Nanofiber-Based Delivery System for Voriconazole Targeting Enhanced Efficacy Against Fungal Infections

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Abstract: Nanofibers have been investigated and studied for the possible topical administration of medicines. Nanotechnology has produced nanostructure-based medication delivery techniques. Nanofibers are structures that resemble threads or filaments and are made of different polymers, either synthetic or natural, or a combination of both, with a size range in the nanometer range. A broad-spectrum triazole antifungal medication called voriconazole (VCZ) has been approved for the treatment of invasive candidiasis, invasive aspergillosis, and fungal infections salvage therapy. By specifically blocking a cytochrome P450 enzyme, it prevents the creation of ergosterol, a crucial part of the fungal cell membrane. The amount of voriconazole deposited in the skin's deeper layers was greater in the nanofiber formulations than in the control formulation. Numerous initiatives have been put out to improve VCZ's skin penetration and delivery capabilities. Voriconazole has a topical carrier system that helps it get beyond its restrictions and improve penetration into the skin's deeper layers, reduce adverse effects and strengthen antifungal properties against cutaneous candidiasis.

Keywords: Nanofiber, Voriconazole, Candidiasis, Lipidic barrier, Nanomaterial, Electrospinning.

Introduction: The skin, which is the body's outermost lipidic barrier, has a thickness of 20–25μm. In addition to its barrier role, it facilitates the absorption of a range of compounds, both medicinal and non-therapeutic. The passive absorption of drug molecules via the transdermal route may also be caused by the presence of skin appendages such as hair follicles. This barrier allows medication molecules to access the systemic circulation directly, which is why pharmaceutical scientists have been studying drug delivery through this route for the past 20 years. Due to its higher bioavailability, first-pass hepatic metabolism, and capacity to prevent dosage variations, the transdermal route of administration of medications is seen to be superior to the oral method [8].

Nanofibers, a type of one-dimensional (1D) nanomaterial, are well-known for their numerous applications in both science and industry. Compared to other regularly used base materials, nanofibers have superior mechanical properties (such stiffness and tensile power) with a diameter a thousand times smaller than human hair.
Pharmaceutical compounds from BCS classes II and IV may become more soluble and permeable with the use of nanofibers. The longer-release profile, high loading capacity, and high encapsulation efficacy of nanofibers improve therapeutic effects, reduce toxicity and side effects, and facilitate alternative administrations. The diameter, pore size, and orientation of the nanofibers must be taken into account in order to mimic the nanoscale properties of human tissues. There are numerous uses for nanofibers in drug delivery systems and medical equipment. They are used to detect, measure, restore, correct, or alter the body's functioning for health-related reasons, as well as to prevent, diagnose, or cure disorders. Applications for nanofiber medical devices include adhesive bandages, dentures, more sophisticated devices, and cardiac pacemakers [1].

PVA/SA nanofibers that were electrospun and subsequently crosslinked with GTA were integrated into VCZ. The crosslinking of nanofibers resulted in a decrease in the burst drug release. The Higuchi square root kinetic model, which suggests that drug release is regulated by drug diffusion from hydrated polymers, shows that the drug was released from both crosslinked and non-crosslinked nanofibers. Despite the penetration enhancer effect of PG, both nanofiber formulations boosted VCZ deposition in deeper layers of skin by improving drug solubility due to having a higher surface to volume ratio than that of the control formulation of 1% (w/v) VCZ solution in PG. The susceptibility and time-kill assays revealed that none of the nanofiber formulations were cytotoxic to mouse fibroblast cells and all of them exhibited antifungal efficacy against Candida albicans. In summary, VCZ integrated PVA/SA nanofibers show promise as nanocarriers for topical treatment in terms of improving antifungal efficacy and cutaneous penetration in vitro [12].

Preparation of Nanofibers: There are several methods used in the preparation of nanofibers. Nonetheless, the self-assembly method, phase separation technique, template synthesis, and electrospinning approach are the four main fabrication techniques that are commonly used for biomedical applications. Because of its instrumental setup and influencing parameters, electrospinning is one of the practical methods that has been employed in industry for large-scale production. As a result, it has given rise to many ways to regulate the qualities of the produced nanofibers. There is one more method, called the drawing method, which is restricted to the laboratory scale and mostly uses viscoelastic materials to fabricate nanofibers [8].

Various manufacturing methods of Nanofibers:

**Electrospinning Method:** Recent years have seen a particular focus on the use of electrospun nanofibers for drug delivery applications. This is primarily because of their ultrafine structure, high porosity with small pore size, large surface area to volume ratio, ease of manufacture, and low cost. Polymers that are natural, synthetic, or mixtures of both can be used to create nanofibers. The selection of the polymer or polymers is an important factor to achieve the required drug release qualities. Release occurs more quickly with a fast-dissolving polymer than with an insoluble substance. Indeed, in order to avoid the burst release effect, have improved stability in water, or increase their mechanical, thermal, and chemical properties, drug release could be prolonged through the use of lipophilic polymers or crosslinking. One crosslinking agent that has been used to crosslink hydroxyl-containing polymers, such as PVA (Polyvinyl Alcohol), starch, and gelatin, is glutaraldehyde (GTA) [12].
"(A) Schematic representation of the fabrication of nanofibers by the electrospinning technique. (B) Different fabrication techniques of nanofibers: (a) self-assembly, (b) template synthesis, (c) phase separation, and (d) drawing."

**Fabrication of nanofibers:**

Polymers of various kinds are typically used in the fabrication of the nanofibers. The polymers, the preparation method, and the design specification all affect the nanofiber’s diameter or size.

1. **Natural polymer:** To date, natural origin polymers with a wide range of applications, including proteins like gelatin and collagen and polysaccharides like chitosan, cellulose, dextran, hyaluronic acid, and alginate, have been most frequently employed in nanofibers.

2. **Synthetic Polymers:** PVP, poly (lactic-co-glycolic acid), poly (ethylene oxide), polycaprolactone, PVA, etc. Increased antibacterial activity has been demonstrated by polycaprolactone-based nanofibers, zinc oxide and silver bimetallic nanoparticles encased in PVP.

3. **Mixed or Blended Polymers:** When combined, natural and artificially created polymers are utilized to create mixed polymers, which are then employed to create nanofibers. For instance, PVA, chitosan, and polycaprolactone were combined to create nanofibers that were used to treat cuts and burns.

**Voriconazole (VCZ):**

**General aspects:** VCZ is an azole class antifungal medication that was approved by the FDA in 2002. It is produced by changing the structure of fluconazole. With pKa values of 2.01 and 12.7, Log P of 1.82, and 0.098 mg/ml, it is not highly soluble in water. VCZ inhibits cytochrome P450 (CYP450)-dependent 14-lanosterol demethylation, a critical step in the production of ergosterol in fungal cell membranes. Against most molds, with the exception of Moldorades, it is fungicidal. Amphotericin B affects hyaline fungus like Fusarium spp. and members of the Scedosporium apiospermum complex, except for S. prolificans, and all Aspergillus species, including A. terreus, which is frequently resistant to it. Similar to all azoles, VCZ is fungistatic against Candida species, just like all azoles. While certain species, like C. krusei, are naturally resistant to fluconazole, others, like C. glabrata, are susceptible to VCZ. Nevertheless, a lot of isolates that develop fluconazole resistance also develop VCZ resistance. Up to two thirds of cases of invasive candidiasis were caused by the most prevalent species, Candida albicans [6,12,15,16].
Possible routes for voriconazole delivery from Nanoparticles:

**Topical**  
Increase sustained release, stability, permeation, therapeutic efficacy

**Parenteral**  
Increased solubility and dissolution, pharmacokinetic parameter

**Ocular**  
Increase sustained release, stability, permeation, therapeutic efficacy

**Oral**  
Increase solubility and dissolution, increase pharmacokinetic parameter

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**PREPARATION OF VORICONAZOLE NANOFIBRES BY ELECTROSPINNING:**

16% (w/w) PVA and 2% (w/w) SA solutions were combined in volume ratios of 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, (3:7), (2:8), and 1:9 in this study. The optimal ratio was found to be 8:2, which also had the most uniform fiber shape, using light microscopy (data not shown). Using the other blend solutions at different ratios made electrospinning difficult because, in most cases, beads formed or electrospraying took place in place of nanofibers.

First, 20% methanol (v/v, 20% of the polymer blend) was used to dissolve the VCZ because it is a water miscible solvent. Next, while stirring continuously at 900 rpm, VCZ was added dropwise to the polymer mix at a concentration range of 0.7-7.0% (w/w, based on polymer weight). With a logP value of 1.8, VCZ is a moderately lipophilic active agent that is weakly water soluble. A uniform and non-precipitated VCZ dispersion was found inside the blended solution at a concentration of 2.1% (w/w). Moreover, 2.1% (w/w) was the highest drug concentration in the solution at which electrospinning could be effectively finished. Consequently, it was found that 2.1% (w/w) was the optimal drug-integrated formulation. The PVA/SA (8:2, v/v) solution was integrated by VCZ [12].

**Antifungal activity of formulations:**

Using the disc diffusion method, the antifungal activity of formulations containing voriconazole was evaluated against Aspergillus flavus, Aspergillus fumigatus, Aspergillus terreus, Candida albicans, and Candida tropicalis. Since Candida albicans is the most prevalent pathogen that causes fungal infections, it was used. Research indicates that formulations containing voriconazole may exhibit antifungal effects. Inhibition zones were seen in voriconazole-loaded fiber compositions, per the results. Furthermore, depending on concentrations, the zone of inhibition increased as concentration increased. The incorporation of voriconazole into nanofiber formulations was improved to enhance drug penetration and deposition in the lower layers of the skin. This resulted in notably higher effective drug delivery into the deeper layers of the skin [7,9,12].

Minimum inhibitory concentration (MIC) values determined for the nanofiber formulation [12]:

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Advantages of nanofiber formulations:

1) Nanofiber naturally has a high surface area-to-volume ratio because of its nanoscale dimension. As the nanofiber's radius gets smaller, the surface area to volume ratio rises. In applications where a huge surface area is required, such as affinity membranes and sensors, this characteristic is very desirable.

2) The large surface area of nanofiber membranes makes them superior to cast film. The larger surface area of nanofibers allows for speedier disintegration in situations when rapid medication release is sought. Processes including mass transfer, drug loading, cell adhesion, and proliferation can be supported by the nanofiber composite with a high surface area to volume ratio.

3) Various substances and polymers are used to create nanofibers. Important physicochemical characteristics of materials and polymers include molecular weight, solution viscosity, electrical, mechanical, thermal, electrical conductivity, charge carrier mobility, tensile modulus and tensile strength, wettability, thermal stability, and degradation.

4) Relatively cheap initial outlay: The average cost of a simple electrospinning device is between $3,000 and $4,000. Store-bought pieces can be used to self-build a setup in a laboratory environment.

5) Simple to learn: With the guidance of a mentor and a basic understanding of electrostatics and polymers, someone can pick up the basics of electrospinning in a matter of weeks.

6) Fibre deposition onto alternative substrates is simple.

7) The collecting surface must have less static charge in order to deposit electrospun fiber.

8) Metal, glass, micro-fibrous mats, and water are common surfaces on which electrospun fibers are deposited.

9) Many different types of nanofibrous structures have been built. Electrospinning setup and method modification have enabled the production of three-dimensional blocks of nanofibers, yarns, and tubular nanofibrous structures.

10) Mass production capacity: Large-scale manufacture of nanofibers can also be achieved by commercially available electrospinning devices.

11) Commercial applications: The electrospinning process has been used to create a number of products that are available for purchase.

Disadvantages of nanofiber formulations:

Because the commonly utilized electrospinning processes have several drawbacks, including:

1) The difficulties in obtaining in situ deposition of nanofibers on various substrates.

2) The low yield and high operating voltage requirements.

3) It is still difficult to produce nanofibers with these characteristics on a big scale.

4) Conclusion:

There are many benefits to using loaded-VCZ nanocarrier systems. We can emphasize the improvement in VCZ solubility and dissolution rate in an aqueous media among the results shown. Various release profiles were displayed by the release control. The majority of them permitting a prolonged or continuous release following an initial burst effect. Furthermore, pharmacokinetic characteristics enhance topical application safety and mucosal adherence. The physicochemical properties vary depending on the nanostructured system, and these results are confirmed using widely accepted characterisation techniques. By utilizing nanotechnology, VCZ therapy may be able to overcome biological and physicochemical obstacles by improving parameters pertaining to drug targeting, release, and therapeutic effects. Because the nanofiber formulations had a higher surface to volume ratio than the control, they were more soluble.
in the medication and boosted VCZ deposition in deeper layers of the skin. s VCZ solution was formulated in PG in spite of the penetration enhancer effect.

Accepted PG manuscript. The susceptibility and time-kill assays indicated that all nanofiber formulations were non-cytotoxic to mouse fibroblast cells and had antifungal efficacy against Candida albicans. In summary, VCZ-incorporated PVA/SA nanofibers show promise as topical therapy nanocarriers for improving antifungal efficacy and skin penetration in vitro.

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