les marques ont passé avec succès le test d'uniformité du poids, mais seulement trois ont réussi le test de friabilité. Une marque de comprimés et de gélules a échoué au test de temps de désintégration. Il convient de noter qu'une seule marque a réussi au test d'analyse du contenu. Les comprimés ont libéré plus de 80% de fluconazole en 30 minutes, tandis que toutes les gélules, y compris la marque innovante, ont présenté une libération en rafale. Deux marques n'ont montré aucune activité contre Candida albicans. La marque innovante avait une activité antifongique significativement plus élevée ($p < 0,05$) que les génériques.

Conclusion: Les différences de qualité entre les marques suggèrent qu'aucune ne pourrait remplacer adéquatement la marque innovante.

Mots clés: Antifongique, fluconazole, médicaments génériques, équivalence pharmaceutique, Ibadan

INTRODUCTION

Drug therapeutic failure is currently a significant problem affecting the country's healthcare system and can be caused by various factors. One is the failure of a drug to elicit the desired pharmacologic effect on a patient due to poor bioavailability or lack of efficacy due to low drug content. The influx of cheaper generic brands of drugs into the market raises the issue of the unequal performance of a drug product. Many of these generic medicines are affordable but their interchangeability (quality, safety, and efficacy) with the innovator/reference brands is highly uncertain.

There have been reports of inconsistent batch-to-batch results and variable clinical reactions to generic medications.[1] Studies on biopharmaceuticals have demonstrated that the bioavailability and therapeutic effectiveness of almost all drug products are significantly affected by formulation factors such as the particle size of active pharmaceutical ingredients, excipients, flow properties, etc. The therapeutic efficacy of a drug product can only be assured by evaluating its chemical and biopharmaceutical equivalency.[2-4] All branded and generic products are expected to be therapeutically and chemically equivalent.

The quality and interchangeability of many generic drug products have been a major challenge in developing countries despite multi-sourcing these drug products to improve healthcare delivery through their competitive pricing.[5] However, therapeutic failures related to generic drugs have been reported worldwide including in Nigeria, particularly with antimicrobials such as ciprofloxacin and metronidazole.[6,7] Problems relating to treatment failure and pharmaceutical in-equivalence have also been reported in other drugs and drug products in Nigeria, examples include amlodipine tablets,[8] artemether injection,[9] and ibuprofen tablets.[10] It is noted that most generics are far less expensive than innovative medicines since not much is spent on drug discovery and development. This raises the question of whether these products will perform differently, as many consumers usually opt for these generics. It is important to ascertain their quality and interchangeability with the innovator brand.

Fluconazole is a first-generation triazole anti-fungal agent effective against oropharyngeal/oesophageal candidiasis and other fungal infections.[11] As a fungi-static agent, fluconazole blocks the conversion of fungal lanosterol to ergosterol, which stops the synthesis of membrane sterols and stops fungal cell division.[12] It is clinically important because of its lack of endocrine side effects of other antifungal drugs, and its excellent penetrability into the CSF of normal and inflamed meninges. Oral fluconazole is rapidly and fully absorbed (bioavailability > 90 %) and food or gastric pH does not usually impact the absorption of fluconazole. The plasma half-life is approximately 30 hours, allowing fluconazole to be administered once daily. Besides Diflucan (Pfizer Inc.) an expensive innovator product, several generics are marketed in Nigeria that are less expensive. Thus, there is a need to evaluate the bioequivalence of these generic brands with the innovator product to evaluate their interchangeability.

This study, therefore, aimed to assess the quality of the seventeen brands of fluconazole randomly purchased in Ibadan, Nigeria to determine their pharmaceutical equivalence and interchangeability with the innovator brand.

MATERIALS

Fluconazole tablets and capsules of different brands (Table 1) were randomly collected from major pharmacies across six local governments within the Ibadan metropolis area, Nigeria. Fluconazole reference samples (Gift from Bond Chemicals, Ltd. Awe, Oyo, Nigeria). All other reagents used were of analytical standard.

Table 1. Properties of the brands of fluconazole

Brand Code	Dosage Form	Batch Number	Expiry Date	Country of Origin	NAFDAC Number
T1	Tablet	GT18449	08/2021	India	B4-7568
T2	Tablet	KF7001	11/2020	India	A4-0421
T3	Tablet	QN9002	04/2022	India	B4-1645
T4	Tablet	GT19208	04/2022	India	B4-1543
T5	Tablet	S798168	06/2021	India	B4-6796
C1	Capsule	ETC/9001E	04/2022	Nigeria	B4-2723
C2	Capsule	C-1417	08/2021	India	A4-8615
C3	Capsule	N-1607	09/2020	India	A4-4024
C4	Capsule	170715	07/2020	China	B4-3571
C5	Capsule	C8004	09/2021	Nigeria	B4-2972
C6	Capsule	FK0011304	07/2022	India	04-8859
C7	Capsule	HR4186	10/2020	Germany	A4-2128
C8	Capsule	18009	11/2021	Nigeria	04-8591
C9	Capsule	350701	06/2022	Nigeria	04-4514
C10	Capsule	90677001	02/2021	Nigeria	A4-2773
C11	Capsule	F10011901	02/2023	India	A4-3325
IB	Capsule	B728303	04/2027	France	04-1426

METHODS

Sampling process

Ibadan metropolis is made up of 11 Local Government Areas (LGAs). Of these, six local government areas (Akinyele, Egbeda, Ibadan North, Ibadan Northwest, Lagelu and Oyo) were chosen, and seventeen brands of fluconazole, including the innovator brand, were randomly purchased from major pharmacies in the chosen LGAs. Thus, making the process a stratified random sampling.

Weight uniformity

Using a weighing balance (Fuzhou MinHeng Instruments, FA 2104A, China), twenty capsules and tablets from each brand were weighed separately, and their average weight was calculated.

The weight uniformity was computed using the differences between each tablet and capsule's average and individual weights. The percentage differences between each tablet's weight and average were also calculated.

Assay of fluconazole

A 100 ml volumetric flask containing the weight equivalent to 100 mg of fluconazole from one tablet/capsule of fluconazole that was crushed, was filled with 50 ml of 0.1 M HCL solution, which was then sonicated for 10 minutes while shaking intermittently to distribute and dissolve the contents. The volume was then increased to 100 ml with 0.1 M HCL solution to yield

1 mg/ml of fluconazole solution, filtered through a 0.45-micron membrane filter and further diluted with 0.1 M HCL solution to yield 0.2 mg/ml. The absorbances were read at a wavelength of 260 nm using a UV Spectrophotometer (Spectrolab 752s, Wincom Company Ltd., Shanghai, China).

Mechanical Properties

Crushing strength

A hardness tester (R00060 type EH01 DBK Instruments, Mumbai, India) was used to measure the tablets' crushing strength. Tablets were randomly selected and held between the anvil and the axis of the hardness tester. The tablet was subjected to increasing force until it broke into two clean halves. The force was recorded as the crushing strength.

Friability test

The friability of the tablets was determined using a DBK friabilator (DBK Instrument, Mumbai, India). Selected tablets were weighed and allowed to tumble in the friabilator at 25 rpm for four minutes. The tablets were taken out, cleaned from dust, and weighed again, and the new weight was recorded. The weight loss was calculated as a percentage of the final weight of the tablets to their initial weight. A maximum weight loss of less than 1 % is considered acceptable.

Release Properties

Disintegration time test

The disintegration test apparatus (DBK Instrument, Mumbai, India) was used for the determination of the disintegration time (DT) of the tablets and capsules. The tablets/capsules were placed into the baskets of the disintegration apparatus. Through simple harmonic motion, the baskets were raised and lowered into the immersion fluid (distilled water), which symbolises the churning movement of the stomach in the disintegration process. The immersion liquid was maintained at a temperature of 37 ± 0.5^{o}C. The duration for the tablets to disintegrate into particles and pass through the sieve was recorded.

Dissolution test

The dissolution test was carried out using the dissolution test apparatus (DBK Instruments, Mumbai, India). The basket method was used with rotation at 100 and 50 rpm for capsules and tablets respectively in 900 ml 0.1 M HCL solution kept at 37 ± 0.5^{o}C. At predetermined intervals, 5 ml samples of the dissolving medium were removed and replaced with an equivalent volume of fresh dissolution medium. The amount of fluconazole released was determined using a spectrophotometer (Spectrolab 752s, Shanghai, China) at a wavelength of 260 nm.[13]

Antifungal test

Using the cup plate method, a 24-hour-old culture of the test organisms (0.1 ml) - *Candida albicans* was added to 9.9 ml of distilled water and streaked on Sabouraud's dextrose agar. After setting, wells were bored into the plates using a 6 mm sterile cork borer. The different fluconazole brands were filled into the wells and allowed to stand for 1 h for diffusion into the agar. The plates were then incubated for 48 h at 25 ^{o}C. After that, the zones of inhibition were then measured and documented.

Data analysis

Statistical analysis was performed to compare the brands using Analysis of Variance (ANOVA) on the computer software GraphPad Prism® 5 (GraphPad Software Inc., San Diego, USA) at 95% confidence interval, p values ≤ 0.05 (that is 5%) were considered significant.

RESULTS

The physical characteristics of the fluconazole brands are presented in Table 2. Of the sixteen brands, five were 150 mg fluconazole tablets while the others were capsules; eight were 50 mg and three were 150 mg fluconazole. The innovator brand was a 50 mg blue and white capsule. Three of the five tablet brands were white and oblong shaped, while of the other two; one was white and round and the other pink and oblong. Out of the eleven brands of capsules, seven were coloured blue (in various shades) and white, one was only blue, another was only pink, another was white and green and the last was yellow and green.

Table 2. Physical characteristics of the brands of fluconazole

Codes	Dosage Forms	Colour	Appearance	Strength (mg)
T1	Tablet	White	Oblong	150
T2	Tablet	White	Oblong	150
T3	Tablet	White	Oblong	150
T4	Tablet	White	Round	150
T5	Tablet	Pink	Oblong	150
C1	Capsule	White and green	Cylindrical	50
C2	Capsule	Blue	Cylindrical	150
C3	Capsule	Blue and white	Cylindrical	50
C4	Capsule	Blue and white	Cylindrical	150
C5	Capsule	Blue and white	Cylindrical	50
C6	Capsule	Pink	Cylindrical	150
C7	Capsule	Sky blue and white	Cylindrical	50
C8	Capsule	Royal blue and white	Cylindrical	50
C9	Capsule	Cadmium blue and white	Cylindrical	50
C10	Capsule	Cyan blue and white	Cylindrical	50
C11	Capsule	Yellow and green	Cylindrical	50
IB	Capsule	Blue and white	Cylindrical	50

*IB; Innovator Brand

The fluconazole brands' physicochemical properties are presented in Tables 3 and 4 for tablets and capsules, respectively. The tablets had a weight range of 338.0 ± 3.0 to 945.0 ± 19.0 mg. The capsules had a weight range of 160.0 ± 2.0 to 482.0 ± 17.0 mg whereas the weight of the innovator brand was 156.0 ± 4.0 mg. The fluconazole contents are shown in Figure 1. All brands failed the content assay test except C3, which had a fluconazole content of 105.8 %.

Table 3. Mechanical and release properties of the tablet brands of fluconazole {Mean (SD), n=20}

Brands	Weight of dosage form	Crushing Strength	Friability (%)	Cs/fr	Disintegration Time	Dissolution time (min)	
	(mg)	(N)			(min)	t_{50}	t_{80}
T1	490.0(4.0)	14.0(0.0)	0.17(0.00)	82.35	3.30(0.80)	4.8	10.0
T2	741.0(6.0)	19.3(2.3)	0.10(0.00)	193.3	0.37(0.06)	14.8	27.0
T3	338.0(3.0)	10.0(1.0)	0.21(0.00)	47.62	1.70(0.45)	8.9	15.5
T4	945.0(19.0)	12.7(2.5)	3.04(0.10)	4.22	6.94(1.09)	11.5	21.6
T5	591.0(5.0)	7.3(1.5)	2.47(0.05)	2.97	23.42(0.78)	8.0	14.0

Table 4. Weight and release properties of the capsule brands of fluconazole [Mean (SD), n=20]

Brands	Capsule Weight (mg)	Disintegration Time (min)	Dissolution time (min)	
			t_{50}	t_{80}
C1	297.0(20.0)	4.84(0.63)	3.0	5.0
C2	463.0(13.0)	27.47(20.91)	–	–
C3	193.0(6.0)	6.48(0.46)	1.8	2.8
C4	296.0(9.0)	16.71(0.30)	–	–
C5	437.0(31.0)	4.55(0.91)	–	–
C6	346.0(10.0)	39.03(31.40)	–	–
C7	160.0(2.0)	8.05(4.77)	1.2	1.8
C8	482.0(17.0)	4.71(0.55)	0.5	1.0
C9	295.0(8.0)	4.64(0.61)	2.0	3.5
C10	370.0(13.0)	1.42(0.05)	–	–
C11	347.0(6.0)	5.62(0.57)	0.5	1.0
IB	156.0(4.0)	1.58(0.11)	4.0	7.2

– Capsules of 150 mg fluconazole were not tested.

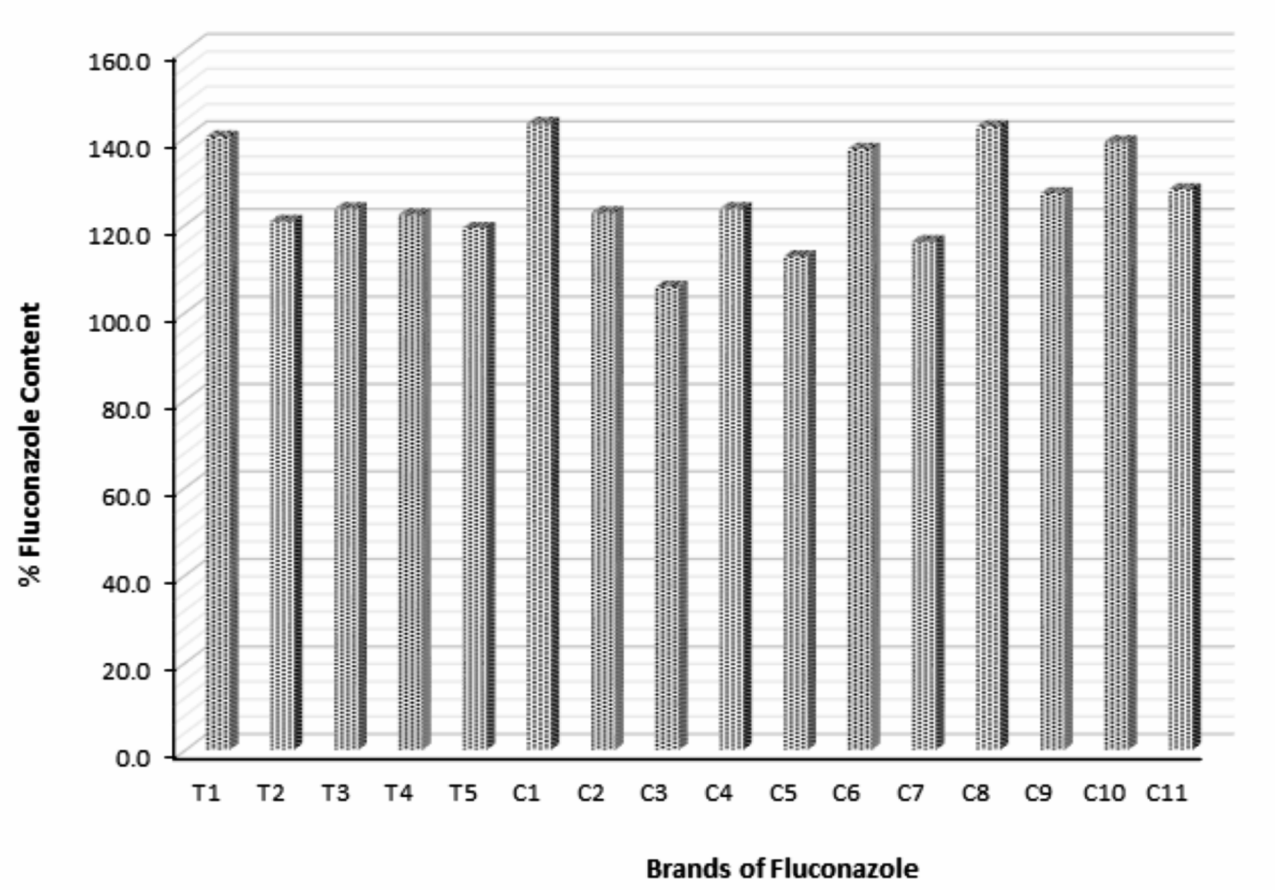

Figure 1. Fluconazole content (%) in all brands

The mechanical properties of the tablet brands presented in Table 3 showed that the tablets' crushing strength was in the rank order of $T_2 > T_1 > T_4 > T_3 > T_5$, and the friability and crushing strength/friability (Cs/Fr) ratio ranking was $T_2 < T_1 < T_3 < T_4 < T_5$ with T_4 and T_5 failing the friability test for uncoated tablets.

The disintegration time for the tablets and capsules is presented in Tables 3 and 4, respectively. All tablets passed the disintegration time test for uncoated tablets of ≤ 15 min except T_5, which had a DT of 23.42 ± 0.78 min. The rank order for disintegration time was $T_2 < T_3 < T_1 < T_4 < T_5$. All capsules passed the disintegration time test for capsules of ≤ 30 min except C_6, which had a DT of 39.03 ± 31.40 min.

The dissolution times for the tablet and capsule brands are shown in Figures 2 and 3, respectively. While all the tablets released 80% of their drug content before 30 minutes, all the capsules had a burst release including the innovator brand, releasing their drug content before 15 minutes. Capsules of 150 mg fluconazole were not tested here as there was no bases for comparison.

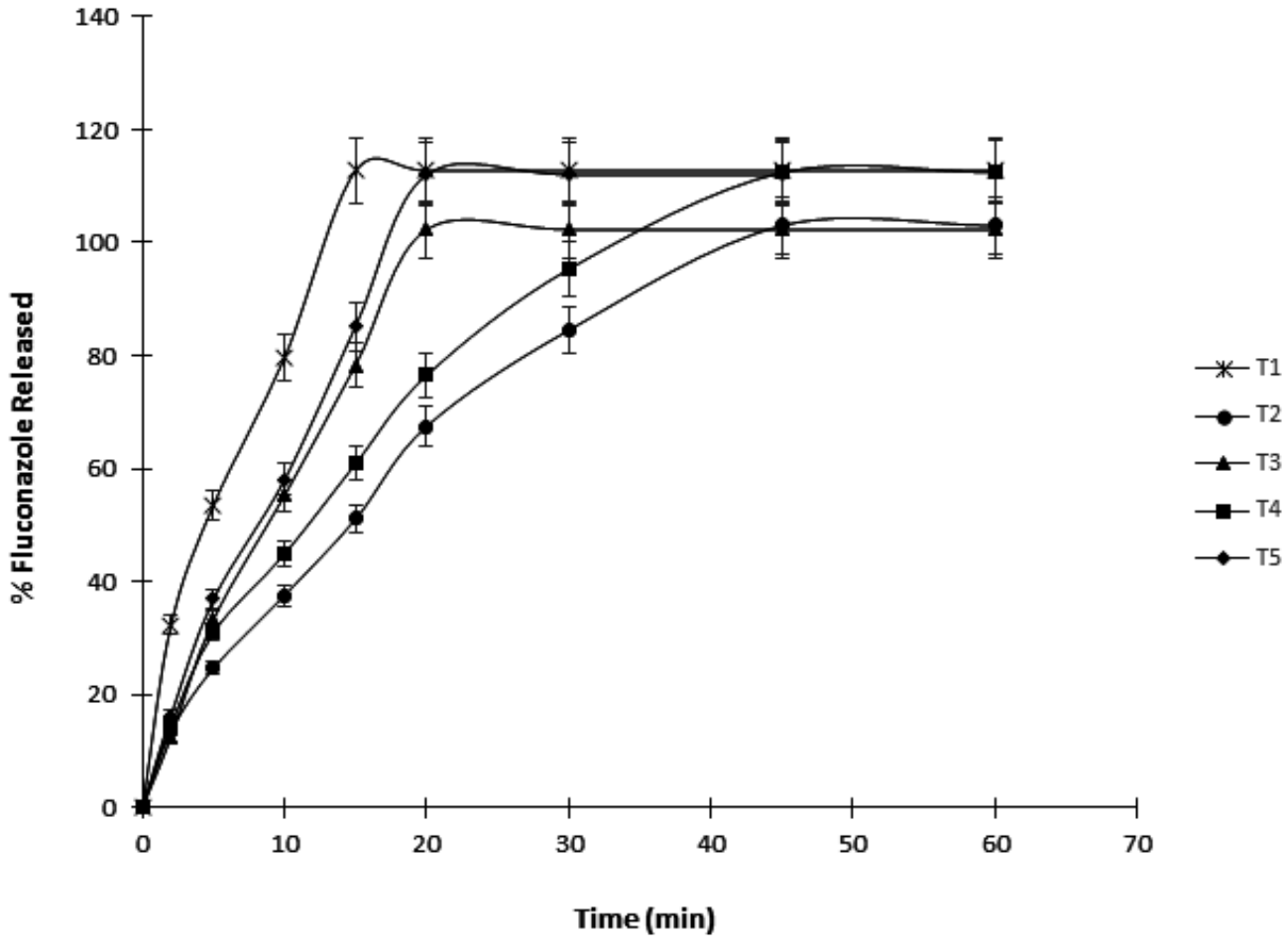

Figure 2. Percentage fluconazole released against time for the tablets

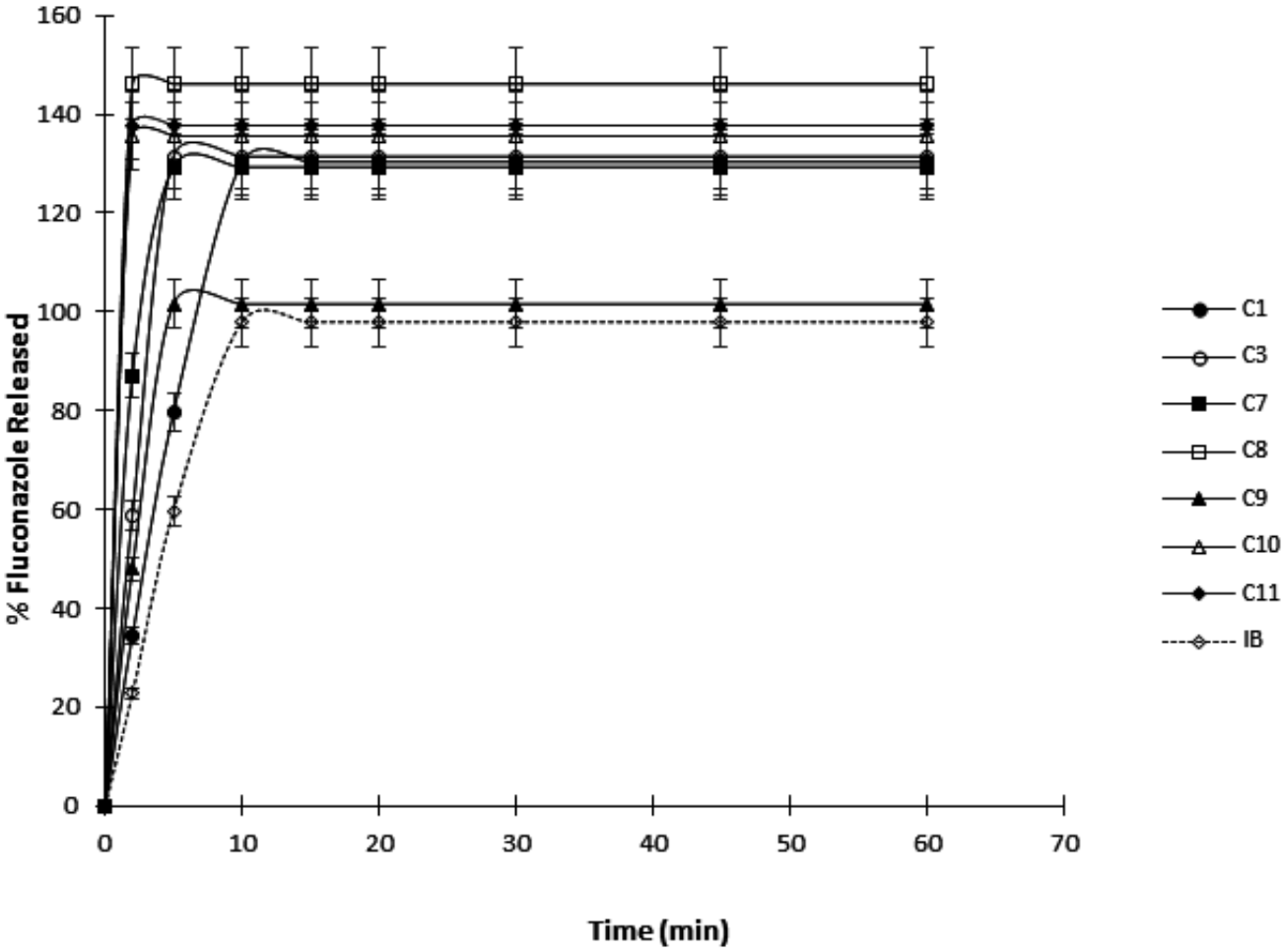

Figure 3. Percentage fluconazole released against time for the capsules

The antifungal activity (shown as zones of inhibition) of the formulations against the organisms tested is shown in Figure 4. The tablets generally had greater activity against Candida albicans than Candida species. The capsules exhibited similar activity except in brands C8 and C11, which had greater activity against Candida species than Candida albicans. The antifungal activity of the innovator brand was significantly higher ($p < 0.05$) than the tested brands.

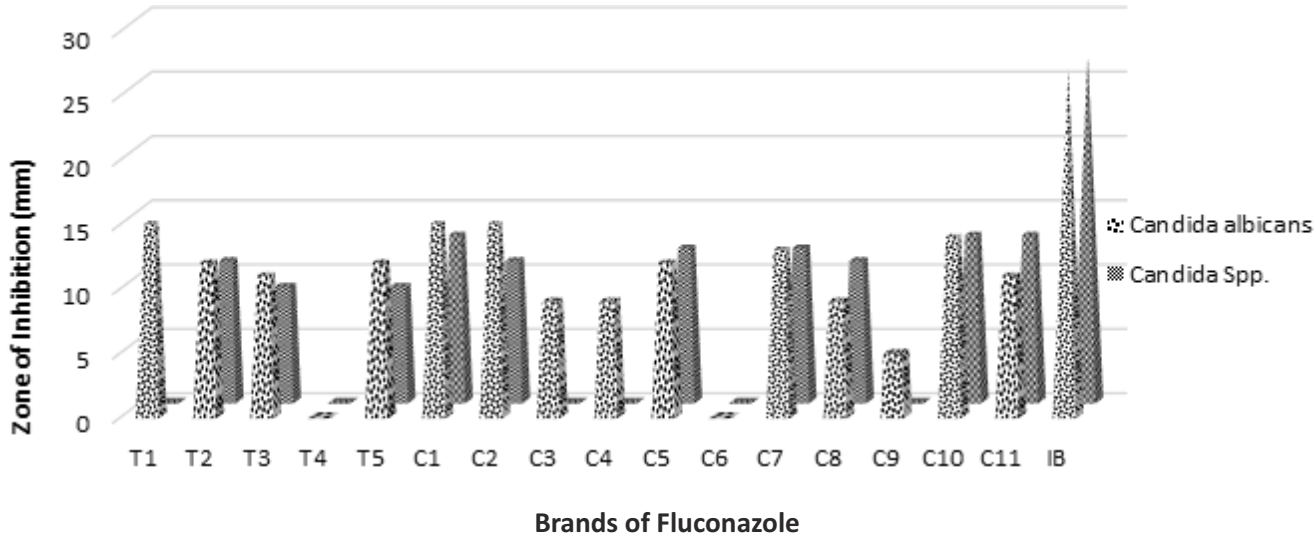

Figure 4. Zone of inhibition for the brands of fluconazole

The results of the various tests conducted in comparison with official standards are presented in Table 5.

Table 5. Compliance with Standards

	Weight Uniformity	**Friability**	**Disintegration**		**Content Assay**	**Dissolution**		**Antibacterial activity**
			Tablet	Capsule		Tablet	Capsule	
Standard	±7.5%	<1%	= 15min	= 30min	90.0 – 110.0%	75% to be released within 45 min		X or ✓
T1	✓	✓	✓		X	✓		✓
T2	✓	✓	✓		X	✓		✓
T3	✓	✓	✓		X	✓		✓
T4	✓	X	✓		X	✓		X
T5	✓	X	X		X	✓		✓
C1	✓	-		✓	X		✓	✓
C2	✓	–		✓	X		✓	✓
C3	✓	–		✓	✓		✓	✓
C4	✓	–		✓	X		✓	✓
C5	✓	–		✓	X		✓	✓
C6	✓	–		X	X		✓	X
C7	✓	–		✓	X		✓	✓
C8	✓	–		✓	X		✓	✓
C9	✓	–		✓	X		✓	✓
C10	✓	–		✓	X		✓	✓
C11	✓	–		✓	X		✓	✓
IB	✓	–		✓	✓		✓	✓

DISCUSSION

All brands of fluconazole investigated were within their shelf life and had labelled strengths of either 50 mg or 150 mg fluconazole. All the tablet brands and four brands of capsules were manufactured in India, five capsule brands were manufactured in Nigeria, while the remaining two capsule brands and the innovator brand, were manufactured in China, Germany, and France, respectively. All seventeen brands were registered in Nigeria with the National Agency for Food, Drug Administration and Control (NAFDAC).

The weight uniformity test is important because it guarantees that the tablets in each lot are within the required size range.[14] According to the compendia criterion for tablet weight uniformity, the percentage deviation from the average weight for tablets weighing more than 0.250 g should not exceed ± 5%.[15] Every tablet, regardless of brand, complied with the requirement. All the brands passed the weight uniformity test with very little variation from their average weight. According to the USP/NF 2020, the permissible fluconazole content is 90.0 - 110.0 %. Only brand C3 passed the content assay test. All

the other brands did not comply with USP/NF 2020 specifications, and their fluconazole content exceeded specification, implying a possible surplus of fluconazole in circulation, and thus suggesting higher chances of adverse reactions, therapeutic failure, or other medical complications. Fluconazole is a critical antifungal medication used to treat various fungal infections, particularly in immunocompromised patients (e.g. HIV/AIDS), thus, when substandard has several public health implications such as; increased mortality rates in vulnerable populations, increased health costs, increased drug interactions, development of drug-resistant fungal strains and distrust in the healthcare system.

Crushing strength is a measure of the ability of a dosage form to withstand stress on handling without damage. Crushing strength of 4 kgF i.e. 39.23 N is generally considered satisfactory for tablets. The crushing strength of all the tablets was below this value. Friability is a measure of tablet weakness. Brands T4 and T5 failed the friability test but all other tablet brands met the official requirement for friability, as their values were less than 1 %. This depicts the ability of the tablets to withstand abrasion in packaging, handling, and transportation. The disintegration time of the brands met the compendial[16] requirements for uncoated tablets (DT ≤ 15 minutes) except for brand T5, and all capsules complied (DT ≤ 30 minutes) except for brand C6. The satisfactory disintegration time displayed by most of the brands implies that the dosage forms will be broken down immediately in the gastrointestinal system, presenting enhanced surface area for dissolving and absorption of the medications. Brands T2 and C10 exhibited the fastest disintegration times of the tablets and capsules, respectively, with both brands disintegrating faster than the innovator brand.

In-vitro dissolution studies are used to predict the *in-vivo* bioavailability of most oral drugs rather than *in-vitro* disintegration tests that have a poor correlation.[17] Dissolution testing of drug products, therefore, serves as an *in-vitro* substitute for *in-vivo* performances as well as monitoring batch-to-batch consistencies of drug release from dosage forms.[18] The in-vitro drug release profiles showed that for all the brands, t_{50} (the time taken for 50 % of the drug to be released) was less than 20 minutes while the t_{80} (the time taken for 80 % of the drug to the released) was also lower than 30 minutes. This showed that all the tablet and capsule brands had similar drug release patterns, and the active pharmaceutical agent would be released within a short period. The drug being an antifungal agent would therefore be released in time to lower the fungal load, which is advantageous in achieving quick relief of symptoms and hence treatment success. All brands met the requirement of 75 % of the labelled contents being released within the first 45 minutes.

The capsules generally had higher activity against *Candida albicans* than Candida species and higher antifungal activity than the tablets, though the difference was not significant ($p > 0.5$). The dosage forms thus, did not seem to affect the antimycotic activity of the drug.

Although, all the brands passed weight uniformity tests, in comparison with official compendia, brands T4 and T5 failed the friability test while only the capsule brand C3 passed the content assay test. Brands T5 and C6 failed the disintegration time tests. The drug release studies showed the tablet brands to have attained t_{80} in less than 30 min while all the capsule brands exhibited a burst release. This is in order, as the gelatine shell of the capsule disintegrates once in contact with fluid releasing the active into the immediate surroundings, unlike the tablet which must be permeated with fluid before the active dissolves in the fluid and then flows out through the pores of the tablet. Interestingly, brands T4 and T5, which were readily friable did not disintegrate as fast as expected, and neither did T2 nor T3, which had the shortest disintegrating times, give the fastest release of fluconazole. It has been reported that even though the disintegrated particles are small enough to pass through the screen of the dissolution basket, they may retain the active drug within their cores. As a result, the drug is not released into the dissolution medium as quickly.[14] This means that the product may not release a significant amount of the medicine during absorption into the systemic circulation, resulting in therapeutic failure. Brands T4 and C6 showed no antifungal activity against the organisms tested. This was unexpected as the content assay revealed that most of the brands had a higher content of fluconazole than claimed. Poor diffusion of the drugs through the agar may have been the case here. There, however, was a significant difference ($P< 0.05$) in the antimycotic activity between the innovator brand and all other brands.

CONCLUSION

All the fluconazole brands passed the weight uniformity test, but only three brands passed the friability test. One brand of each of the tablets and the capsules failed the

disintegration time test while only one brand of capsule passed the content assay test. The differences between the generic brands of fluconazole and the innovator brand, would not permit their interchangeability with the innovator brand.

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