Enhanced Topical Antifungal Activity of an Isavuconazole Nanoparticles-Loaded Cream Against Clinically Relevant Fungal Pathogens

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Abstract
Superficial fungal infections continue to pose a significant therapeutic challenge due to their growing prevalence, recurring nature and emergence of antifungal resistance. Antifungal products in the topical environment have limited penetration and drug retention that can lead to the poor performance of the medicine. In this study, we investigated the in vitro antifungal properties of Isavuconazole nanoparticles-loaded cream for topical drug delivery and antifungal treatment in the skin. The nanoparticle-loaded cream was used in clinical studies on three important fungal pathogens, Candida albicans, Aspergillus niger, and Trichophyton rubrum with agar well diffusion. The effectiveness of the medication therapy was also tested with the minimum inhibitory concentration (MIC) analysis based on the broth microdilution method. The nanoparticle-loaded cream showed significantly higher zones of inhibition than the marketed antifungal cream on all fungal strains, and the highest concentration on Candida albicans was observed. The nanoparticle-loaded cream had lower MIC levels and thus had more antifungal activity. The plain cream base had no antifungal activity and hence the inhibition was due to the Isavuconazole. The nanoparticle-loaded cream has a better antifungal ability as it can penetrate more into the cells, interact with the infected tissue and release drug from the nanoparticulate carrier system. This indicates that the nanoparticle-mediated topical delivery substantially enhances the antifungal drug activity of Isavuconazole and is a promising approach for treating the superficial fungal infection. Further ex vivo, in vivo and clinical studies are recommended to assess the therapeutic benefits and long-term safety of the developed formulation.

Keywords: Isavuconazole, Nanoparticles-loaded cream, Antifungal activity, Minimum inhibitory concentration, Topical antifungal therapy

Introduction

Superficial fungal infections are among the most common infectious diseases affecting the skin, hair, and nails worldwide. Most fungal infections are caused by pathogenic fungi such as Candida albicans, Aspergillus niger, and Trichophyton rubrum, leading to persistent infections, inflammation, discomfort, and recurrent episodes, especially in immunocompromised individuals. Although a number of topical antifungal drugs are available, treatment results can be compromised by poor penetration through the stratum corneum, poor drug retention at the site of infection, and the increasing incidence of antifungal resistance [1]. Hence, a specialized topical drug delivery system is required to enhance local drug bioavailability and therapeutic efficacy. Isavuconazole is a broad-spectrum triazole antifungal that inhibits fungal lanosterol 14α-demethylase, and thus prevents ergosterol biosynthesis and disrupts the structure of fungal cell membrane. The drug works effectively against a variety of clinically important yeasts and filamentous fungi. However, conventional topical formulations may not penetrate the skin and stay long in infected skin tissues, which hinders its effective use 2]. Nanoparticle-based drug delivery systems are now a promising approach for improving topical antifungal therapy. Nanoparticles have a large surface area and could penetrate very close to the skin, help to permeate the drug through the stratum corneum, keep it from degradation, and release in a controlled time. The encapsulation of the drug by the cream is further beneficial as this formulation is stable and easy to apply as well as patient acceptability [3-4]. In this study, the in vitro antifungal activity of Isavuconazole nanoparticles-loaded cream was investigated against Candida albicans, Aspergillus niger, and Trichophyton rubrum. Antifungal activity was determined by agar well diffusion and minimum inhibitory concentration assays to determine whether nanoparticle-mediated topical delivery could enhance the antifungal performance of Isavuconazole compared with a popular marketed formulation.

Methodology

Antifungal activity of Isavuconazole nanoparticles-loaded cream

The antifungal activity of the optimized Isavuconazole nanoparticles-loaded cream was compared with three clinically relevant fungal strains, Candida albicans, Cryptococcus neoformans, and Aspergillus flavus, in the agar well diffusion method. Sterile Sabouraud Dextrose Agar (SDA) plates were prepared according to standard microbiological procedures and the fungal suspension (about 1×10^6 CFU/mL) was inoculated with sterile cotton swabs to obtain a uniform fungal lawn. Wells of 6 mm diameter were prepared in the agar medium using a sterile cork borer and an appropriate amount of the optimized nanoparticles-loaded cream (specifically Isavuconazole concentration) was introduced into each well.

The negative control was a plain cream formulation without the drug and the positive control was a marketed antifungal cream. The inoculated plates were kept at room temperature for 1 h to allow the formulation to be pre-diffused with the agar and then incubated at 28-30°C for 48-72 h depending on the growth of the fungal strain. At the end of incubation, the antifungal activity was measured by measuring the diameter of the clear zones of inhibition (mm) around each well using a digital Vernier caliper. All the experiments were performed in triplicate and the results were reported as mean ± standard deviation (SD). The antifungal activity of the formulation was compared with those of the negative and positive controls by measuring the mean zone of inhibition. A larger zone of inhibition was associated with a higher antifungal activity [5-6].

Determination of Minimum Inhibitory Concentration (MIC)

The minimum inhibitory concentration (MIC) of the optimized Isavuconazole nanoparticles-loaded cream was measured against Candida albicans, Aspergillus niger, and Trichophyton rubrum in broth microdilution according to the standard antimicrobial susceptibility testing criteria. For experiments, SDB was used as the test medium and fungal inocula from fresh cultures were prepared and set at 1×10^6 CFU/mL. Two-fold dilutions of Isavuconazole formulation (~0.0625–8 µg/mL) were done in sterile 96-well microtiter plates. The wells containing broth with fungal inoculum were used as the growth control while broth without inoculum was used as the sterility control. A marketed Isavuconazole cream was tested in the same manner. The microtiter plates were incubated at 28-30°C for 48-72 h depending on the fungal strain. After incubation, the wells were visualized for fungal growth and the MIC was defined as the lowest concentration of the formulation that completely inhibited the fungal growth compared to the growth control. All the experiments were done in triplicate and the MIC was calculated as the lowest concentration that completely inhibited the fungal growth [7-8].

Results and Discussion

Antifungal activity of Isavuconazole Nanoparticles-Loaded Cream. The antifungal activity of the optimized Isavuconazole nanoparticles-loaded cream was tested against Candida albicans, Aspergillus niger and Trichophyton rubrum by agar well diffusion method. The cream showed high antifungal activity on all tested fungal strains and had larger zones of inhibition than the marketed antifungal cream. Among all the tested organisms, the highest antifungal activity was observed against Candida albicans, followed by Trichophyton rubrum and Aspergillus niger. On the other hand, the plain cream base had no zone of inhibition and so the antifungal activity was caused only by Isavuconazole. The optimized nanoparticles-loaded cream produced inhibition zones of 28.6 ± 0.8 mm, 24.8 ± 0.7 mm and 26.3 ± 0.6 mm against Candida albicans, Aspergillus niger and Trichophyton rubrum, respectively, which are higher than those obtained with the marketed formulation. The nanoparticle-loaded cream also showed lower minimum inhibitory concentration (MIC) values of 0.125 µg/mL, 0.50 µg/mL and 0.25 µg/mL against Candida albicans, Aspergillus niger and Trichophyton rubrum, respectively, indicating better antifungal activity. The improved antifungal performance of the nanoparticle-loaded cream is due to the nanoscale particle size, larger surface area, penetration into fungal cells and the long-lasting drug release characteristics compared to the conventional formulation. Lower MIC values indicate greater antifungal potency.

Table 1: Zone of Inhibition of Isavuconazole Nanoparticles-Loaded Cream Against Selected Fungal Strains

Fungal Strain	Nanoparticles-Loaded Cream (mm)	Marketed Antifungal Cream (mm)	Plain Cream (mm)
Candida albicans	28.6 ± 0.8	23.4 ± 0.7	ND
Aspergillus niger	24.8 ± 0.7	20.3 ± 0.6	ND
Trichophyton rubrum	26.3 ± 0.6	21.7 ± 0.5	ND

Values are expressed as mean ± SD (n = 3); ND = No detectable zone of inhibition.

Table 2: Minimum Inhibitory Concentration (MIC) of Isavuconazole Nanoparticles-Loaded Cream

Fungal Strain	Nanoparticles-Loaded Cream (µg/mL)	Marketed Antifungal Cream (µg/mL)
Candida albicans	0.125	0.25
Aspergillus niger	0.50	1.00
Trichophyton rubrum	0.25	0.50

Conclusion

In this study, Isavuconazole nanoparticles-loaded cream is shown to show a significantly better antifungal activity against Candida albicans, Aspergillus niger and Trichophyton rubrum in vitro compared to a conventional marketed antifungal cream. This formulation also showed larger zones of inhibition and lower minimum inhibitory concentration values, indicating an even better antifungal activity. The absence of antifungal activity for the plain cream was also confirmed to be a consequence of the Isavuconazole. The enhanced antifungal activity of nanoparticle-loaded cream is probably due to its enhanced drug dispersion into fungal cells and infected skin layers, surface interaction and the persistence of its drug release from the nanoparticulate carrier system. These findings show that

nanoparticle-based topical drug delivery is an effective method of local treatment of superficial fungal infections. The developed formulation can have better therapeutic effects, longer drug action, and better patient compliance compared with the traditional topical formulation. Ex vivo skin permeation studies, in vivo antifungal therapy, stability studies and clinical evaluation are needed to confirm its translational and therapeutic utility.

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