FORMULATION OF ELECTROSPUN MICROSCOPIC THREAD STRUCTURES OF POSACONAZOLE: AMPLIFYING DISSOLUTION AND SKIN PERMEABILITY

A.Aroon[1]*, B.Jayanthi[2], Satyanarayana[3]

[1]Department of pharmaceutics, Sarojini Naidu Vanitha Pharmacy Maha Vidyalaya, Hyderabad.

Research Scholar: Department of Pharmacy, FEAT, Annamalai University.

[2]Department of Pharmacy, FEAT, Annamalai University, Annamalainagar, Chidambaram 608002, Tamil Nadu, India.

[3]Department of Pharmaceutics, Princeton College of Pharmacy, Hyderabad.

ABSTRACT

Fungal infections pose a significant global health threat, especially for individuals with compromised immune systems[1]. Posaconazole, a class II drug, presents challenges due to its high permeability and low water solubility[2]. Innovative formulations are crucial for effective delivery. This research explores an electrospun nanofiber formulation of posaconazole, aiming to improve solubility and optimize drug release profiles. Additionally, the study focuses on developing transdermal patches as a non-invasive alternative to oral formulations, addressing potential gastrointestinal side effects. Posaconazole, generously provided by Rachem Pharma Ltd, was encapsulated in polyvinyl pyrrolidone (PVP) using an electrospinning technique. Characterization involved UV spectrophotometry, SEM, DSC, XRD, and FTIR. Laboratory experiments mimicked drug movement and penetration through skin to evaluate release patterns and absorption. The electrospun microscopic thread structures[3] exhibited successful encapsulation of posaconazole, with SEM confirming nanofiber formation. XRD and DSC analyses indicated amorphization of posaconazole in the nanofiber formulation, enhancing solubility. FTIR showed compatibility between posaconazole and PVP. In vitro studies revealed higher and faster drug release from microscopic thread structures compared to solvent-solidified sheets. Ex vivo skin permeation studies demonstrated superior performance of microscopic thread structures, with increased flux and permeability coefficient. The study demonstrates the successful preparation of posaconazole-loaded microscopic thread structures with improved drug delivery kinetics compared to as-solidified sheets. The amorphization of posaconazole, molecular dispersion

within PVP, and increased dissolution area contribute to enhanced performance. The findings suggest the potential of transdermal patches using microscopic thread structures as a promising alternative for optimizing posaconazole delivery and improving biopharmaceutical properties.

***KEYWORDS*:** Posaconazole, Electrospun, Microscopic thread structures, Dissolution, microscopic thread structures, solidified sheets

INTRODUCTION

Fungal infections, often underestimated, pose a significant global health threat, particularly to individuals with compromised immune systems. Posaconazole's absorption properties align with those of Class II drugs in the Biopharmaceutics Classification System and stands out as an effective triazole antifungal against various fungi, including Aspergillus and Candida species. However, the inherent challenge lies in the high permeability but low water solubility[4] of BCS class II medications, necessitating innovative formulations beyond traditional delivery systems.

Electrospun microscopic thread structures[3,5], emerging as a nanotechnology-based drug delivery system, offer a compelling avenue to enhance medication bioavailability and dissolution rates. For BCS class II drugs like posaconazole, where irregular absorption[6] may compromise efficacy, addressing solubility becomes paramount. This research aims to explore a posaconazole-encapsulating electrospun nanofiber formulation, emphasizing solubility improvement and optimized drug release profiles. By leveraging the unique characteristics of electrospun microscopic thread structures, we aim to transcend challenges posed by posaconazole's BCS class II classification, contributing to the advancement of more potent antifungal therapies.

The study extends its focus to the development of transdermal patches[7] containing posaconazole, evaluating their potential advantages over commercially available Noxafil tablets. Unlike oral formulations, which may induce gastrointestinal side effects[8] and exhibit varied absorption, transdermal patches offer a non-invasive alternative. The high permeability[9] of the skin allows systemic medication administration, ensuring controlled and sustained release of posaconazole while minimizing gastrointestinal adverse effects. Delving into the complexities of creating posaconazole electrospun microscopic thread structures, our primary objective is to address the critical process of solubility enhancement, making strides

in pharmaceutical advancements against fungal infections, particularly those involving BCS class II drugs.

MATERIALS AND METHODS

Rachem Pharma Ltd, based in Hyderabad, India, generously provided the gift of Posaconazole. Hetero Labs, also located in Hyderabad, gifted Polyvinyl pyrrolidone (PVP K-30). The procurement of Methanol and N, 2-methyltetrahydrofuran (MeTHF) was carried out through purchases from New Arihant in Mumbai and Zhengzhou Meiya Chemical Products in Zhengzhou, China.

Preparation of Spinning Solutions:

To create a Polyvinyl Pyrrolidine (14% w/v), a precisely dispensed quantity of powder form of PVP was solubilized in a methanol/ MeTHF (4 to 1 volume by volume) solution. The base PVP solution was added to posaconazole (18% by weight of dry PVP) while being continuously stirred about 3 hours at 150 rpm (IKA RW28 Overhead Stirrer, Sigma Aldrich.)

Fabrication of Microscopic Thread Structures

Electrospinning process was conducted using a unique approach to enhance the production of ultrafine fibers. The solution was filled into 0.05 inches diameter needle orifice syringe (Cohance Lifesciences Ltd, Hyderabad, India). The feeding rate, set at 0.6 milli liters per hour, managed with a pumping system. Our modified electrospinning system employed a high voltage source set to 13 kilovolts connected to a metallic needle. To collect the resulting ultrafine fibers, a sheet of aluminum foil was positioned horizontally 16 centimeters away from the needle's tip. This electrospinning method, performed on suitable environment, utilized Bionica’s Fluidnatek® LE-500 model electrospinning equipment, Valencia, Spain. For comparative analysis, In addition, PVP membranes containing posaconazole were fabricated using solutions with comparable components through a solution disposition method.

Evaluation

In the evaluation process, drug content and encapsulation efficiency of Posaconazole (PCZ) within PVP microscopic thread structures and solvent-solidified sheets were quantified using a UV spectrophotometric method. The PCZ-loaded electrospun PVP nonwovens and

Evaporative deposition PCZ fibers, meticulously sliced into uniform circles, each 2.6 cm across in diameter and individually diluted in methanol of 5 millilitres. These solutions were then adjusted to a final volume of 10 mL with a buffer solution of pH 6.8. Subsequently, the optical density of each solution was determined at a wavelength of 260 nm by UV spectroscopy (Thermo Fisher UV Genesys 50, USA) to precisely determine the PCZ content. This meticulous approach, leveraging UV spectrophotometry, aimed at ensuring an accurate assessment of drug-loading efficiency and encapsulation within the distinct nanofiber and solidified sheet formulations, providing valuable insights for comprehensive characterization. The results of the drug content analysis were utilized to calculate the EE using Eq[10].

$$\%EE = \frac{\text{Weight of the Posaconazole inside nanofiber}}{\text{Amount of Pasaconazole used}}$$

Electron Microscopy Examination

Electron Microscopy Examination was utilized for evaluating the physical structure of both unprocessed and Posaconazole (PCZ) filled electrospun Poly Vinyl Pyrrolidine fibers, as well as solvent-solidified sheets. The analysis was performed using a scanning electron microscope (Zeiss, Carl Zeiss AG, Germany). Each fiber sheet was individually put an aluminum pins, then coated with a sputtered platinum coating through a coater which is automated (Buhler Leybold Optics, Germany) prior to analysis. This preparation ensured optimal visualization of the samples. The SEM analysis aimed to offer a detailed insight into the surface morphology and structure of the electrospun mats and solidified sheets, particularly highlighting the impact of PCZ loading. Notably, the ket dimension of the PCZ infused electrospun mesh assessed during the characterization process.

Thermal Analysis

To understand how Posaconazole (PCZ) behaves when heated, a technique called differential scanning calorimetry was employed. Same technique was used for find the behaviour of unprocessed electrospun PVP sheets, and PCZ-loaded nanofiber sheets. Utilizing a MicroCal PEAQ-DSC instrument (Malvern, united kingdom), Individual samples, ranging from 12 to 18 milligrams, were enclosed in aluminum capsules. The temperature increased steadily at a rate of 10 degrees Celsius per minute, ranging from an initial 25 degrees Celsius to a final temperature of 300[11] degrees Celsius. A continuous flow of nitrogen gas at 50 milliliters per minute maintained an inert environment during the DSC analysis. This comprehensive methodology facilitated a thorough investigation of the thermal characteristics of PCZ,

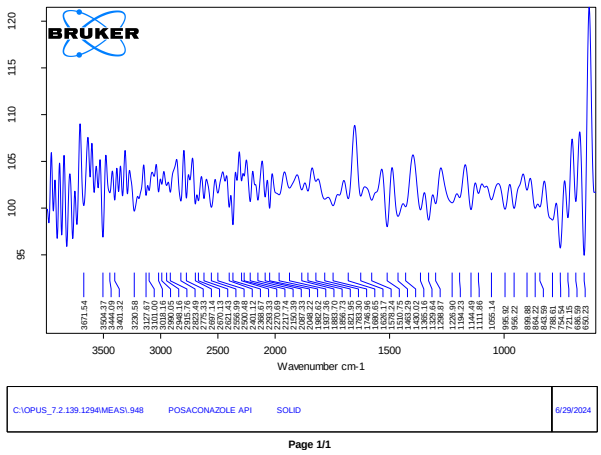
electrospun PVP mats, and PCZ-loaded microscopic thread structures, providing valuable insights into their thermal stability and behavior across the specified temperature range.

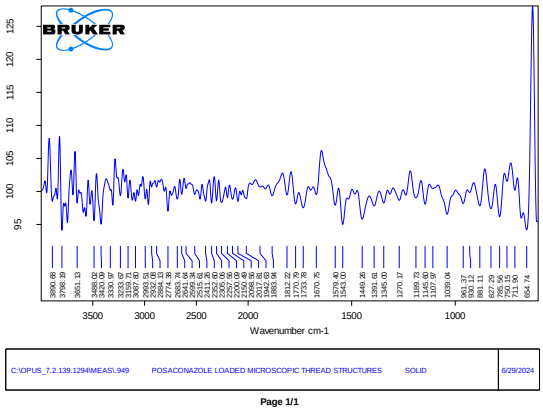
Crystallographic Analysis with Electromagnetic Radiation

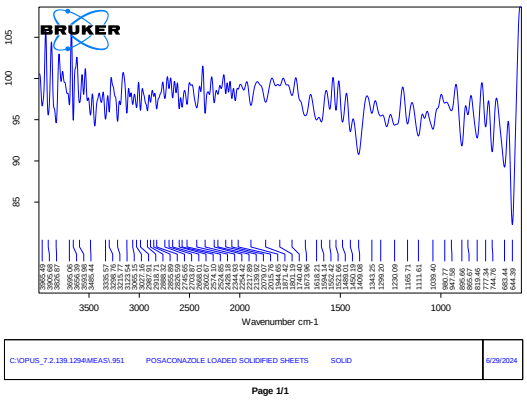
Independent analyses using Crystallographic analysis with electromagnetic radiation were conducted on posaconazole (PCZ) to investigate its crystalline structure in three forms: pure powder, microscopic thread structures loaded with PCZ, and PCZ-loaded solidified sheets cast from solvent. The analyses were conducted using an Aeris X-Diffractometer, Malvern Panlytical, Netherlands. The analytes were exposed to Cu Ka X-rays and were meticulously analyzed within the 2θ range of 10–60°C. This systematic approach allowed for a detailed examination of the crystalline structure and diffraction patterns of PCZ, both within the context of electrospun microscopic thread structures and solvent-solidified sheets. The utilization of Cu Ka radiation and a precise 2θ range contributed to the comprehensive understanding of the XRD profiles of PCZ across different formulations.

FT-IR Spectroscopy

Utilizing FT-IR spectroscopy, analysis was conducted on Posaconazole (PCZ) in isolation, blank PVP microscopic thread structures, PCZ-loaded microscopic thread structures, and PCZ-loaded solvent-solidified sheets. The examination was performed using an ReactIR 702L instrument from Mettler- Toledo., Ltd., Mumbai, India. Prior to analysis, materials underwent pre-analysis processing by combining them with potassium bromide in a 1:100 mass ratio (2 mg sample : 200 mg KBr). The mixture was then loaded into the mold for infrared spectroscopic measurement. Spectra were meticulously acquired across a wide mid-infrared range, encompassing wavenumbers from 4000 to 400 cm-1. This FTIR analysis provided a comprehensive understanding of the molecular composition, functional groups, and interactions within PCZ, blank PVP microscopic thread structures, and the PCZ-loaded formulations in both microscopic thread structures and solvent-solidified sheets.







In Vitro Drug Diffusion Studies

Laboratory investigations explored the movement of dry Posaconazole (PCZ)-loaded microscopic thread structures and solidified sheet samples. A Franz diffusion cell system (Meditech Technologies India Pvt Ltd, Chennai, India) with a 32 mL reservoir capacity was used for this purpose.

Disc-shaped samples (diameter: 1.6 cm, PCZ content: 100 mg) were prepared from each material. These were placed in the donor compartment on a cellophane membrane and sealed securely.

Experiments were conducted at a constant temperature of 37°C with the receptor compartment containing phosphate buffer (pH 6.8). To quantify PCZ permeation, 1 mL aliquots were withdrawn from the receptor compartment at specific intervals. To maintain sink conditions, the withdrawn volume was replaced with fresh buffer.

Collected samples were filtered using Whatman paper and analyzed using a spectrophotometer at 260 nm to determine the PCZ concentration. This approach provided valuable information regarding the drug release characteristics of the microscopic thread structures and solidified sheets

Investigations of Penetration through Isolated Skin Samples

Skin penetration studies were conducted for PCZ loaded microscopic thread structures and solidified sheets. For this hairless rat (SKH-1) abdominal skin was used. Before fitting on to the Franz diffusion cell wiping of the residual fat from the dermis side of the skin was done. Apply a solution containing dispase, a proteolytic enzyme that breaks down proteins in the BMJ. Incubate the skin for a controlled period (potentially shorter than 7 hours) to allow the enzyme to work. Gently rinse the skin with a buffered solution to remove the dispase and loosened epidermal layer. The obtained skin underwent approval by the Animal Ethics Committee of Chilkur balaji Pharmacy College, Hyderabad (Approval no.: CPCSEA/10P/2021). The Franz diffusion cell with a surface area of 3.52 centimetre square and reservoir capacity of 44 Ml was used.

Ex vivo skin permeation studies were conducted for Posaconazole (PCZ) loaded microscopic thread structures and solidified sheet samples using Franz diffusion cells fitted with excised rat skin[12]. The abdominal hairs of Wistar rats were shaved following sacrifice via chloroform inhalation. The subcutaneous tissue was surgically removed from the excised skin, and isopropyl alcohol was applied to wipe the dermis side, eliminating residual fat[13]. Subsequent steps included washing with distilled water, treatment with a 2 M sodium bromide solution for 7 hours, and the use of a cotton swab moistened with distilled water to separate and clean the epidermis. The obtained skin underwent approval by the Animal Ethics Committee of Chilkur balaji Pharmacy College, Hyderabad (Approval no.: CPCSEA/10P/2021). A vertical Franz diffusion cell, featuring a surface area of 2.54 cm^2 and a reservoir capacity of 32 mL, was employed. The receptor compartment was filled with phosphate buffer at pH 7.4, constantly stirred using a magnetic stirrer at 37 ± 1°C. PCZ loaded microscopic thread structures, solidified sheets (PCZ equivalent to 100 mg), and Posaconazole alone (100 mg) were separately applied to the skin's epidermal surface. Media samples (2.5 mL) were withdrawn at fixed intervals, maintaining sink conditions throughout the experiment. The samples were filtered through Wattman filter paper and analyzed for PCZ content using an HPLC method upon appropriate dilution. HPLC was chosen for quantification due to

potential interference from skin components at 260 nm, and the system consisted of a chromatographic pump (LC-20AT, Shimadzu, Kyoto, Japan) fitted with a UV detector. A reversed-phase C18 column (4.6 × 150 mm, micelle size 5 μm, Thermo Scientific, Massachusetts, United States) was employed for HPLC separation, with a mobile phase comprising acetonitrile: ammonium acetate buffer (pH 5.5) in a 30:70 ratio and a flow rate of 1.5 mL/min. The analysis runtime was 10 minutes, and the detection wavelength was set at 235 nm.

Skin Penetration Studies with Microscopic Thread Structures

Skin penetration studies were conducted for Posaconazole (PCZ) incorporated microscopic thread structures and control solidified sheet samples using Franz diffusion chambers equipped with extracted rat skin. The belly fur of Wistar rats was removed after euthanasia with a carbon dioxide chamber. The fatty layer beneath the skin was meticulously removed, and the backside of the skin was swabbed with isopropyl alcohol for residual fat elimination. Subsequent steps included rinsing with purified water, treatment with a 2-Molar sodium bromide solution for 7 hours, and utilization of a cotton bud moistened with purified water to detach and cleanse the topmost skin layer. The obtained skin was approved by the Institutional Animal Care and Use Committee (Approval no.: CPCSEA/10P/2021). A vertical Franz diffusion cell with a surface area of 2.54 cm^2 and a reservoir capacity of 32 mL was employed. The receiving compartment was filled with phosphate buffer at a pH of 7.4, continuously stirred using a magnetic stirrer at 37°C ± 1°C. PCZ-infused microscopic thread structures, control solidified sheets (PCZ equivalent to 100 mg), and pure Posaconazole (100 mg) were separately applied to the skin's uppermost layer. Samples of the medium (2.5 mL) were withdrawn at predetermined intervals, upholding sink conditions throughout the experiment. The samples were passed through a filtration paper and analyzed for PCZ content using a high-performance liquid chromatography (HPLC) technique following appropriate dilution. HPLC was chosen for quantification due to potential interference from skin components at 260 nm. The system consisted of a chromatography pump with a UV detector. A reversed-phase C18 column was used for HPLC separation, with a mobile phase composed of acetonitrile:ammonium acetate buffer (pH 5.5) in a 30:70 ratio and a flow rate of 1.5 mL/minute. The analysis ran for 10 minutes, and the detection wavelength was set at 235 nm.

The liquid used for analysis, after being passed through a specialized filter with a pore size of 0.45 micrometers and treated with sound waves to remove trapped air, was employed

following the introduction of a 20 microliter sample. The time it took for the key component (PCZ) to travel through the system was measured to be 7.2 minutes. The total quantity of PCZ that passed through the barrier (measured in micrograms per square centimeter) was plotted against the elapsed time (in minutes), and the rate of consistent flow ('J') (expressed in micrograms per square centimeter per hour) was determined from the slope of the straight section of the graph. The coefficient representing the ease of passage ('Kp') (in centimeters per hour) was calculated using the formula $Kp = J/C_0$, where C_0 signifies the concentration of the drug in the starting area, and J represents the rate of consistent flow.

RESULTS AND DISCUSSION

In the realm of pharmaceutical development, a well-established strategy involves leveraging water-soluble polymers to improve the solubility of drugs with poor aqueous solubility. These polymers act as potent stabilizers, modifying the surface properties of precipitated particles, thereby hindering their growth and aggregation. Selecting an appropriate water-soluble polymer is critical to maximizing these effects. In this investigation, polyvinyl pyrrolidone (PVP) was chosen for the fabrication of nanofibers due to its inherent characteristics, such as exceptional biocompatibility and reasonable solubility in both aqueous and organic solvents. Initial studies emphasized the effectiveness of PVP in meticulously controlling the particle size and distribution of Posaconazole (PCZ).

The solvent employed plays a pivotal role in the successful production of electro spun nanofibers. The solvent must effectively dissolve the drug while preserving the electro spinnability of polymer solutions. Through a systematic evaluation of various individual solvents and combinations for PCZ and PVP dissolution, a blend of methanol and N,N-dimethylacetamide (MeTHF) emerged as a promising solvent system. This solvent mixture not only facilitated the dissolution of PCZ and PVP but also ensured uninterrupted electrospinning. The high boiling point of MeTHF proved advantageous in promoting the formation of a stable Taylor cone, preventing clogging of the spinneret, and averting gel formation at the surface of the jet. This study cantered on the preparation of PCZ-loaded PVP nanofibers using the electrospinning technique. Subsequent investigations were conducted to characterize the morphology and dimensions of the resultant fibres, with the aim of ensuring originality and contributing valuable knowledge to the field of drug delivery.

SEM Study of Microscopic Thread Structures

SEM was employed to confirm the formation of microscopic thread structures in PCZ-loaded PVP mats (Fig. 1). The SEM images exhibited discrete Posaconazole (PCZ) loaded PVP mats with sizes ranging from 60 to 80 nm. Interestingly, the lack of visible drug crystals or clumps in the microscopy analysis indicates that the drug has likely been incorporated and scattered throughout the individual fibers at the molecular level. This is in stark contrast to the PCZ-laden sheet produced using the solvent casting method, which exhibited drug crystals on its surface [14]. This difference in the presence of drug clusters on the fiber or sheet surfaces may be attributed to variations in the rate of solvent removal (methanol and MeTHF) during the creation process. The electrospun fibers experienced rapid solvent evaporation during their journey to the collection device, whereas the slower solvent evaporation from the drug-loaded, freshly solidified sheets could explain the observed accumulation of drug particles on their surface. This SEM analysis provides valuable insights into the morphology of electrospun microscopic thread structures, emphasizing successful drug encapsulation and shedding light on the impact of solvent evaporation rates on drug aggregate formation in different formulations.

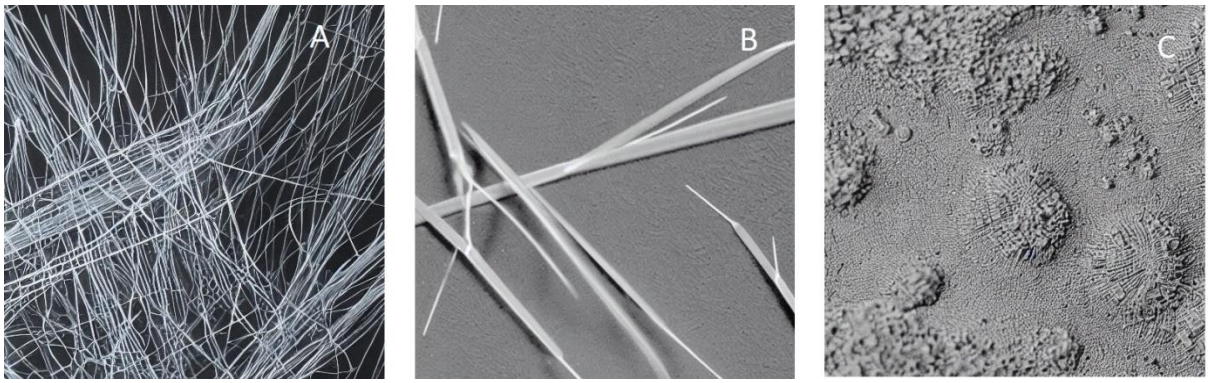


Fig. 1. Microscopic visualizations showcasing (A) PCZ-incorporated nanofibers at a magnification of ten thousand times, (B) PCZ-incorporated nanofibers at a magnification of thirty thousand times, and (C) PCZ-laden solidified sheets at a magnification of ten thousand times.

Analysis Using X-Ray Diffraction (XRD)

This section investigated potential changes in the molecular structure (polymorphic transitions) of Posaconazole (PCZ) when incorporated into nanofibers using X-ray diffraction analysis. Additionally, XRD patterns were used to evaluate the degree of crystallinity within

the samples by examining the relative intensity of peaks across a specific range of angles (2Θ). Figure 2 presents the XRD patterns of pure PCZ, PCZ-loaded solidified sheets, and PCZ-incorporated nanofibers.

The XRD pattern of pure PCZ revealed sharp peaks at distinct 2Θ angles (5.45°, 8.25°, 16.48°, 19.52°, 27.43°, and 30.25°) [16], confirming its crystalline nature. In contrast, the diffraction pattern of PCZ-loaded nanofibers displayed broad and weak peaks, suggesting a conversion of PCZ to an amorphous state within this formulation. This amorphous form is known to offer several benefits, including increased solubility, improved interaction with water (wettability), and a faster dissolution rate compared to the crystalline form. Interestingly, PCZ-loaded solidified sheets retained peaks characteristic of crystalline PCZ, indicating the presence of both amorphous and crystalline forms in these sheets

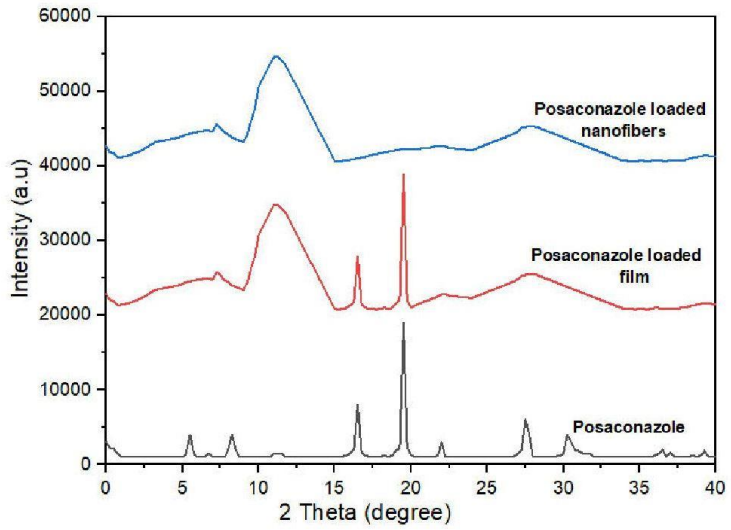


Fig. 2. XRD of Posaconazole, Posaconazole loaded solidified sheet(film) and Posaconazole loaded microscopic thread structures(nanofibers).

Differential Scanning Calorimetry (DSC) Analysis

The DSC thermograms of the samples provided complementary information to the XRD studies, shedding light on the material's phase transitions and crystal organization. Pure Posaconazole displayed a well-defined endothermic peak at 129.6 °C, with an associated energy change of 38.4 J/g, corroborating its crystalline nature. The DSC thermogram of PVP K-30 revealed a broad endothermic peak at 92.62 °C, signifying the release of water molecules from the highly water-attracting PVP polymer chains. The DSC analysis of PCZ-

loaded solidified sheets aligned with the XRD results, showcasing melting endotherms at 128.2°C and 251.6°C, further confirming the crystalline state of the drug. Interestingly, the DSC thermogram of the PCZ-loaded nanofiber mat exhibited a single endothermic peak at 131.8°C, noticeably lacking the peak corresponding to Posaconazole's melting point. This observation suggests the complete conversion of PCZ to an amorphous state within the nanofiber formulation. Therefore, the DSC findings strongly support the conclusions drawn.

Fourier Transform Infrared Spectroscopy (FTIR) Analysis

FTIR spectroscopy was used to analyze Posaconazole by itself, in solidified sheets, and encapsulated within nanofibers. Pure Posaconazole exhibited distinct peaks at 3452.73 cm-1 (indicating NH stretching), 1731.25 cm-1 (characteristic of C=O stretching), 1461.32 cm-1 (representing C-C stretching), and 1622.38 cm-1 (associated with NH bending). The FTIR spectrum of PVP K-30 displayed characteristic peaks at 2974.18 cm-1 (indicating CH stretching) and 1723.84 cm-1 (characteristic of C=O) [17]. Notably, the FTIR spectra of both PCZ-loaded nanofibers and solidified sheets retained all the distinctive peaks associated with both Posaconazole and PVP. Importantly, there were no significant shifts in existing peaks or emergence of new ones, confirming the compatibility of Posaconazole with PVP and the absence of substantial chemical interactions between the two components.

Drug Content and Encapsulation Efficiency

The PCZ content in the prepared electrospun Poly viny Pyrrolidine microscopic thread structures determined as 99.21 ± 3.17% w/w, while solvent solidified sheets exhibited a PCZ loading of approximately 79.6 ± 3.26% w/w. Moreover, the encapsulation efficiency (EE) of electrospun PVP microscopic thread structures was measured at 99.49 ± 0.41% w/w, but solvent solidified sheets demonstrated an entrapment efficiency of about 82.3 ± 1.42% w/w. The solidified sheets cast at higher temperature (80 ± 2°C) to ensure complete solvent removal.

In Vitro PCZ Diffusion Studies

In the context of in vitro PCZ diffusion studies, the release profiles from microscopic thread structures and solvent solidified sheets were investigated in phosphate buffer pH 6.8 and compared to the release curve of PCZ powder (Fig. 5). The e-spun microscopic thread structure loaded with PCZ exhibited a release of 98.4 ± 1.24% after 60 min, whereas the as-

solidified sheet showed PCZ release of about 76.52 ± 1.76 % after 2 hours. The diffusion of PCZ alone was limited to 43 ± 1.84% after 2 hours, confirming its low solubility in phosphate buffer at pH 6.8. The observed slower rates and lower maximum release of PCZ from as-solidified sheets, compared to nanofiber counterparts, were attributed to the crystalline nature of PCZ and the slow swelling of PVP solidified sheets.

The gradual swelling of the solidified sheet resulted in slow diffusion of PCZ from the polymer matrix. Additionally, PCZ aggregates formed on the solidified sheet surface, potentially leading to lesser dissolution. Conversely, microscopic thread structures contained non-aggregated PCZ in an amorphous state, known for higher solubility than the crystalline form. The significant increase in surface area for dissolution, amorphization of PCZ, and absence of PCZ aggregates were identified as contributors to the improved diffusion of PCZ when formulated as microscopic thread structures. The drug diffusion through the swollen polymer matrix was supported by the PCZ release curves of microscopic thread structures and as-solidified sheets, which were subjected to model fitting. Both release curves adhered to the Korsmeyer–Peppas model[18] (R2 = 0.998), confirming diffusion-controlled drug release as expressed by Eq. (3) and aligning with previous suggestions.

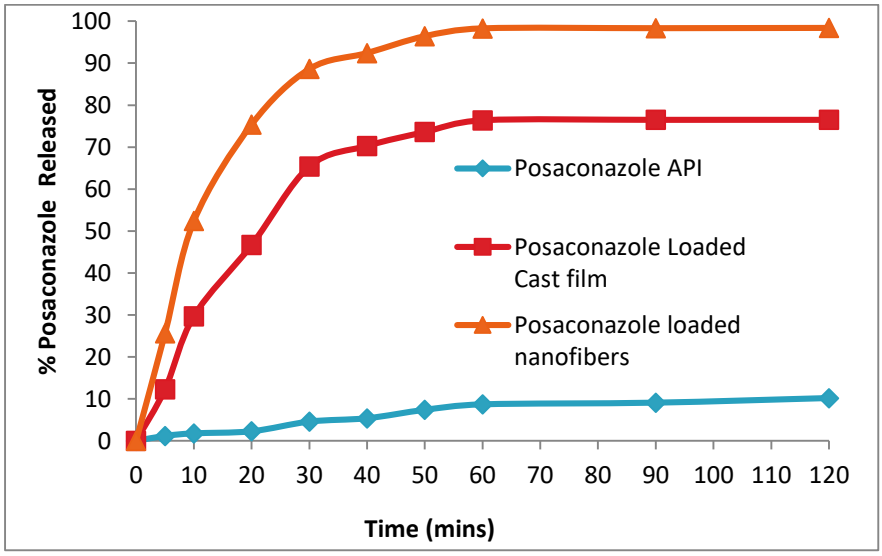


Fig. 3. The invitro diffusion study of Posaconazole loaded microscopic thread structures (nanofibers) and as solidified sheets (cast film)

The drug release kinetics were assessed using the equation Q = kt^n, where Q represents the percentage of drug released at time t, k is a kinetic constant, and n is the diffusional exponent indicative of the release mechanism. A value of n = 0.5 signifies Fickian diffusion, while values below 0.5 suggest non-Fickian transport of the drug. In the case of PCZ-loaded microscopic thread structures, the diffusion exponent 'n' was determined to be 0.574,

indicating adherence to Fick's law of diffusion. Conversely, for the as-solidified sheet, the 'n' value was 0.3735, suggesting that drug release from the solidified sheet is likely controlled by a combination of diffusion and erosion mechanisms[19]. The permeation of the drug from a transdermal drug delivery system is predominantly influenced by the factor of diffusion.

Table 1 Skin permeation kinetics of Posaconazole from PCZ loaded microscopic thread structures and as cast PVP solidified sheet		
Formulation	PCZ loaded microscopic thread structures	PCZ loaded solvent solidified sheets
Flux	5.32 ± 0.42	0.642 ± 0.29
Permeability	0.00395	0.000832
Mean ± SD.		

Extracorporeal Skin Penetration

The extracorporeal skin penetration findings showcased the superior efficacy of PCZ-loaded microscopic thread structures over cast films (Figure 4, Table 1), with the flow rate of microscopic thread structures being 12 times higher compared to that of the solidified sheets. Additionally, the permeability coefficient exhibited a greater value for microscopic thread structures in contrast to the solidified sheets. This dominance can be ascribed to the heightened solubility of PCZ, attained through molecular dispersion within Polyvinyl Pyrrolidine, along with the swift expansion of porous microscopic thread structures due to their diminutive size and substantial augmentation in surface area

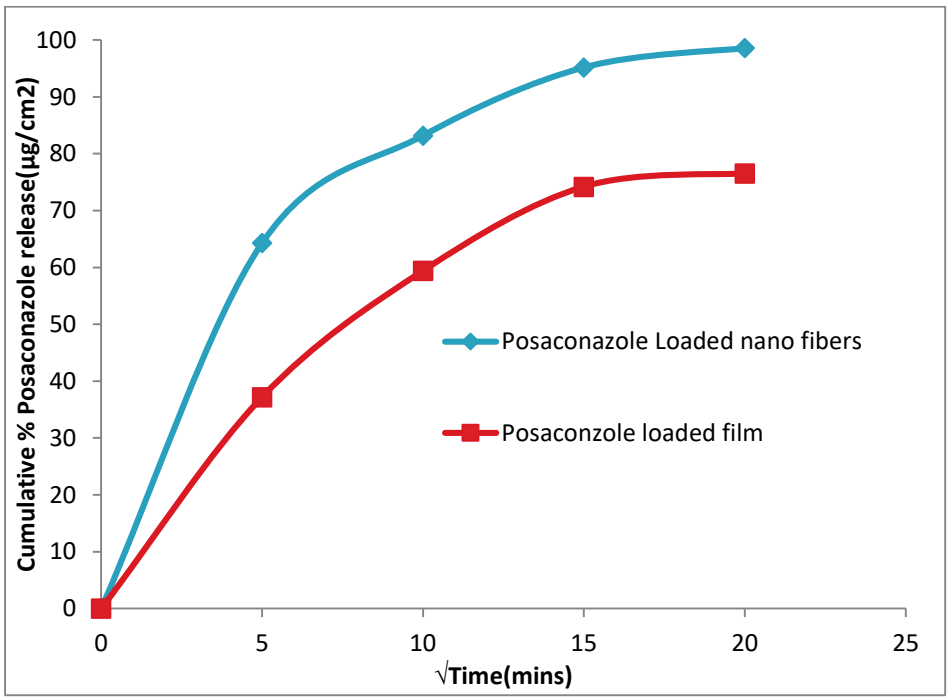


Fig. 4. Skin permeation profile of Posaconazole loaded microscopic thread structures and as solidified sheet

Consequently, this results in the hastened release of PCZ molecules in comparison to the cast films. Furthermore, a linear escalation in penetration flow was observed with an elevation in PCZ concentration in both PCZ-loaded microscopic thread structures and cast Polyvinyl Pyrrolidine sheets. This occurrence can be associated with the decline in the relative proportion of polymer, which serves as a barrier to PCZ diffusion, thereby leading to an augmented PCZ release. Hence, the heightened concentration gradient facilitated increased PCZ penetration from the microscopic thread structures.

CONCLUSION

In this investigation, we effectively produced microscopic fiber constructs laden with PCZ via electrospinning, showcasing their supremacy over PCZ-loaded solidified sheets in both PCZ release assays conducted in vitro and studies on PCZ penetration through skin conducted ex vivo. The enhanced delivery dynamics of PCZ-loaded microscopic fiber constructs can be attributed to the amorphization and diminished particle dimensions of PCZ, dispersion of PCZ molecules within the Polyvinyl Pyrrolidine framework, and a significant augmentation in the dissolution surface of PCZ through nanosizing, as evidenced by SEM, XRD, and DSC examinations. Consequently, considering these advancements, a dermal patch employing PCZ-loaded microscopic fiber constructs emerges as a promising alternative dosage format, aiming to refine the biopharmaceutical characteristics and enhance the drug delivery efficiency of posaconazole.

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