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Research Article

In Vitro Assessment of Some Brands of Fluconazole Capsules Marketed in Port Harcourt, Nigeria

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ABSTRACT

Objectives: A routine *in vitro* pharmacopeial quality assessment of five brands of fluconazole capsules with label claims of 50.0 mg marketed in Port Harcourt, Nigeria was carried out to ascertain their consistencies.

Methods: The brands were procured from various pharmacies in Port Harcourt and coded Fluco-A, Fluco-B, Fluco-C, Fluco-D and Fluco-E. Visual assessments of the samples were carried out besides *in vitro* quality considerations such as identification of the active pharmaceutical ingredient (API), capsules uniformity of weight, disintegration, an assay of the total content of fluconazole and dissolution studies.

Results: Each brand contained fluconazole with relevant product packet information uncompromisingly conspicuous. The label claims for fluconazole contents were satisfactory. The weight variation of the capsules across the brands were between 170.25 mg ± 2.25% -333.14 mg ± 1.50 %. Each brand disintegrated within 10 min. Total drug content was within 88.43 ± 0.12% to 102.96 ± 0.53 %.Above 80.0% of fluconazole was released within 30.0 min in the release studies of the respective brands.

Conclusion: The results obtained for the capsules uniformity of weight, disintegration time, the total content of the API and the drug release profiles were within acceptable limits of the United States Pharmacopoeia (USP).

Keywords: Fluconazole capsule, *in vitro*, quality, fake, standard methods.

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INTRODUCTION

A great number of the available pharmaceutical dosage forms are administered orally and most of them are in the solid dosage forms such as tablet and capsule. These have a high preference in usage due to the great advantage they convey in usage such as convenience and ease of handling, administration, masking of obnoxious tastes and odors, etc.[1].Capsules which exist either as the hard or soft form are often prepared from gelatin and are relevant in the packaging of pharmaceutical powders, semi-solids or oily preparations. Encapsulation of powdered medicaments enhances physical stability of the products as well as their identification, administration and release of their API [2-6].

Pharmaceutical medicinal dosage forms are manufactured in compliance to officially approved standards which are expected to be retained by the products within the shelf life to ensure their suitability for the intended purposes as well as having available safe and efficacious medicines for the population.

The circulation of sub-standard, inferior or counterfeit drug products pose a serious challenge to public health especially amongst the poor and developing nations [7]. The developing nations are more at risk due to poor and ineffective regulation of drug products manufacture and distributions. Though there are necessary legislation and regulatory bodies in place,the developing countries in most cases, do not have effective methods of monitoring the quality of generic or branded drug products in circulation, especially in those countries where pharmaceutical

products are distributed through the unregulated open markets. This results in the widespread distribution of substandard, fake and/or counterfeit drug products [7-13].It has been reported that counterfeit drugs account for about 40 – 60 % of drugs circulated worldwide [14]. Counterfeit drugs are drugs prepared or designed to look like the original and include products with little or no active ingredients or products that its excipients have been replaced by less expensive alternatives [15, 16]. Several classes of pharmaceutical products are involved in this challenge, including, but, not limited to the anti-infective agents, particularly antibiotics and anti-parasitic agents, antimalarial agents, etc. [17, 18].This has created a decline in confidence in the public health systems by the general public and health care providers. A huge financial burden has been placed on the consumers and pharmaceutical companies.

Fluconazole, a bis-triazole, is a first-generation antifungal agent used in the treatment of vaginal candidiasis and similar infections in the mouth, throat, and bloodstream. It has also been found useful in the prevention of candidiasis in people with compromised immunity especially those on cancer chemotherapy [19].Considering that high prevalence of fake and counterfeit drug products stems from the existence of unregulated open drug markets especially with the chaotic drug distribution networks in Nigeria, it becomes necessary to engage in a routine check of the quality control factors of such drug products that stand the chances of being tampered with by charlatans. This consideration brought about this routine assessment of the quality of some available brands of Fluconazole capsules in Port Harcourt, Nigeria.

MATERIALS AND METHODS

Materials

Five brands of Fluconazole capsules, pure Fluconazole powder (Galen, India) and hydrochloric acid (Sigma, USA).

Methods

Collection of Fluconazole capsules

Several samples each of five brands of Fluconazole capsules were procured from various pharmacies in Port Harcourt, Nigeria.

Evaluation of Fluconazole capsules

Physical evaluation of samples

The product packages and capsules were examined physically for firmness. The basic information expected to be present on the packages were investigated, such as brand name, label claim of potency, address of the producer, production and expiry dates, batch number and product registration number or status with a regulatory agency such as the National Agency for Food, Drug Administration and Control (NAFDAC) in Nigeria.

In vitro quality assessment of samples

Weight variation test

Twenty capsules per batch of each brand were weighed individually using an analytical balance (Ohaus, China). Later, the caps were separated from the bodies of the capsules and the contents were weighed to determine the net weight of each fluconazole capsule. The mean, standard deviation and coefficient of variance were calculated.

Disintegration time test

Both the British Pharmacopoeia (BP) and United States Pharmacopoeia (USP) recommend that the procedure used for the determination for disintegration time in uncoated tablets should also be applicable for the determination of disintegration time in capsules (20-21). Using a disintegration test apparatus (model ZT 200, Erweka, Germany), the disintegration time of six capsules of each sample of each brand were evaluated. A 500.0 mL volume of 0.1 N hydrochloric acid (HCl) placed in a 1.0 L beaker and immersed in a water bath at 37 ± 1 ^{o}C was used as the disintegration fluid. A capsule each from a batch sample per brand was singly kept in the cylindrical tube and guided with a glass disc. The time taken for the complete breakdown of the last capsule and its fragments passing completely through the wire mesh at the bottom of the disc was noted (21).

Determination of maximum wavelength (λ_{max}) of absorption and standardization of fluconazole

A 1.0 mg/mL stock solution of a pure sample of fluconazole was prepared using 10 mg of the fluconazole placed in a 10 mL volumetric flask and dissolved with sufficient 0.1 N HCl and the volume made up to 10mL using the same medium. Serial dilutions of the stock solution were made to obtain 0.2, 0.4, 0.6, 0.8 and 1.0 mg % solutions. The 0.4 mg % solution was scanned using a spectrophotometer (Jenway 6405, England) to determine the maximum wavelength (λ_{max}) of absorption of fluconazole. The λ_{max} of 261nm obtained was used to read the absorbance of the serially diluted solutions of fluconazole. The standard curve of fluconazole was plotted and utilized in the determination of the concentrations of various readings of absorbance got from the release studies.

Determination of total drug content

The individual weights of twenty capsules selected from each of the brands of the fluconazole capsules were noted. The total weight of the entire drug contents of the twenty capsules was noted after they were emptied. The mean weight was weighed and dissolved in a 100.0 mL volumetric flask with enough amount of 0.1 N HCl. The volume of the flask was made up to the mark using 0.1 N HCl and filtered. A ten-fold dilution of the filtrate was made. Its absorbance was obtained in the spectrophotometer. Triplicate determinations were carried out.

Drug release studies

The requirements established for the dissolution of fluconazole capsules in the USP, 2009 was adopted (21). Dissolution equipment (Erweka DT 600, Germany) was used with 900.0 mL of 0.1 N HCl in a 1.0L flasks set at 37±1^{o}C. The basket method was used with the baskets set to rotate at 75.0 revolutions per minute (rpm). One capsule was introduced into each flask and the equipment was run. Five (5.0mL) volume samples were withdrawn at 5.0min intervals over a 30.0 min period. At each withdrawal, there was also a replacement of the media using 0.1N HCl maintained at the same temperature. The absorption of the samples was read in the model 6405 Jenway UV/Vis

spectrophotometer (Jenway, England) at a maximum wavelength of 261nm.

RESULTS AND DISCUSSIONS

Results of a visual examination of samples

The results of the physical examination of the samples are presented in Table 1. The entire packaging and capsules were intact. The necessary product/label information including the brand name, the strength of the API, quantity of capsules per pack, batch number, dates of production and expiry, name and address of the producer and indication of product registration with the regulatory agency such as the NAFDAC in Nigeria, were properly documented and intact.

Uniformity of weight

Results of the uniformity of weight of the fluconazole capsules are shown in Table 2. The weight of the various capsules varied based on the brands and the manufacturers ($p < 0.05$). This could be attributed to the differences in the sizes of capsule shells used as well as the variation in the excipients involved in the formulation by the respective producers. The coefficient of variance in weight for all the brands of fluconazole capsules evaluated was within the range of 1.19-2.25%. This is within the acceptable compendial limits. The USP, 2009 (21)stipulates a limit of the coefficient of variance of 7.5 % for capsules that weigh between 130 – 324 mg and 5.0 % for capsules that weigh more than 325 mg.

Table 1: Relevant product package information onthe samples of fluconazole capsules.

Sample code	Label strength (mg)	Date of production	Expiry date	Producer's address	Country of production	NAFDAC Status
Fluco-A	50.0 mg	10/2017	10/2020	Present	Germany	Registered
Fluco-B	50.0 mg	08/2017	07/2021	Present	India	Registered
Fluco-C	50.0 mg	07/2017	06/2021	Present	Nigeria	Registered
Fluco-D	50.0 mg	02/2016	01/2021	Present	USA	Registered
Fluco-E	50.0 mg	07/2017	05/2021	Present	Nigeria	Registered

Table 2: Mean weight of fluconazole capsules

Brand name	Weight (mg) ± CV (%)	Disintegration time (min)	Total drug content (%)
Fluco-A	170.25 ± 2.25	2.14±0.21	103.84±0.31
Fluco-B	333.14 ± 1.50	5.88±0.06	92.86±0.25
Fluco-C	308.31 ± 2.15	6.23±0.15	87.36±0.11
Fluco-D	169.55 ± 1.19	2.09±0.02	99.96±0.20
Fluco-E	245.23 ± 1.24	3.58±0.10	97.92±0.10

CV: Coefficient of variance

Disintegration time

The results of the disintegration time tests are shown in Table 2. The range of disintegration time across the brands was 2.09-6.23 min. This implies that the respective drug contents had a short time to get discharged from the shell to permit the dissolution of the fluconazole which would further give room for drug bioavailability and onset of action.The British Pharmacopeia, 2012 (20) specifies an upper disintegration time limit of 15.0 min while the USP, 2009 (21) specifies 30.0 min for the disintegration of uncoated tablets.Since the same parameters of disintegration that are used for uncoated tablets are also used for capsules, the disintegration time for different brands of fluconazole capsules is satisfactory.

Total drug content

The results of the total drug content of brands of fluconazole capsules are presented in Table 2. The percentage assay was least in Fluco-C (88.43 ± 0.12 %) and highest in Fluco-A (102.96 ± 0.53%). All the brands met with specifications of both the BP and USP for the content of active ingredient which should be within 85.0-115 % (20, 21).

Drug dissolution studies

The dissolution profiles of fluconazole for the various brands are presented in Figure 1. The drug release was to a great extent consistent and released maximally within the duration of the release studies. The release profiles of the various brands were compared in terms of the time for the release of 50 %, 80 % and 90 % ($T_{50,}$ T_{80} and $T_{90)}$ respectively. The brands attained T_{50} as follows in minutes:Fluco-B (4.75) <Fluco-A =Fluco-C =Fluco-D=Fluco-E (5.00) (Fig.2).Considering $T_{80,}$ the outcomes were as follows in minutes: Fluco-C (9.50) <Fluco-B (16.25)<Fluco-A (17.00)<Fluco-D (19.50)<Fluco-D (24.50) (Fig.3). The attainment of T_{90} occurred at the following times in minutes as follows: Fluco-C (15.00) <Fluco-A = Fluco-B (19.00) <Fluco-D (23.75) (Fig.4). Fluco-E failed to attain T_{90} after 30 min. With early disintegration of the respective samples of the brands studied, very effective drug release was recorded among the entire brands considering the brief periods at which they released up to 80.0% of their drug contents. This indicates good formulations of the various brands since their excipients contents did not slow down the release of their API. Among the brands, Fluco-E presented with the slowest release of its API.

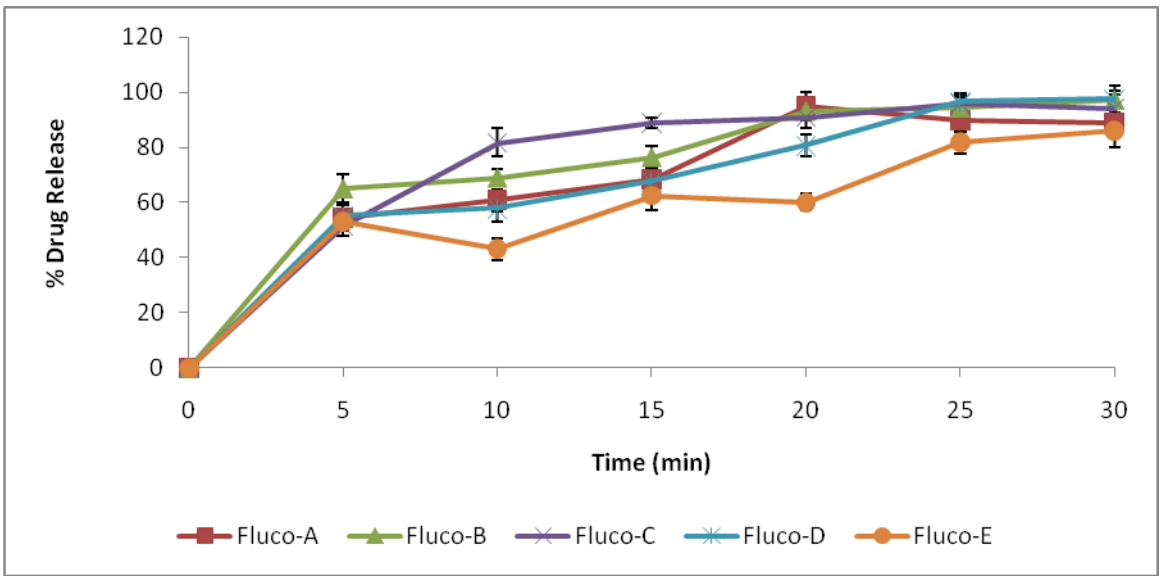

Figure 1: Dissolution profile of the various brands of fluconazole capsules.

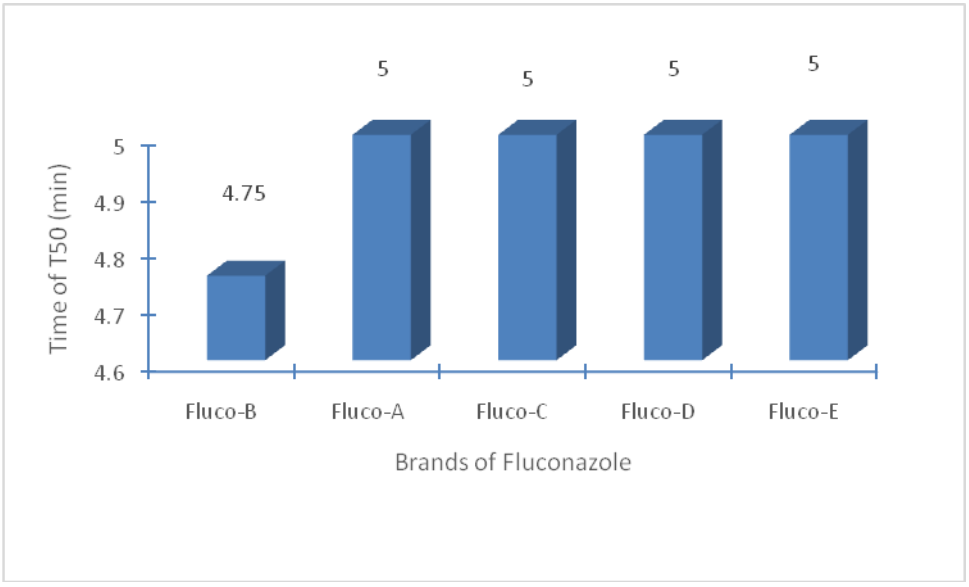

Figure 2: Time of attaining T_{50} for the brands of fluconazole

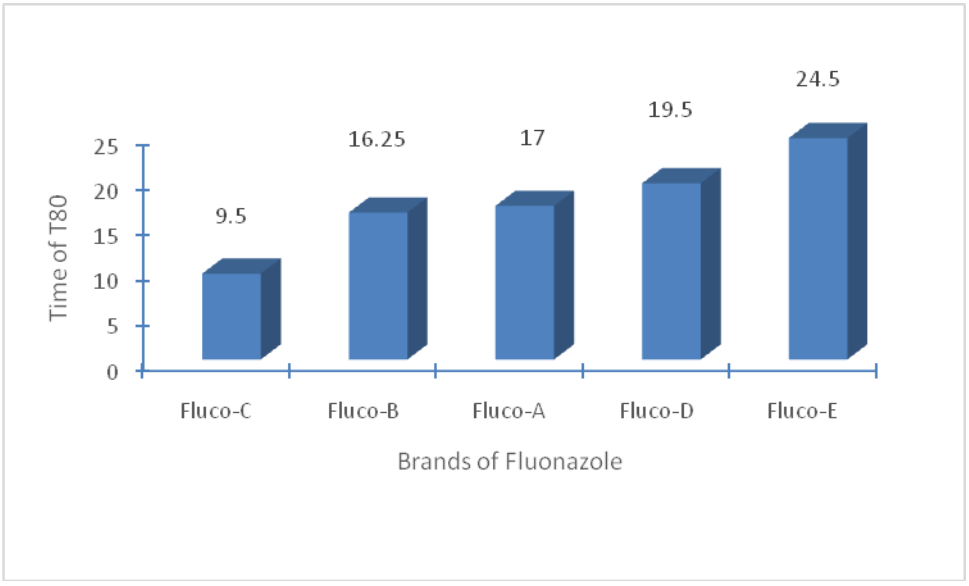

Figure 3: Time of attaining T_{80} for the brands of fluconazole

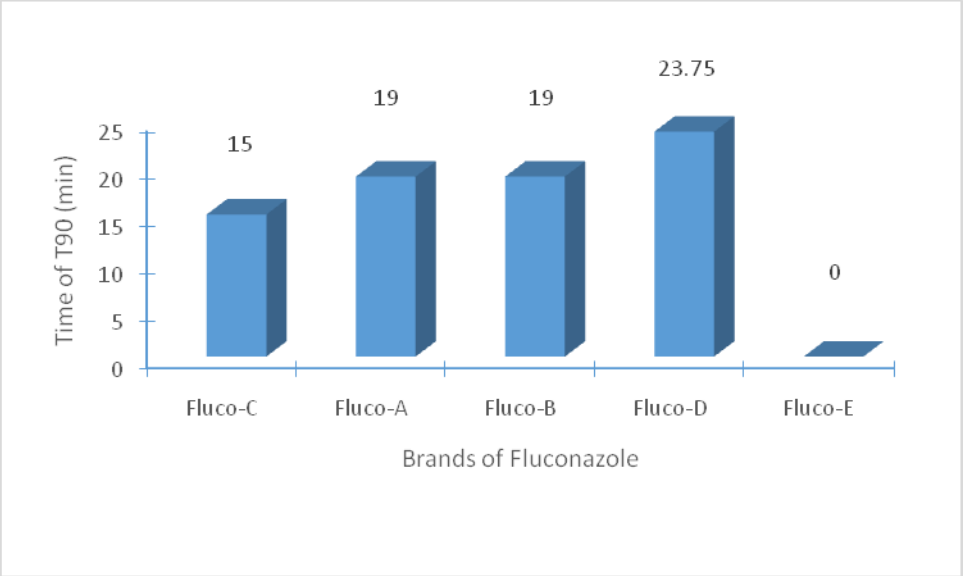

Figure 4: Time of attaining T_{90} for the brands of fluconazole

CONCLUSION

The physical assessment of the different brands of fluconazole capsules shows that the capsules were intact in their blister packs. The packets contained all the relevant information concerning the products brand or generic names, the potency of the API, the quantity of capsules per pack, the name and address of the manufacturer, the dates of manufacture and expiry, the batch number, and the NAFDAC registration status. The results of the other quality control parameters investigated were satisfactory as complying with the compendial limits for fluconazole capsules. The respective brands were capable of releasing their API maximally with the duration of release studies.

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CONFLICTS OF INTEREST

The authors have no conflict of interest.

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