Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2020, 12(7): 11-23

Research Article

ISSN: 0975-7384
CODEN(USA): JCPRC5

Comparative Study of Two Commercial Caspofungin Products

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ABSTRACT

Currently, patients and physicians need to know that the quality of generic medications is equal, greater or less than their brand equivalent. In the case of antibiotics, their performance must be evaluated by in vitro and in vivo methods, to ensure their performance as a therapeutic agent. Caspofungin were studied by microbiological assays to determine its potency (content), Minimal Inhibitory Concentration (MIC), Mutant Prevention Concentration and pharmacodynamics. In regard to potency the products fulfill the requirements for the content (107.00-107.57%) without significant differences. The value MICs for Candida and Aspergillus species using standard and the commercial products are the same, then the products behave equally. There are not significant differences between the number of mutants recuperated from the different concentrations of Caspofungin (Kafum [generic one] and Cancidas [innovator one]) evaluated. The pharmacodynamic study at different concentrations of Caspofungin (Kafum and Cancidas) showed similar behavior, again without significant differences. Finally, we can say that the products evaluated are pharmaceutical equivalents, and have similar antimicrobial activity, so the products could be considered therapeutically equivalent.

Keywords: Caspofungin; Quantitative bioassay; In vitro susceptibility testing (MIC); Mutant Prevention Concentration (MPC); Pharmacodynamics

Abbreviations: MIC: Minimal Inhibitory Concentration; MPC: Mutant Prevention Concentration; B1: Batch 1; B2: Batch 2; S1: Sample 1; S2: Sample 2; S3: Sample 3.

INTRODUCTION

A generic drug is defined as a faithful imitation of an established drug lacking patent protection and marketed with the chemical name of the active pharmaceutical ingredient. Generic drugs are meant to be interchangeable with the original, although in practice there are three categories: branded generics, which are copies of the brand name (innovator) product with their own branded names; semibranded generics, which are products marketed only under the International Nonproprietary Name (INN) followed by the name of the manufacturer; and unbranded generics, which are marketed solely under the INN [1].

One concern is that the widespread use of generic antimicrobial products in the treatment of infections is responsible for the increase in resistance to antibiotics [2]. However, Tattevin et al. [3] stated that there is no convincing evidence showing that generic antibacterial products approved by regulatory authorities are suboptimal compared to brand name products.

Regarding the quality of generic antimicrobials, several studies have been conducted that emphasize the lack of therapeutic equivalence, despite their pharmaceutical equivalence [4]. Because of the alarm raised by the potential for public health problems caused by using generic antimicrobials, other researchers have attempted to corroborate the findings of Vesga et al. [4] by evaluating the quality of generic vancomycin products marketed in the United States [5-7]. The researchers found that the products were pharmacologically and therapeutically equivalent, which undermined the speculations proposed by Vesga et al [4].

Caspofungin is a licensed antimicrobial used for the treatment of invasive candidiasis in adult patients, for the treatment of invasive aspergillosis in patients who are refractory or intolerant to amphotericin and/or itraconazole (patients are considered refractory if infection progresses or there is no improvement after a minimum of 7 days of effective antifungal therapy at therapeutic doses), and as empiric therapy for presumed fungal infections (Candida or *aspergillus*) in febrile neutropenic adult patients [8].

The possibility of a less costly alternative to brand name caspofungin is welcomed, as it would be more available to medical professionals and would provide more flexibility in adjusting patient treatments, especially when considering medication-medication interactions or comorbidities.

A comparative study between generic itraconazole products and the brand name product found no significant difference in its efficacy for the treatment of *tinea pedis* [9]. The same result was found when generic and brand name itraconazole products were used in dogs and cats [10]. In 2015, Gonzales et al. demonstrated that three generic fluconazole drugs were therapeutically equivalent to the brand name product.

To increase the information available on the quality of generic antifungals, we have conducted a comparative study of the performance of generic versus brand name caspofungin products.

MATERIALS AND METHODS

Microorganisms

The following strains were used in this study: *Candida tropicalis* ATCC 750, *Candida krusei* ATCC 6258, *Candida albicans* ATCC 90028, *Candida parapsilosis* ATCC 22019, *Candida albicans* LA1 (received from Hospital de Engativá, Bogotá D. C. Colombia), *Candida parapsilosis* HT5 (receivedfrom Hospital de Tunal, Bogotá D. C. Colombia), *Candida auris* (received from Secretaría de Salud, Bogotá D. C. Colombia), *Cryptococcus sp.* HT2 (received from Hospital de Tunal, Bogotá D. C. Colombia), *Cryptococcus neoformans* HT4 (received from Hospital de Tunal, Bogotá D. C. Colombia), *Aspergillus fumigatus* ATCC 204305, *Aspergillus flavus* (received from Hospital de Engativá, Bogotá D. C. Colombia), *Aspergillus fumigatus*, *Aspergillus niger* RN6 (received from Hospital de Engativá, Bogotá D. C. Colombia) , *Aspergillus niger* INC 01 (received from Hospital de Engativá, Bogotá D. C. Colombia), and *Aspergillus* spp (received from Hospital de Engativá, Bogotá D. C. Colombia). *Candida* strains were cultivated on YM agar (3.0 g yeast extract, 3.0 g malt extract, 5.0 g peptone, 10.0 g glucose, 20.0 g agar, and distilled water to 1 liter) and incubated at 37°C for 48 hours. The cultures were harvested with a diluent solution

(10.0 g tryptone, 8.0 g nutritive broth, 30 g base broth, 50 g sucrose, 150 g glycerol, 50 ml dimethyl sulfoxide, and distilled water to 1 liter), and their optical density was adjusted to 25% T (λ =600 nm) and stablished the colony count for each suspension. *Aspergillus* strains were cultivated on YM agar and incubated at 37°C until sporulation. Spores were harvested with diluent solution plus 0.5% (w/v) Tween 80. The number of spores per ml was determined in a Neubauer chamber. All of the suspensions were stored at -70°C until studies were performed.

Analytical bioassay

The analytical bioassay was established and validated to quantify the amount of caspofungin in the commercial products. First, the most appropriate microorganism was selected, then the appropriate concentration range was stablished, and finally the linearity and accuracy were evaluated [11,12]. All samples were then evaluated under the specified conditions by the statistical parallel lines model described by Hewitt (1977) and the mean dose model described in the USP (2018). The content calculation was performed according the above methods. The standard caspofungin was purchase from Sigma Aldrich.

***In vitro* susceptibility testing**

It was performed by broth microdilution test following CLSI protocol MA27 A2 (CLSI-1, 2002) and *Candida albicans* ATCC 90028, *Candida parapsilosis* ATCC 22019 were used as control strains; and MA38- A (CLSI-1, 2002) and *Aspergillus fumigatus* ATCC 204305 was used as control strain [13,14]. The assay was performed five times for each microorganism.

Mutant Prevention Concentration (MPC):

To determine the concentration required to prevent the generation of mutants, the procedures described by Brodallo-Cardona et al. (2018) were followed. Briefly, strains suspensions were adjusted to 2.5 × 109 to 6.3 × 109 CFU/ml (mean of 4.1 × 109 ± 1.51 × 109) for *Candida* species and 1.9 × 109 to 64.9 × 109 Spores/ml (mean of 3.1 × 109 ± 1.03 × 109) for *Aspergillus* species. Each suspension was stroked directly (100 µl) onto YM agar plates containing concentrations equivalents at once, twice, 4- and 8-times MICs value (Minimal Inhibitory Concentrations) of caspofungin. Plates were incubated at 35°C for 48 h and visually inspected. MPCs were defined as the lowest caspofungin concentration leading to complete inhibition of fungal growth on caspofungin-containing agar plates [15].

Pharmacodynamics

The pharmacodynamics of the samples were assessed based on the procedures described by Di Bonaventura et al. [16] and Cota et al. [17]. The assay was performed onto 25 ml of RPMI 160 medium added with caspofungin at once, twice, 4- and 8-times MICs value, inoculated to give to initial population of approximately 1 × 106 UFC/ml. It was taken samples of 3 ml each 3 hours for yeast and 4 hours for molds, four times. Centrifuge 1 ml of the sample (5000 RPM/15 min), discard the supernatant, add isotonic saline solution, homogenize, centrifuge, discard the supernatant, add isotonic saline solution, homogenize again. The sample plate count was performed with YM agar. The strains evaluated were *C. albicans* ATCC 90028, *C. albicans* LA1, *Candida parapsilosis* HT5, *Criptococcus sp*. HT2, *Criptococcus neoformans* HT4, *Candida auris*, *Aspergillus fumigatus* ATCC 204305, *Aspergillusflavus*, Aspergillusfumigatus, Aspergillusniger RN6, *Aspergillus niger* INC and *Aspergillus spp*.

Samples

The samples under study were Cancidas (batches: N014729 and N024513; Merck Sharp & Dohme (MSD) Colombia SAS) and Kafum (batches: AAF704X y AAF705X; Dr. Reddy's Laboratories Limited). Five samples were obtained from each batch. Three random samples were taken from each batch for the studies and two were left in reserve. Each sample was quantitatively reconstituted in 50 ml of sterile distilled water, fractionated into 5 ml vials, and stored at -70°C.

Statistical analysis

The Microsoft Excel ® statistical tool was used to analyze the data.

RESULTS

Analytical bioassay

The microorganism selection criterion for the gel diffusion bioassay was the production of well-defined inhibition halos, no larger than 30 mm in diameter, and without spontaneous mutants in the inhibition zone [18,19]. Figures 1 and 2 shows the response of the different strains of *Candida* to caspofungin. Based on these results, *C. parapsilosis* ATCC 22019 was selected as the model organism for validation because it met the requirements to be used as a biological model.

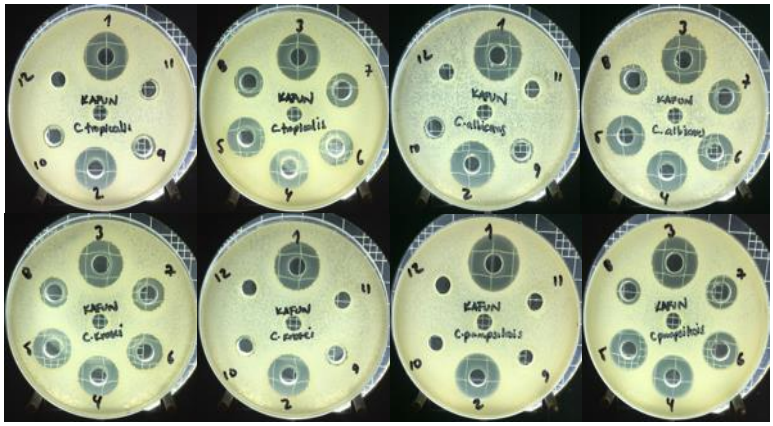

Figure 1. Halo inhibition responses of *Candida tropicalis* ATCC 750, *Candida krusei* ATCC 6258, *Candida albicans* ATCC 90028, and *Candida parapsilosis* ATCC 22019 to twelve concentrations of KAFUM (1:2 dilutions from 1000 to 0.488 µg/ml, C1 to C12).

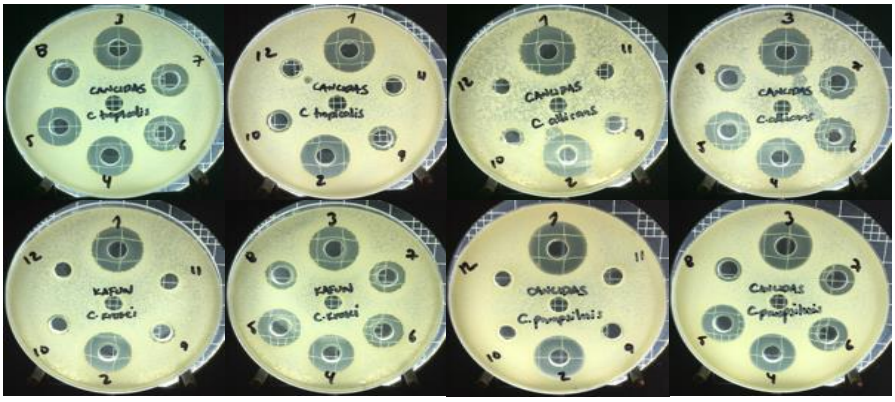

Figure 2. Responses of *Candida tropicalis* ATCC 750, *Candida krusei* ATCC 6258, *Candida albicans* ATCC 90028, and *Candida parapsilosis* ATCC 22019 to twelve concentrations of CANCIDAS (1:2 dilutions from 1000 to 0.488 µg/ml, C1 to C12).

Twelve concentrations were used (1:2 dilutions from 1000 to 0.488 µg/ml, C1 to C12) to establish the range. The best linearity was obtained in the range of C5 to C9 for *C. parapsilosis* ATCC 22019 (62.5 to 3.906 µg/ml; R2=0.9972), which is shown in Figure 3. For practical reasons, the highest concentration was set at 70.0 µg/ml.

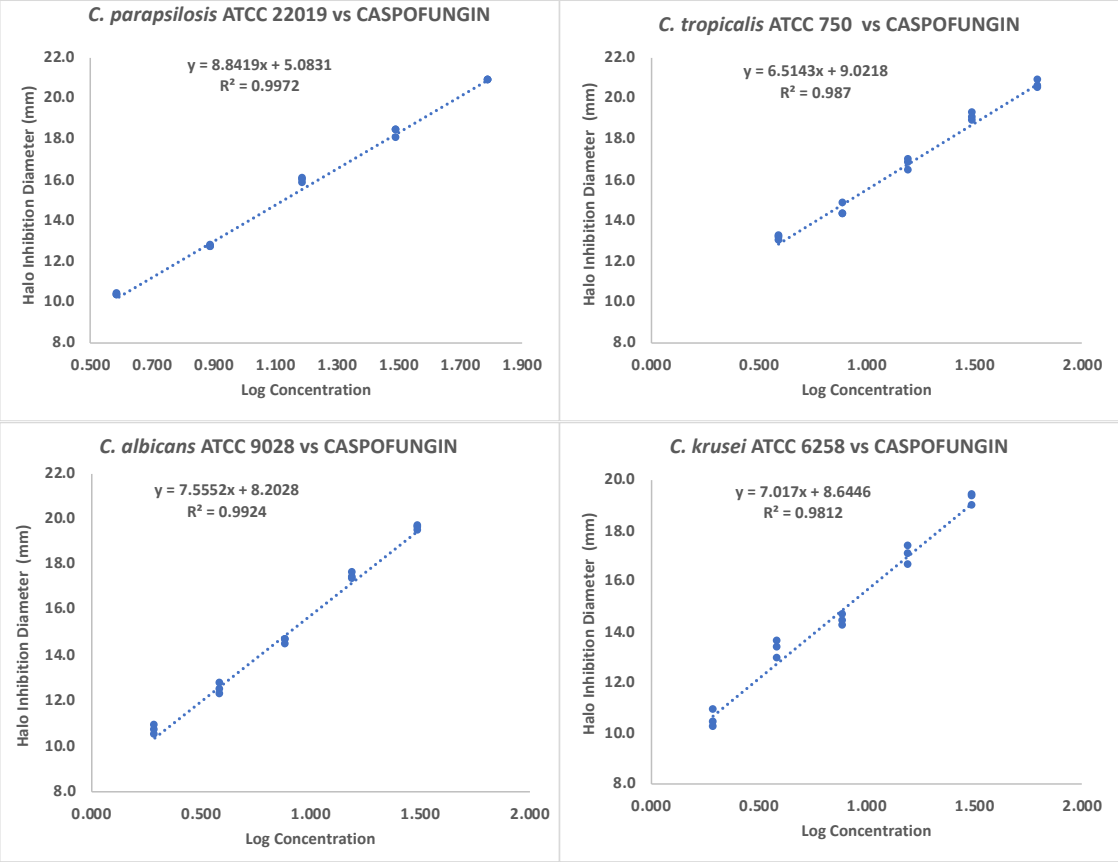

Figure 3. Calibration curves of five caspofungin concentrations for evaluating the concentration range.

The accuracy was evaluated by repeatability, where the intraday Coefficients of Variations (CV) were between 0.439 and 1.116% and the interday CVs were between 0.432 and 1.248%, which are lower than the CV accepted for bioanalytical techniques (CV <5%) [11,19]. Therefore, we can affirm that the technique is accurate and reproducible. Finally, the Lower Limit of Quantification is 3.906 µg/ml and the Upper Limit of Quantification is 70.0 µg/ml.

Analysis of the Samples

The samples were analysed by two methods, the statistical parallel lines model described by Hewitt (1977) and the mean dose model described in the USP (2018).

Tables 1 and 2 shows the caspofungin content in the commercial samples (107.5 to 107.7 %), demonstrating that the products meet necessary specifications (no more than 110% of the labelled content). The null hypothesis (H_o) is: "there aren´t significant differences between generic and the innovator products", so the F value is minor than Critical Value of F the Ho is accepted.

Table 1. Caspofungin content using the parallel lines model.

BATCH	SAMPLE	POTENCY (%)	MEAN (%)	$\delta_{(n-1)}$
Kafum B1: AAF704X	S1	107.22		
	S2	107.57		
	S3	107.53	107.56	0.09
Kafum B2: AAF705X	S1	107		
	S2	107.17		
	S3	107.37	107.54	0.0569
Cancidas B1: N014729	S1	107.45		
	S2	107.5		
	S3	107.39	107.45	0.0551
Cancidas B2: N024513	S1	107.49		
	S2	107.41		
	S3	107.52	107.47	0.0569

Table 2. Caspofungin content using the mean dose model.

BATCH	SAMPLE	POTENCY	MEAN	$\delta_{(n-1)}$
Kafum B1: AAF704X	S1	107.8		
	S2	107.51		
	S3	107.72	107.53	0.0631
Kafum B2: AAF705X	S1	107.72		
	S2	107.59		
	S3	107.47	107.54	0.281
Cancidas B1: N014729	S1	107.58		
	S2	107.46		
	S3	107.55	107.68	0.1491
Cancidas B2: N024513	S1	107.76		
	S2	107.22		
	S3	107.63	107.59	0.124

The Table 3 shows that the responses did not differ significantly, which allows us to conclude that Kafum and Cancidas are pharmaceutically equivalent.

Table 3. Analysis of variance for caspofungin content

TEST	F	PROBABILITY	CRITICAL VALUE OF F
Parallel lines	1.91604	0.20552	4.06618
Mean Dose (USP)	0.27844	0.83956	4.06618

Antimicrobial susceptibility test

It was tested by Minimum Inhibitory Concentration (MIC). The samples were analyzed in groups of six per plate, where rows A and E corresponded to a standard solution of caspofungin and the remaining rows to commercial samples.

All samples of Kafum and Cancidas had the same MIC values for C. auris, 32 µg/ml at the 24-hour reading and 64 µg/ml at the 48 hours reading. The same pattern occurred with the other organisms examined (Table 4). This result indicates that there were no differences between the antifungal activity of the products.

Table 4. Minimal inhibitory concentrations of Kafum and Cancidas

STRAIN	MIC (mg/ml)	
	24 h	48 h
C. parapsilosis ATCC 22019	0.25	0.25
C. albicans ATCC 90028	0.25	0.25
C. albicans LA1	< 0.125	< 0.125
C. parapsilosis HT5	0.25	0.25
Cryptococcus sp. HT2	16	16
C. neoformans HT4	16	16
C. auris	32	64
A. fumigatus ATCC 204305	0.5	0.5
A. flavus	1	1
A. fumigatus	0.25	0.25 mg/ml
A. niger RN6	4	4
A. niger INC 01	< 0.125	< 0.125
Aspergillus spp.	2	2

Mutant prevention concentration

Petri dishes with YM agar were prepared containing caspofungin at a concentration equivalent to once, twice, 4- and 8-times MICs value. A 0.100 ml aliquot of an inoculum of the microorganism under study was spread over the surface, resulting in a population of approximately 108 CFU or spores/ml. Figures 4-7 shows the mutant frequency for each strain and concentration.

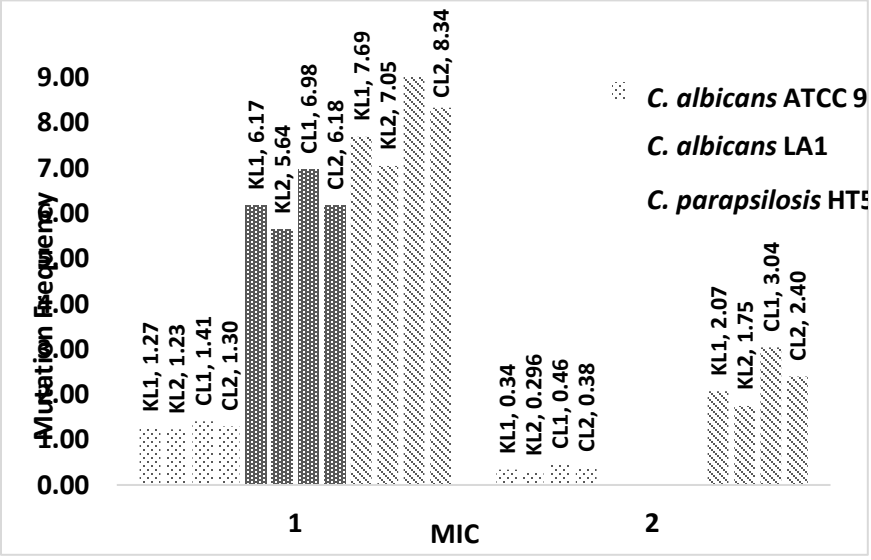

Figure 4. Mutation frequency (values x 10-7) of *C. albicans* ATCC 90028 (MIC: 0.25 µg/ml), *C. albicans* LA1 (MIC: 0.25 µg/ml), *C. parapsilosis* HT5 (MIC: <0.125 µg/ml) tested on agar YM plate at once, twice, 4- and 8-times MICs value.

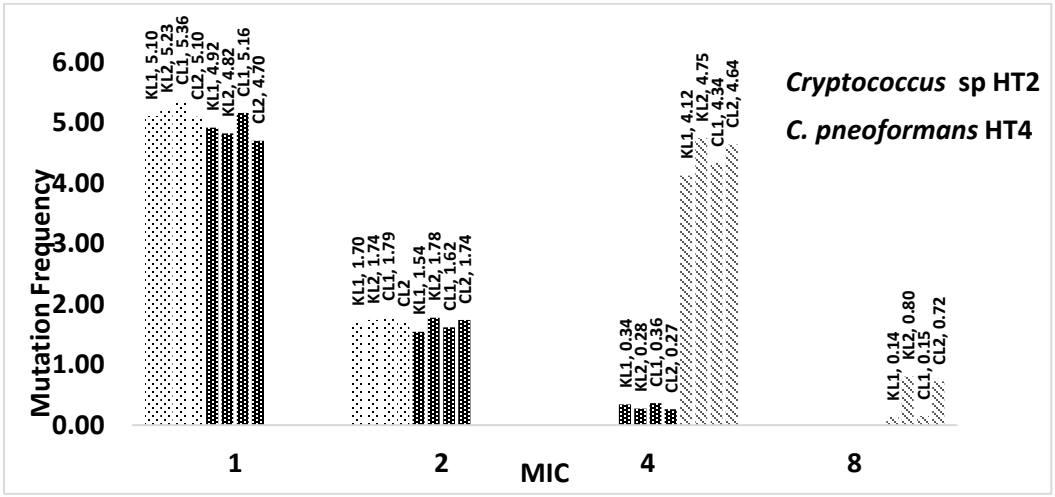

Figure 5. Mutation frequency (values x 10-7) of *Cryptococcus sp.* HT2 (MIC: 0.25 µg/ml), *C. neoformans* HT4 (MIC: 16.0 µg/ml), *C. auris* (32.0 µg/ml) tested on agar YM plate at once, twice, 4- and 8-times MICs value.

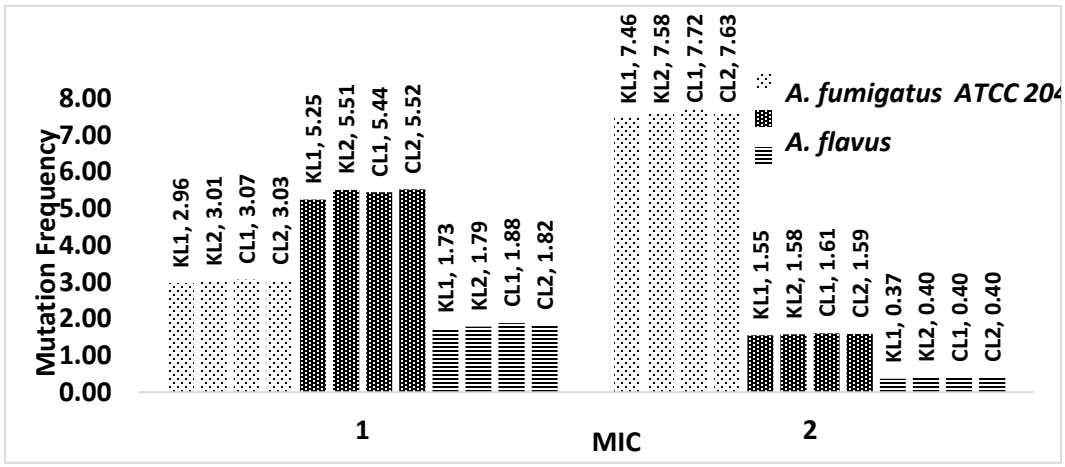

Figure 6. Mutation frequency (values × 10-7) of *A. fumigatus* ATCC 204305 (0.50 µg/ml), *A. flavus* (1.00 µg/ml), *A. fumigatus* (0.25 µg/ml) tested on agar YM plate at once, twice, 4- and 8-times MICs value.

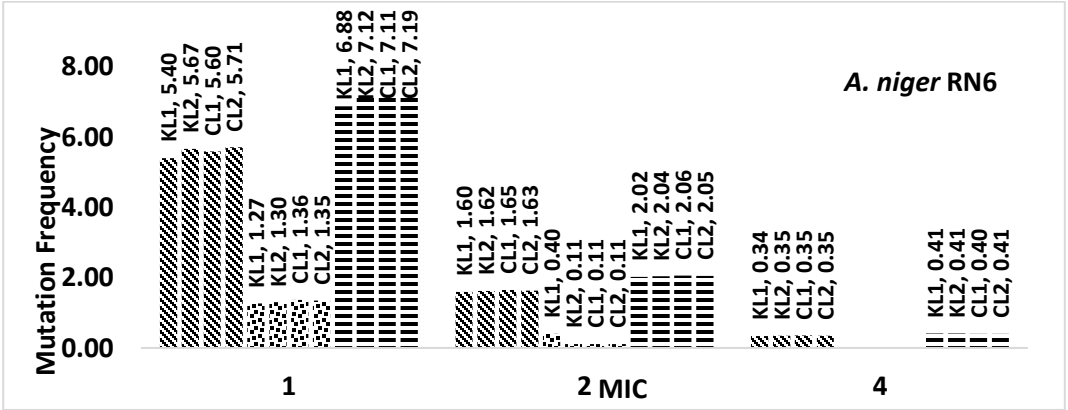

Figure 7. Mutation frequency (values × 10-7) of *A. niger* RN6 (4.00 µg/ml), *A. niger* INC 01 (<0.125 µg/ml), *Aspergillus spp.* (2 µg/ml) tested on agar YM plate at once, twice, 4- and 8-times MICs value.

The evaluation of average of mutant frequency by one-way ANOVA indicate that there are no significant differences, as is seen on Table 5. In view of the above, Kafum and Cancidas are equivalent in their antimicrobial activity.

Table 5. Analysis of variance of mutant frequency generated with the tested strains evaluated at once, twice, 4- and 8-times MICs value. (Fcritical=4.3874).

	1 X MIC		2 X MIC		4 X MIC		8 X MIC	
STRAIN	**F exp**	**P**	**F exp**	**P**	**F exp**	**P**	**F exp**	**P**
C. albicans **ATCC 90028**	1.6227	0.285	2.948	0.1103	NA	NA	NA	NA
C. albicans **LA1**	3.0019	0.1067	NA	NA	NA	NA	NA	NA
C. parapsilosis **HT5**	3.0019	0.1067	3.0019	0.1067	NA	NA	NA	NA
Cryptococcus ***sp.*** **HT2**	0.3352	0.8747	0.3352	0.8747	0.4102	0.8266	NA	NA
C. neoformans **HT 4**	0.1271	0.9806	0.0436	0.9983	0.0163	0.9998	NA	NA
C. auris	NA	NA	NA	NA	0.0448	0.9982	0.0163	0.9998
A. fumigatus **ATCC 204305**	3.22	0.0935	3.4022	0.0841	NA	NA	NA	NA
A. flavus	0.8662	0.5531	3.1863	0.0954	NA	NA	NA	NA
A. fumigatus	1.7646	0.2541	0.5312	0.7478	NA	NA	NA	NA
A. niger **RN6**			0.8593	0.5566	3.1485	0.0976	2.4716	0.1507
A. niger **INC 01**	3.7918	0.0677	0.498	0.7693	NA	NA	NA	NA
Aspergillus **spp.**	1.6393	0.2811	3.4603	0.0813	0.4063	0.8291	NA	NA

P: Probability; NA: Not applicable

Pharmacodynamics

The mortality rates of the yeasts and molds were determined at once, twice, 4- and 8-times MICs value of caspofungin. The rates were determined based on the correlation between the logarithm of survivals *vs.* time (Figures 8 and 9). The above was performed for all samples under study.

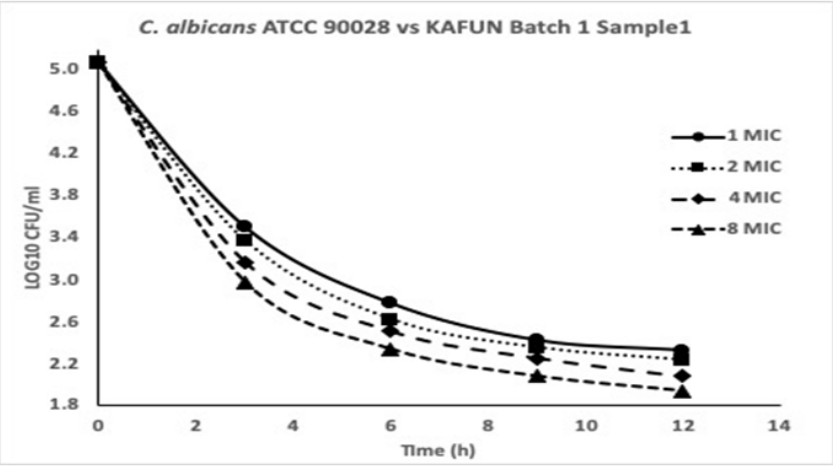

Figure 8. Time-Kill plot for *Candida albicans* ATCC 90028 (MIC: 0.25 µg/ml) *vs.* Kafum (Batch 1, Sample 1). Antifungal was teste once, twice, 4- and 8-times MICs value.

Tables 6 and 7 shows the average of mortality rates per product batch and the ANOVA results.

Table 6. Analysis of variance of average of average of mortality rates of yeasts per product batch at once, twice, 4- and 8-times MICs value (Fcritical=4.06618).

MIC	SAMPLE	Candida albicans ATCC 90028			*Candida albicans* LA1			*Candida parapsilosis* HT5		
		Mortality Rate	Fexp	P	Mortality Rate	Fexp	P	Mortality Rate	Fexp	P
1	KL1	-0.3823			-0.3203			-0.3428		
	KL2	-0.3809			-0.3079			-0.3464		
	CL1	-0.3891			-0.3116			-0.3423		
	CL2	-0.3878	1.5226	0.2816	-0.3121	1.1218	0.3961	-0.3449	3.5835	0.0661
2	KL1	-0.408			-0.3402			-0.3827		
	KL2	-0.4055			-0.3306			-0.3841		
	CL1	-0.4064			-0.3319			-0.3832		
	CL2	-0.4047	0.8938	0.485	-0.3328	0.7149	0.5702	-0.3858	0.774	0.5404
4	KL1	-0.4264			-0.3645			-0.4101		
	KL2	-0.4224			-0.3626			-0.4092		
	CL1	-0.4232			-0.3566			-0.4116		
	CL2	-0.4213	2.2622	0.1583	-0.358	0.2441	0.8633	-0.4127	3.81	0.0579
8	KL1	-0.4677			-0.39547			-0.4447		
	KL2	-0.4481			-0.3894			-0.4435		
	CL1	-0.4441			-0.38643			-0.4457		
	CL2	-0.4394	2.4082	0.1425	-0.38813	0.6575	0.6007	-0.4482	1.253	0.003

Table 7. Analysis of variance of average of mortality rates of molds per product batch at once, twice, 4- and 8-times MICs value (Fcritical=4.06618).

MIC	SAMPLE	*Aspergillus fumigatus*			*Aspergillus niger RN6*		
		Mortality Rate (h^{-1})	Fexp	P	Mortality Rate (h^{-1})	Fexp	P
1	KL1	-0.3222			-0.2624		
	KL2	-0.3219			-0.2626		
	CL1	-0.3229			-0.2626		
	CL2	-0.3232	2.5693	0.1272	-0.2619	1.761	0.2321
2	KL1	-0.34747			-0.2992		
	KL2	-0.3475			-0.2991		
	CL1	-0.3482			-0.2984		
	CL2	-0.34807	1.8251	0.2206	-0.2977	2.6743	0.1183
4	KL1	-0.3657			-0.3282		
	KL2	-0.3654			-0.3277		
	CL1	-0.3655			-0.3268		
	CL2	-0.3663	2.323	0.1515	-0.3256	3.1154	0.0883
8	KL1	-0.3848	0.3537	0.7879	-0.3545	2.6019	0.1243

	KL2	-0.3867			-0.3548		
	CL1	-0.3861			-0.353		
	CL2	-0.3872			-0.3535		

DISCUSSION

The activity of an antibiotic can be determined using well-established methods under controlled conditions by comparing the inhibition of microorganisms known to be sensitive to given concentrations of an antibiotic to the reference standard. These methods have produced significant results in several well-characterized trials [4,12,18,20,21].

Evaluation of the bioassay used to quantify caspofungin content demonstrated that it met all the requirements (linearity, repeatability, and accuracy). Using the selected organism (*C. parapsilosis* ATCC 22019), the best linearity (R^2=0.9972) was found in the range between 62.5 to 3.906 µg/ml (Figure 3). Reproducibility and precision between days had CVs<1.1%, and an ANOVA showed that there were no significant differences at the different concentrations examined.

Like previous work [12,20,21], we were able to establish that antibiotics can be evaluated using analytical bioassays with an appropriate microorganism under well-established and controlled conditions.

The determination of the caspofungin content in Kafum and Cancidas was measured by two different methods (Tables 1 and 2), which both demonstrated that their contents met international standards with values that did not differ significantly (Table 3). Therefore, we can conclude Kafum and Cancidas are pharmaceutically equivalent.

It has been recently suggested that generic antibiotics behave very differently from their brand name counterparts, with claims that they are one of the main reasons for the increasing antimicrobial resistance of microorganisms [2,4,22-26]. However, other studies have shown that generic products with active ingredients and excipients that meet all of the quality standards demanded by regulatory agencies behave similarly to brand name products [5,6,7,27,28].

In our study, the antimicrobial activity measured by MIC, mutant prevention concentration (MPC), and pharmacodynamics showed that the caspofungin-derived products (Kafum and Cancidas) do not differ significantly in their behavior.

The MICs for Kafum and Cancidas were similar (Table 4) which means that the products behave in a similar way. In a more detailed study of the antimicrobial activity based on the generation of spontaneous mutants (Figures 5-8), we see that both drugs showed similar results in terms of mutant frequency. The ANOVA analysis (Tables 5) indicated that there were no significant differences in the responses. Regarding the MPCs for each microorganism examined, the two products showed the same behavior and in general, the MPC was 4 MICs, unless the strain was very sensitive (*C. albicans* LA1, MPC=2 MICs) or clearly resistant (*C. auris*, MPC>8 MICs), as shown in Table 5. Comparing our study with that of Bordallo-Cardona et al. [15], our MPC values ranged from 0.5 and 2 MICs because each isolate behaved differently according to its sensitivity. The above confirms that Kafum and Cancidas are equivalent in their antimicrobial activity.

The pharmacodynamics studies at different MIC values showed a similar behavior for Kafum and Cancidas (Figures 7 and 8). For a more comprehensive evaluation, the mortality rate was calculated for the different strains examined

(Tables 6 and 7). The ANOVA of the calculated slopes of these results showed that there were no significant differences in the responses (Tables 6 and 7). Therefore, we can say that the behavior of the two products is similar. When comparing our study with that of Di Bonaventura et al. [16], they observed that caspofungin showed a stronger activity against Candidakefyr at 8 MICs, compared to the results at 4, 0.25, and 0.125 MICs, while the behavior of the isolates evaluated in the present study did not show such a steep increase in activity from 4 to 8 MICs. This could be due to the Candida species and not to caspofungin, which was supplied by MSD Italy, the owner of Cancidas.

The experience in the clinical success suggest that the *in vitro* and *in vivo* data (MICs, Time-Kill studies) could be predictive of responses to therapy [17].

CONCLUSION

Comparing the behavior of new products to the brand name/innovator products would be redundant; it would be enough to demonstrate that they fully comply with the standards of regulatory agencies, which can be shown using exact, accurate, and reproducible methods.

The conclusions of the present study are that Kafum and Cancidas are pharmaceutical equivalent. Their antimicrobial activities, measured by MIC, MPC, and pharmacodynamics, did not differ significantly. It could be assumed that the products might be therapeutically equivalent when used in clinical practice.

COMPETING INTERESTS

The present study was a joint venture between the Science Faculty of National University of Colombia and Dr. Reddy´s Laboratories SAS, and was also financed by Dr. Reddy´S Laboratories SAS.

AUTHORS' CONTRIBUTIONS

Jiménez, researcher at the National University of Colombia, developed a process to validate the quantitative assay for Caspofungin, and the all other assays. Silva conceived the study, obtained necessary funding, designed and directed the execution and analysis of data, edited the manuscript and approved it for publication.

All the authors read and agree with the whole all of article text.

ACKNOWLEDGEMENTS

The authors wish to express their gratitude to Dr. Reddy´s Laboratories SAS for its support of this collaborative research, a joint venture between Dr. Reddy´s Laboratories SAS and the National University of Colombia.

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