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Performance SWOT of Micronized Voriconazole to Augment Health Security and its Bioassay

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ABSTRACT

Nowadays fungal diseases certainly affect people with undermined immune system. Fungal infections are most likely impinge on skin, lungs, nails etc and it leads to systemic infection. Voriconazole (VCZ) is an antifungal medication of the triazole class used to treat infections caused by a fungus. VCZ is used to treat patients suffering with invasive fungal infections. The focus of this paper was to study the performance swot of antifungal activity of untreated VCZ and micronized VCZ. Size reduction of drug treated as an imperative operation to make handling of the drug easier, increase surface area per unit volume, and separate entrapped components. The size reduction process may involve accelerating particles so either particle-to-particle impact. Biological evaluation study was conducted by using *Aspergillus niger* and *Candida albicans* as test organisms'. Zone of inhibition was measured to assess antifungal activity by adopting agar diffusion process. The antifungal activity was conducted to the untreated VCZ material having particle size, about 207 microns and micronized VCZ having particle size 12 microns. The determination of size distribution of VCZ particles was examined through Dynamic light scattering (DLS) and Scanning Electron Microscopy (SEM) for treated and untreated VCZ.The structural identification study was conducted by Ultraviolet spectroscopy (UV) and Fourier transform Infrared spectroscopy (FT-IR). The anti fungal activity effectiveness of micronized VCZ illustrates increased efficiency when compared to untreated VCZ material.

Keywords: Voriconazole, Micronization process, Electron microscopy, *Aspergillus niger, Candida albicans.*

INTRODUCTION

Voriconazole ($C_{16}H_{14}F_3N_5O$)(VCZ) is a antifungal drug. VCZ has an incomparable bioavailability, stumpy toxicity, and activity against many pathogenic species. VCZ belongs to triazole class and used orally for systemic fungal infections. VCZ is particularly active against *Aspergillus species* and *Candida species*. The VCZ drug exhibits wide spectrum fungicidal activity against molds and fungistatic activity. As like all azole agents, VCZ is inhibition of cytochrome P450 (CYP 450)-dependent 14α-lanosterol demethylation, which is a vital step in cell membrane ergosterol synthesis by fungi[1]. Symptoms of overdose include abnormal vision, nausea, headache, vomiting, dizziness and dry mouth.

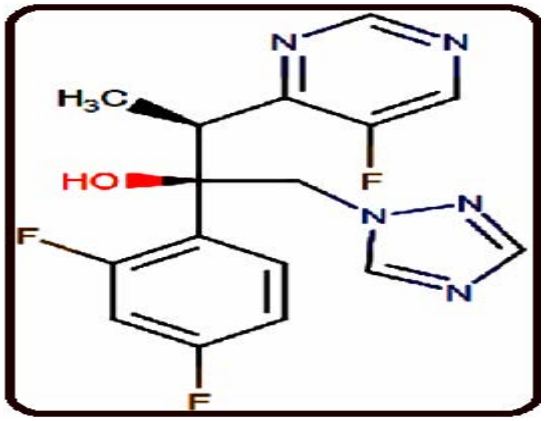


Fig. 1. Structure of Voriconazole

Voriconazole (VCZ) is a second-generation triazole that has an enhanced antifungal spectrum, compared with older triazoles like fluconazole and itraconazole[2-4]. Reduction in the therapeutic time and/or increase the quality of life of patients and tolerance was possible when new antifungal strategies developed[5-6]. VCZ was acceptably tolerated, despite the diverse nature of the patients studied and their severe illnesses[7]. The in-vitro activity of VCZ fully comprises Aspergillus, and other moulds like Fusarium, Pseudallescheria boydii, and Penicillium marneffei. The minimal inhibitory concentrations of VCZ for *Candida krusei* and *Candida glabrata*, were less susceptible to fluconazole[8]. VCZ drug-drug contacts are exceedingly clinically relevant. This was necessary for the treatment of patients with leukemia[9]. Roya Vahedi-Shahandashti describes novel antifungals, with a focus on the *Aspergillus species*[10]. Mahmoud has studied the increased use and availability of different classes of antifungal agents[11]. The studies reveal the oral bioavailability reaches approximately 95% and safer to use[12]. Researchers have found that VCZ, used to treat fungal infections after lung transplantation, increases the risk of developing skin cancer by 73%[13]. Different studies exemplify VCZ bioassay using *Aspergillus niger* and *Candida genus*. The main focus of the present study intended to appraise the action of micronized VCZ to augment health safety.

MATERIALS AND METHODS

Materials

Voriconazole working standard was provided for the research work from Hetero Labs Ltd, Visakhapatnam, and Andhra Pradesh, India. The fungi strains were obtained from GVK Bio. Sci, Hyderabad, Telangana state, India.

All other chemicals used in the present study were of Analytical reagent grade.

Instrumentation

S.No	Instrument	Make	Purpose
1	Dynamic light scattering(DLS)	Malvern 3000	Size distribution of particles
2	Scanning Electron microscope(SEM)	Zeiss Evol8	surface topology
3	Fourier transform infrared (FTIR)	Bruker-vertex 80	To study functional group
4	UV-spectrophotometer	Shimadzu 1800	Stability and identification of VCZ

Preparation of plain and micronized VCZ

The untreated VCZ material was taken into dry micronizer equipment (Microtech-M50 shown in Fig. 2). With the help of moisture free Nitrogen.the VCZ sample was dispensed into micronizer hopper with a feed rate of 4 Kg air pressure and 7 Kg micronization pressure. Similar method was repeated for two cycles to get maximum micronized material. The impurities present in the final sample are found less than 0.1%. The loss on drying was 0.15% w/w. The particle size was drastically reduced during micronization process. The particle size information was presented in Table 1.

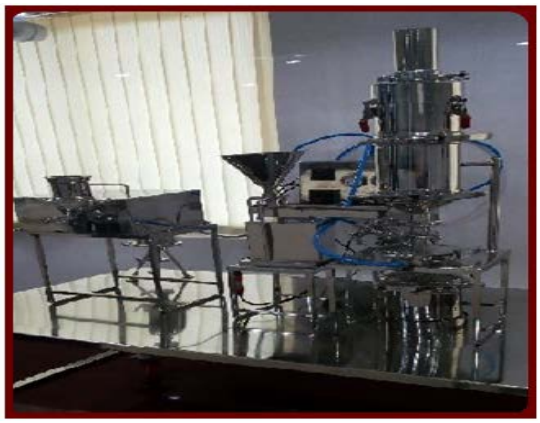


Fig. 2. Micronizer

Table 1: Particle size information of treated and untreated VCZ

S.No	Voriconazole	Particle size-D(0.9)	Particle size-D(0.5)
1	Plain material	207 Microns	64 Microns
2	Micronized material	12 Microns	6 Microns

RESULT AND DISCUSSION

For the treatment of fungal infections antifungal drug performance was crucial. Benefits of particle size reduction of drug materials were increased surface area, downy surface quality and elevated-quality product utility. The surface modification of VCZ particles showed significant augmentation of antifungal activity.

Laser diffraction measurement of particle size analysis

Laser diffraction has become the most widely used particle characterization technique in the pharmaceutical industry. The DLS instrument applied by Particle Analytical has a flow-through cell. The VCZ is a free-flowing powder and non-hygroscopic, the dry mode sampling technique is used to determine the particle size measurement. The measurement was made using 1.0 bar air pressure with a 50% feed rate of specimen sample. The micronized sample resulted to 12 microns from 200 microns, after reduction of particle size using micronization process.

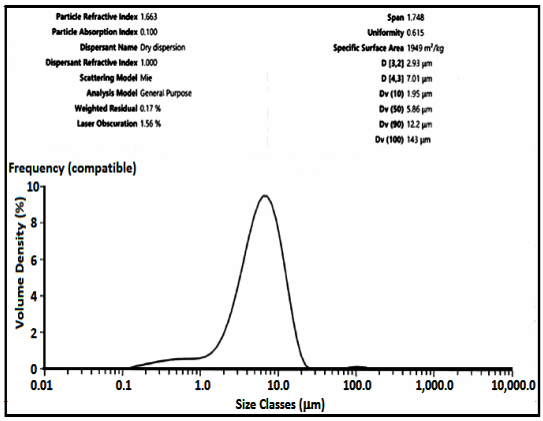
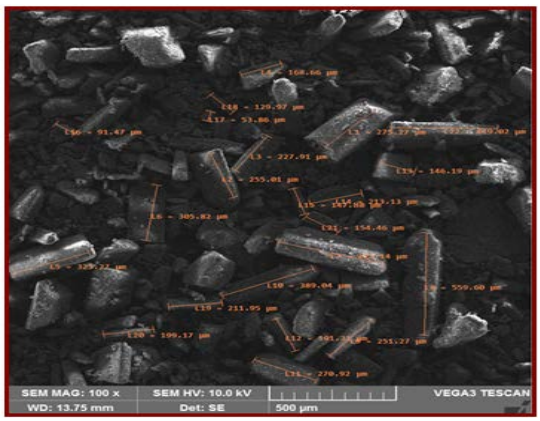


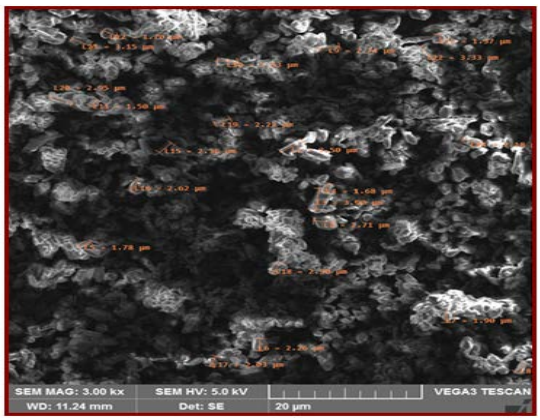
Fig. 3. Particle size distribution of micronized VCZ.

SEM Analysis

To know the size of micronized VCZ and surface topology at diverse magnifications scanning electron microscope was selected. A small pinch of micronized VCZ was taken on the sampler slide. By using sputter coater the sample was subjected to sputtering. This was obtained when the area of specimen intermingled with the electron beam produces signals. Generally in SEM an electron gun produces electron and later accelerated through the condenser. SEM images were shown in Fig. 4 demonstrates the shape of micronized VCZ at a range of magnifications in which micronized VCZ particles appeared as clusters. From SEM images it was found that the size is around 2 microns and shapeless, since the powder is fine.



Untreated VCZ



Micronized VCZ

Fig. 4. SEM images of VCZ (untreated and micronized material)

FT-IR Study

For categorization of the functional groups a diminutive amount of untreated and micronized VCZ in Potassium bromide (KBr) pellets in transmittance mode was processed. About 2.5 mg of VCZ sample was mixed with 250 mg of KBr and grounded to make an apparent disc. Scanning process was done and the respective spectra were recorded. From FT-IR spectra the chemical structure of micronized VCZ material was not changed. The untreated and

micronized VCZ material FT-IR spectra were shown in Figures 5 and 6.

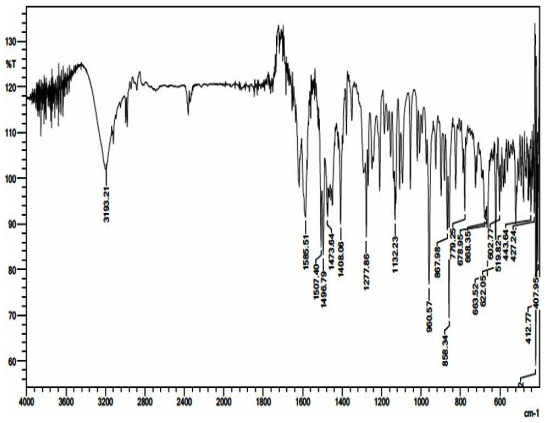


Fig. 5. Untreated VCZ FR-IR spectrum

The informative spectral ranges were examined, the characteristic peaks corresponding to structure were identified.The bands of OH stretching at 3193 cm^{-1}, C-N stretching at 1507 cm^{-1}, and C-F stretching at 1585 cm^{-1}, respectively were identified as a compound functional group. Observation: The structure of the micronized material is similar to plain material and does not have any impact on structure due to micritisation.

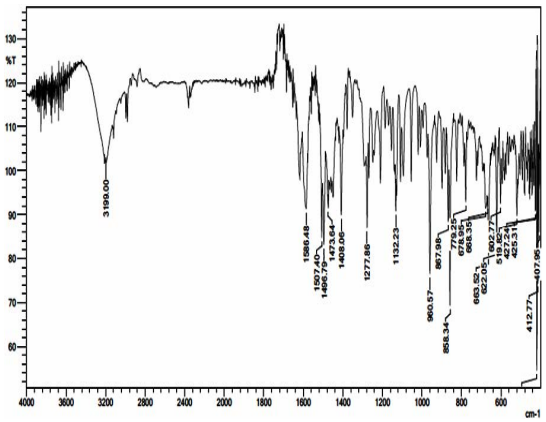
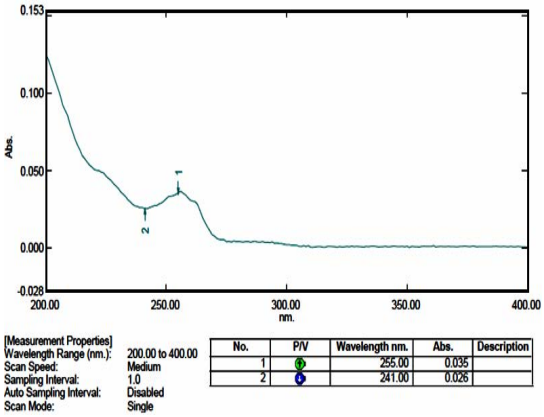


Fig. 6. Micronized VCZ FT-IR spectrum

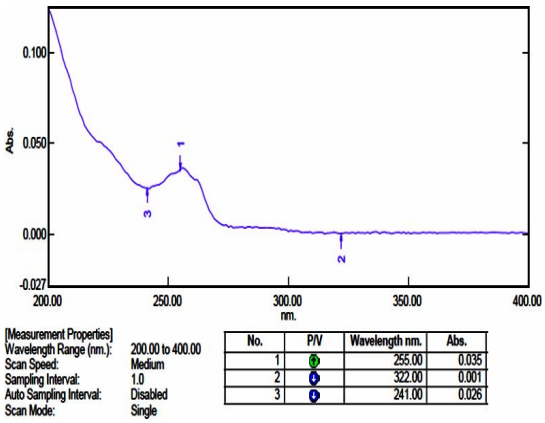
Identification by UV Spectroscopy

The identification of Voriconazole is done using 10 ppm concentration of both Plain and Micronised Voriconazole was prepared and analysed using UV (Shimadzu model) spectrophotometer. The absorption maxima are using beers lamberts principle was observed at wavelength of 255 nanometers. The plain and micronized material showed similar absorptions bands at similar wavelengths. From Fig. 7 and 8 it was concluded that the material identity has no disturbance even after micronisation.



No.	P/V	Wavelength nm.	Abs.	Description
1	P	255.00	0.035	
2	V	241.00	0.026	

Fig. 7. UV spectrum of Untreated VCZ



No.	P/V	Wavelength nm.	Abs.
1	P	255.00	0.035
2	V	322.00	0.001
3	V	241.00	0.026

Fig. 8. UV spectrum of micronized VCZ

Bioassay of VCZ (Agar Diffusion technique)

Fungi like *Aspergillus niger* and *Candida albicans* are the two mainly widespread fungal pathogens causing ruthless invasive diseases. The pathogenic strains stored at 40^{0}C under test were sustained on agar slants (nutrient). 25% glycerol was used for long period storage of slants preservation. To begin with the medium and glass petri-dishes were autoclaved for 25 min by the application of 15 Pa pressure. The methodology incorporates the injection of bacterial cells on nutrient agar Petri dishes. The untreated and micronized VCZ samples are laid over these dishes. The dishes are incubated for 18–24 h at 37°C and subsequently the growth of bacteria is determined. Precisely measured the diameters or areas of the circular inhibition zones and addressed in Table 2. The images are addressed in Fig. 9.The effectiveness of untreated (or plain) and micronized VCZ material against fungi was given in Table 2.

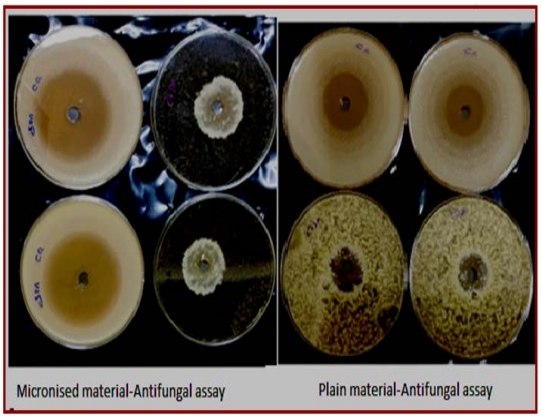


Fig. 9. Antifungal assay of VCZ (Micronised and untreated material)

Table 2: The effectiveness of VCZ against Aspergillus nigerand Candida albicans

S.No	Test organism	Inhibition zone for VCZ (micronized),cm			Inhibition zone for VCZ (untreated),cm		
		Plate-1	Plate-2	Average	Plate-1	Plate-2	Average
1	Aspergillus niger	1.4	1.6	1.5	0.7	0.6	0.65
2	Candida albicans	2.1	1.9	2.0	1.0	1.1	1.05

CONCLUSION

Reduction in particle size of VCZ was shown better results as compared to untreated VCZ material. The efficiency of micronized Voriconazole antifungal activity against *Candida albicans* and *Aspergillus niger* demonstrates increased efficiency, when compared to untreated VCZ material due to micronization process that resulted in very fine particles.

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Conflict of interests

The author declared that, having no conflict of interests.

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